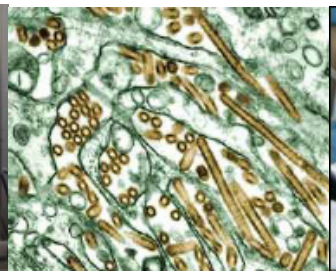
WHO strategic action plan for pandemic influenza




World Health Organization

 WHO/CDS/EPR/GIP/2006.2a

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1 Executive summary

From 7–9 November 2005, a meeting on avian influenza and human pandemic influenza was jointly convened by WHO, the Food and Agriculture Organization, the World Organisation for Animal Health, and the World Bank. The meeting reviewed the status of highly pathogenic H5N1 avian influenza in animals and assessed the related risks to human health, including those that would arise following the emergence of a pandemic virus. Concern about the consequences of such an event steered discussions, on human health matters, towards consideration of two main sets of actions. These were aimed at (1) preventing the emergence of a pandemic virus or, should this prove impossible, delaying the initial international spread of a pandemic, and (2) preparing all countries to cope with a pandemic in ways that reduce morbidity and mortality and also mitigate economic and social disruption.

Participants agreed that the threat of a pandemic was of shared and significant concern for all countries, and that actions to prevent a pandemic or mitigate its consequences were likewise a shared responsibility of all countries. Scenarios of events during the first influenza pandemic of the 21st century painted a grim picture for human health the world over, the survival of existing development projects, and the health of the global economy, with losses expected to reach around US$ 800 billion during the first year of a pandemic.

In seeking solutions to what was widely perceived to be an emergency situation, participants agreed on two main guiding principles. First, use of existing infrastructures and mechanisms, including those for region-wide collaborative actions, was the most rational, predictable, and expedient way to improve capacity to respond to both the present situation and a pandemic. Region-wide approaches, in particular, could be used to find efficient solutions to similar epidemiological situations and needs, compelled by the immediacy of a threat that can rapidly affect neighbouring countries. Second, to the extent possible, the introduction of emergency measures should be combined with longer-term measures aimed at strengthening institutional capacities, as such an approach would leave the world better able to defend itself against the certainty of other emerging and epidemic-prone infectious diseases. Country plans, based on immediate and longer-term needs as perceived by national authorities, were considered the foundation for funding proposals that aim to strengthen collective defences against the pandemic threat.

Participants reached a number of conclusions and agreed on a 12-point action plan. Concerning human health matters, four main opportunities to act were identified: reduce high-risk behaviours associated with human infections; improve the detection, investigation, and reporting of human cases and, in so doing, strengthen the early warning system; contain an emerging pandemic virus; and increase pandemic preparedness. A fifth item – considered by many participants to be the most pressing need for adequate preparedness – concerned world capacity to manufacture sufficient quantities of pandemic vaccines and antiviral drugs, at sufficient speed, and to make these interventions broadly accessible to all countries.

These five actions form the basis of the five-pronged strategic plan set out in this document. The plan aims to achieve two over-arching objectives:

1. to exploit all feasible opportunities to prevent the H5N1 virus from developing the ability to ignite a pandemic and, should this effort fail,
2. to ensure that measures are in place to mitigate the high levels of morbidity and mortality and social and economic disruption that can be expected during the next pandemic.

Each strategic action has a goal that contributes to these larger objectives.

Strategic action		Goal
1	**Reduce human exposure to the H5N1 virus**	Reduce opportunities for human infection and, in so doing, reduce opportunities for a pandemic virus to emerge
2	**Strengthen the early warning system**	Ensure that affected countries, WHO, and the international community have all data and clinical specimens needed for an accurate risk assessment
3	**Intensify rapid containment operations**	Prevent the H5N1 virus from further increasing its transmissibility among humans or delay its international spread
4	**Build capacity to cope with a pandemic**	Ensure that all countries have formulated and tested pandemic response plans and that WHO is fully able to perform its leadership role during a pandemic
5	**Coordinate global scientific research and development**	Ensure that pandemic vaccines and antiviral drugs are rapidly and widely available shortly after the start of a pandemic and that scientific understanding of the virus evolves quickly

The plan sets out expected results and identifies several institutional capacities that will be strengthened by the proposed strategic actions. Apart from preparing the world to cope with the present emergency situation, the strengthening of these capacities will improve the world's ability collectively to defend itself against many other emerging and epidemic-prone diseases.

2 Background

Assessment of the pandemic threat

WHO and international experts believe that the world is now closer to another influenza pandemic than at any time since 1968, when the last of the previous century's three pandemics began. The highly pathogenic H5N1 avian influenza virus, which has been circulating in poultry in parts of Asia since mid-2003, has infected more than 200 humans in 10 countries, but remains primarily a disease of birds. Should the virus acquire an ability to spread efficiently and sustainably among humans, a pandemic is expected to begin.

Opportunities for the virus to acquire this ability will persist. Despite intensive control efforts, the virus has become endemic in poultry in several of Asia's initially affected countries. Evidence has mounted that at least some species of migratory birds have acquired an ability to carry the H5N1 virus in its highly pathogenic form over long distances. The involvement of migratory birds in the epidemiology of this disease increases the likelihood of further spread and adds greatly to the complexity of control measures in animals, as elimination of the virus in wild birds is universally considered impossible. This new role of migratory birds, first recognized in mid-2005, is considered at least partly responsible for the dramatic recent spread of the virus. From early February 2006 to mid-May 2006, 36 countries located in Africa, Asia, Europe, and the Middle East reported their first instances of H5N1 infection in domestic or wild birds, or both. The endemicity of the virus, its presence in wild birds, and its extensive geographical spread have increased the probability that a pandemic will occur.

These events have also given the world its first advance warning that a pandemic may be near and an equally unprecedented opportunity to undertake appropriate protective actions. Such actions are a shared responsibility of the international community. Influenza pandemics are remarkable events in that they can spread, within a matter of months, to affect all countries. All populations are fully susceptible to pandemic viruses, and all countries are equally at risk.

Once international spread of a pandemic virus begins, pandemics are considered unstoppable, caused as they are by a virus that is readily transmitted through the air by coughing or sneezing. Many experts expect the next pandemic to reach all parts of the world within 3 months. Pandemics usually cause abrupt surges in the numbers of people needing medical or hospital care, temporarily overwhelming health services. High rates of worker absenteeism can interrupt other essential services, such as law enforcement, transportation, and communications, and impede business continuity and economic productivity. Experiences during the 2003 outbreak of severe acute respiratory syndrome (SARS) suggest that the associated social and economic disruptions will be amplified in this century's closely interrelated and interdependent systems of trade and commerce. In addition, broad access to electronic communications can be expected to spread public anxiety at equally unprecedented speed. The World Bank has estimated that the first influenza pandemic of the 21st century could cost the world economy US$ 800 billion within a year.

The need for calculated emergency actions

Neither the timing nor the severity of the next pandemic can be predicted with any certainty. At the same time, however, the present threat to international public health is sufficiently serious to call for emergency actions calculated to provide the greatest level of protection and preparedness as quickly as possible. Over the past three years, H5N1 has shown itself to be a tenacious virus for poultry and a treacherous one for humans. In humans, the virus can cause severe disseminated disease affecting multiple organs and systems, with rapid clinical deterioration of patients and high mortality. Almost all patients develop pneumonia. More than half of all laboratory-confirmed cases have died. Scientists do not know if the H5N1 virus will retain its present virulence should it acquire an ability to spread easily among humans. It is nonetheless prudent, when formulating pandemic preparedness plans, to include provisions for responding to high excess mortality.

The most reliable, predictable, and expedient way to improve the world's defences against pandemic influenza is to build on existing structures and mechanisms that have worked well in recent public health emergencies. At the same time, all concerned should keep in mind that no health emergency on the scale of a severe influenza pandemic has confronted the international community for several decades.

A two-fold task: prevention and preparedness

In responding to this significant and shared threat, the principal tasks facing the international community are twofold: (1) to reduce opportunities for the virus to improve its pandemic potential and (2) to be prepared for a pandemic should these efforts fail.

Apart from possibly forestalling a pandemic or delaying its international spread, strategic actions in the first group aim to improve the early warning system and this, in turn, serves better preparedness. Each day gained following the emergence of a pandemic virus – if rapidly detected – allows the world to augment its supplies of pandemic vaccine. Each added day gives countries more time to adapt routine health services to an emergency situation. Time gained also allows WHO to gather data on patterns of spread and issue appropriate alerts.

Opportunities to intervene pre-emptively are reflected in three of the five strategic actions outlined in this document:

1. Reduce human exposure to the H5N1 virus
2. Strengthen the early warning system
3. Intensify rapid containment operations

Preparedness activities are covered in the remaining strategic actions:

4. Build capacity to cope with a pandemic
5. Coordinate global science and research, particularly as this pertains to the availability of a pandemic vaccine and antiviral drugs

3 Goals

The principal objectives of this strategic action plan are twofold:

(1) to exploit all feasible opportunities to prevent the H5N1 virus from developing the ability to ignite a pandemic and, should this effort fail,

(2) to ensure that measures are in place to mitigate the high levels of morbidity and mortality and social and economic disruption that can be expected during the next pandemic.

In pursuit of these objectives, the plan gives priority to five strategic actions. Each of these strategic actions has its own goal that contributes to the larger objectives.

Strategic action	Goal
1 **Reduce human exposure to the H5N1 virus**	Reduce opportunities for human infection and, in so doing, reduce opportunities for a pandemic virus to emerge
2 **Strengthen the early warning system**	Ensure that affected countries, WHO, and the international community have all data and clinical specimens needed for an accurate risk assessment
3 **Intensify rapid containment operations**	Prevent the H5N1 virus from further increasing its transmissibility among humans or delay its international spread
4 **Build capacity to cope with a pandemic**	Ensure that all countries have formulated and tested pandemic response plans and that WHO is fully able to perform its leadership role during a pandemic
5 **Coordinate global scientific research and development**	Ensure that pandemic vaccines and antiviral drugs are rapidly and widely available shortly after the start of a pandemic and that scientific understanding of the virus evolves quickly

The plan also sets out expected results as a focus for these actions.

Implicit in meeting these goals are several capacities at national and international levels:

(1) to conduct surveillance for human cases in countries experiencing poultry outbreaks
(2) to detect imported cases
(3) to confirm diagnosis
(4) to undertake field investigations of cases and interpret the findings
(5) to identify populations at heightened risk of infection and introduce protective measures
(6) to detect the earliest epidemiological signals that the virus may be increasing its transmissibility among humans
(7) to intervene rapidly and adequately when this occurs
(8) to produce sufficient quantities, at sufficient speed, of vaccines and antiviral drugs as measures for mitigating morbidity and mortality during a pandemic, and make these interventions widely available.

Proposed strategic actions aim to strengthen these and other capacities. Apart from preparing the world to cope with the present emergency situation, the strengthening of these capacities will improve the world's ability collectively to defend itself against many other emerging and epidemic-prone diseases.

4 Strategic actions and expected results

1. Reduce human exposure to the H5N1 virus

Goal

To reduce opportunities for human infections to occur and, in so doing, to reduce opportunities for the virus to develop (through adaptive mutation or a reassortment event) into a form readily transmissible among humans.

Strategic approach

- Improve understanding of risk factors for human infection.
- Ensure that each country affected by outbreaks in poultry has a strategy for informing the general public of the associated risks to human health and how to avoid them, and has a policy that facilitates these protective behaviours.
- Ensure that this strategy is based on best practices for bringing about behaviour change, is adapted to the national social and cultural context, reaches populations at greatest risk (including children), and is tested for effectiveness and modified as needed.
- Ensure that each country affected by outbreaks in poultry has a policy in place, supported by appropriate equipment and supplies, for protecting defined groups (poultry cullers and veterinarians, health care staff attending suspected or confirmed human cases, and laboratory workers) considered at high occupational risk of exposure to the virus.
- Ensure that proper isolation and infection control procedures are followed in hospitals caring for suspected or confirmed cases.

Rationale

At present, H5N1 avian influenza is primarily a disease of birds. The species barrier is significant: the virus does not easily cross from birds to infect humans. Despite the infection of tens of millions of poultry over large geographical areas for three years, just over 200 human cases have been laboratory confirmed in nine countries: Azerbaijan, Cambodia, China, Egypt, Indonesia, Iraq, Thailand, Turkey, and Viet Nam. Most infections to date have occurred in rural and periurban households where small flocks of poultry are kept. Very few cases have been detected in presumed high-risk groups, such as commercial poultry workers, workers at live poultry markets, cullers, veterinarians, and health staff caring for patients without adequate protective equipment. Research is urgently needed to better define the exposure circumstances and behaviours and possible genetic or immunological factors that enhance the likelihood of human infection.

While human cases remain comparatively rare at present, each additional case gives the virus an opportunity to improve its transmissibility. Any strategy that reduces the risk of further human cases reduces the risk that a pandemic virus might emerge. Under ideal conditions, complete elimination of the virus from its domestic poultry host would remove the risk of a pandemic at its source. This is the goal being pursued by FAO and OIE, as set out in the jointly issued *Global strategy for the*

progressive control of highly pathogenic avian influenza.[1] The provision of adequate compensation to farmers for lost birds has clearly emerged as a principal strategy for improving the reporting of outbreaks, particularly in remote rural areas that are rarely reached by veterinary services. Compensation schemes encourage the reporting of outbreaks and thus help circumvent the problems caused by weak veterinary infrastructures and surveillance systems for animal disease. This approach is being given prominence by FAO and OIE. However, with the virus now firmly entrenched in many areas, and with wild migratory waterfowl playing a role in further spread, timeframes for achieving control in severely affected countries are now being measured in years. The newly identified role of migratory birds is of particular concern, as bird migration is a recurring event. The possibility that a pandemic virus will emerge prior to the attainment of control in animals cannot be ruled out. For this reason, other strategies for reducing the risk of human cases – and the associated risk of a pandemic – need to be pursued in parallel.

As complete elimination of the virus in birds is not likely to occur in the immediate future, prevention of high-risk human behaviours assumes heightened importance as a strategy for reducing opportunities for human infections to occur. Unfortunately, the virus has established its strongest foothold in small backyard flocks in rural and periurban areas, where control is most difficult, opportunities for human exposure are greatest, and most human cases have occurred to date. At present, the highest risk of human infection is thought to occur during the home slaughter, defeathering, butchering, and preparation for consumption of diseased birds.

During the November 2005 meeting, several frontline countries referred to the difficulty of altering high-risk behaviours, although some public education campaigns have successfully raised awareness among rural farmers.[2] Poverty exacerbates the problem: in situations where a prime source of food and income cannot be wasted, households frequently consume poultry when birds in a flock show signs of illness or die. In other countries, suspicions that human cases of avian influenza may have a non-medical cause have created strong public opposition to control measures and led to extreme stigmatization of patients and their families. On numerous occasions, these attitudes and behaviours have hindered key activities, including contact tracing and monitoring and field investigations to determine the exposure source. When such activities cannot be performed properly, the risk of further human exposures and cases is enhanced.

International experience has shown that well-planned public awareness and social mobilization initiatives are an effective intervention for reducing high-risk behaviours during an outbreak. In 2000, WHO developed the Communication for Behavioural Impact, or COMBI, approach as a strategy for achieving behavioural change during campaigns for the control of infectious diseases. The approach, which is supported by a WHO international centre for social mobilization in Tunisia, has subsequently been tested and refined under challenging conditions, including responses to outbreaks of Ebola and Marburg haemorrhagic fevers in Africa. The approach is flexible and can be readily adapted to the avian influenza situation.

A second way to reduce opportunities for human infections to occur is to protect defined groups at high occupational risk of exposure to the virus: poultry cullers and

[1] A global strategy for the progressive control of highly pathogenic avian influenza. Food and Agriculture Organization, World Organisation for Animal Health in collaboration with the World Health Organization (November 2005).

[2] Olsen SJ, Laosirtaworn Y et al. Poultry-handling practices during avian influenza outbreak in Thailand. Emerg Infect Dis 2005; 11: 10, 1601–1603.

veterinarians, health care workers, and laboratory workers. Protection can be conferred by personal protective equipment and training in its use, infection control in health care facilities, and rigorous biosafety procedures in laboratories. Although only a few cases of infection have been confirmed in these occupational groups, opportunities for exposure to the virus are high; protective measures need to be maintained or introduced, particularly given the propensity of influenza viruses to undergo frequent changes.

Expected results

1. Research, coordinated by WHO, improves understanding of factors that enhance the likelihood of human infection.
2. Advice on risk reduction is more precise in terms of groups at greatest risk, most effective preventive measures.
3. Countries have strategies for reaching these groups with appropriate messages.
4. Compensation schemes are in place and include small rural farms.
5. Occupational groups at heightened risk of exposure are protected.
6. Collaboration between the human health and veterinary sectors improves; governments accept that human health concerns must drive jointly formulated policies.

2. Strengthen the early warning system

Goal

To ensure that affected countries are able to detect and manage cases quickly and that WHO and the international community have the data and clinical specimens needed for an accurate risk assessment in line with the WHO phases of pandemic alert.

Strategic approach

- Strengthen the capacity of national and international surveillance systems, using existing infrastructures, in ways that ensure rapid detection of suspected human cases, rapid and reliable laboratory confirmation, rapid field investigation, and rapid and complete reporting to WHO.
- Strengthen mechanism for formal collaboration between the human health and agricultural sectors.
- Trace and monitor contacts of each human case.
- Ensure that clinical specimens and viruses are shared with the WHO network of reference laboratories specialized in diagnostic work and analyses of H5 influenza viruses.

Rationale

As reported during the November 2005 meeting, most frontline countries have inadequate surveillance and laboratory capacity to support the reliable detection and reporting of human cases, particularly in rural areas where contact with free-ranging poultry is most frequent, the risk of human cases is highest, and access to health care is limited. In such areas, the problem of case detection is compounded by the similarity of early symptoms of H5N1 infection with those of many other respiratory diseases commonly found in affected countries. As a result, some human cases are almost certainly being missed; other cases are being detected too late for antiviral drugs (which should be administered within 48 hours of symptom onset) to be effective in improving the patient's prospects of survival.

Weak surveillance causes other problems as well. Missed cases and late detection undermine the accuracy of risk assessment and leave the epidemiological picture of this disease incomplete. Efforts to improve the situation need to address several specific problems.

As each new human infection gives the virus an opportunity to evolve towards an efficiently transmissible strain, the response to a new human case needs to include a thorough field investigation aimed at determining the source of exposure, whether any close contacts are displaying influenza-like symptoms, and whether human-to-human transmission may have occurred.

Collaboration between the health and agricultural sectors. Close collaboration between the agricultural and public health sectors is essential but has proved difficult to forge at the operational level. The detection of fresh outbreaks in poultry should trigger heightened vigilance for human cases. In reality, the detection of a human case has often been the first signal that poultry outbreaks are occurring in an area. Joint investigations of human cases are needed to determine the exposure source and deepen knowledge about the relationship between outbreaks in poultry and the risk of human infection.

Diagnostic capacity. Because of the significance of each new human case, diagnostic confirmation must be made with full confidence in the reliability of test results. Diagnostic tests to confirm H5N1 infection are technically challenging. The accuracy of results further depends on procedures followed when collecting clinical specimens, access to equipment and up-to-date diagnostic reagents, the expertise of staff, and a quality assurance scheme based on international standards. The challenge of diagnostic testing and confirmation of cases is usually amplified during the demanding conditions of an outbreak, which may include great pressure to produce results quickly for clinical or political reasons.

Because the H5N1 virus belongs to the second most lethal category of human pathogens, some diagnostic work, including virus isolation, can be safely undertaken only in high-containment facilities, which are beyond the reach of the vast majority of affected countries. H5 reference laboratories in the WHO network have these facilities and have been providing essential support in the areas of diagnostic confirmation and virus characterization. Guidelines for sample collection and the correct performance of recommended tests are available. WHO has been supplying diagnostic test kits to countries on request and providing on-site training to improve diagnostic proficiency. As a further support to countries, WHO arranges and finances the safe collection, packaging, and shipment, via courier service, of patient specimens to a designated WHO H5 reference laboratory. All of these activities need to continue, but on a much larger scale.

Adequate facilities, equipment, and training are needed to ensure that test results are reliable. Many affected and at-risk countries have a national influenza centre that is part of the WHO global influenza surveillance network set up to monitor all influenza virus strains, including those responsible for seasonal influenza. The quality of work performed in these laboratories is, however, not consistently high. Ensuring that all priority countries have a national influenza centre, with staff equipped and trained to reliably diagnose H5N1 infection, would also increase world capacity to monitor changes in all influenza viruses and maintain vigilance for other novel virus subtypes that may emerge. Priority countries without such a centre should be aware of procedures for securing external diagnostic support and have a plan for the rapid and safe dispatch of specimens, facilitated by WHO.

Vigilance for imported cases. At the global level, all countries need to remain vigilant for the possible importation of cases, though the risk of this occurring under present conditions (phase 3 in the WHO scale of pandemic alert) is thought to be very low. In the current climate of high awareness of this disease, many countries have investigated possible cases, usually in travellers returning from an infected country. One case exported from Egypt to Jordan has been confirmed, but such incidents are almost certainly exceedingly rare.

Investigations of human-to-human transmission. Within an early warning system, an ability to detect clusters of cases, closely related in time and place, is considered critical, as such cases could provide the first epidemiological signal that the virus has begun to spread more easily among humans. If early signals are missed, the world will lose its one opportunity for pre-emptive intervention near the start of a pandemic. In this regard, the fact that the virus is now present in poultry in some of the world's most densely populated and impoverished areas, poorly served by health care systems, is of particular concern.

Investigations to determine whether human-to-human transmission has occurred encounter several problems. In some countries, the virus is now so pervasive in birds and in environments contaminated with their faeces that it has become difficult

to determine, when cases within a family occur, whether family members acquired the virus from a shared environmental source or from each other. Training of local staff to perform such investigations, guided by a WHO field manual, is one solution. Support from international experts drawn from institutions in the WHO Global Outbreak Alert and Response Network is another. Standardized protocols for the investigation of human cases need to be made available at all levels, thus ensuring that investigations collect the most relevant data from the start, when evidence is fresh.

Vigilance at the family and community level. As demonstrated during the SARS outbreak, public awareness campaigns that encourage self-reporting of influenza-like illness can reduce the time between symptom onset and case detection throughout a country, especially when supported by telephone hotlines and fever clinics. Such approaches can usefully augment other surveillance systems, especially in situations where active case finding is weak.

Virus and specimen sharing. Genetic sequencing of currently circulating viruses is an additional way to gather early signals that the virus is mutating or has acquired human genes during co-infection of a host with a human influenza virus. To ensure that valuable clues from the genetic analysis of viruses are not missed, countries should share clinical specimens and animal samples with specialized laboratories in the WHO network. As the H5N1 virus mutates – or "drifts" – so readily, studies of currently circulating viruses are further needed to ensure that work on a pandemic vaccine stays on track. Experience has shown that major delays in the sharing of clinical specimens and viruses can arise from logistic, legal, biosafety, or budgetary problems or concerns about intellectual property rights. All of these problems need to be addressed as a matter of urgency. WHO continues to offer its full logistical and financial support for the shipment of patient specimens to a designated reference laboratory.

Patient management. Standardized case definitions and management protocols are urgently needed in all countries experiencing human cases. The disease in humans is poorly understood at present, as are the best approaches to treatment. In March 2006, WHO assembled an international panel of clinicians experienced in the management of H5N1 patients to provide advice on the pharmacological management of cases and the most appropriate use of antiviral drugs for chemoprophylaxis. The resulting guidelines are available at:
http://www.who.int/csr/disease/avian_influenza/guidelines/pharmamanagement/en/index.html

Obligations and timeframes for urgent actions. During the November 2005 meeting, participants asked that a proposal for immediate voluntary compliance with relevant provisions of the revised International Health Regulations (IHR) be prepared for consideration by the WHO Executive Board at its 117th session in January 2006. This proposal was accepted, and a draft resolution has been prepared to move the matter forward immediately. The Regulations, which will not come into force until 15 June 2007, are the only international legal instrument for responding to infectious diseases of international concern. They set out requirements and responsibilities, establish mechanisms and procedures for undertaking required activities, and specify timeframes for completing activities of particular urgency.

Several provisions in the Regulations could be applied immediately to improve information sharing and risk assessment, expedite communications, and harmonize measures being implemented by countries, particularly pertaining to international travel. The Regulations include a procedure for determining when an event

constitutes a public health emergency of international concern, at which point a set of procedures, with designated actions and short timeframes for completing them, becomes operational. Under the Regulations, human influenza caused by a new virus subtype is one of four notifiable diseases that may constitute a public health emergency of international concern.

The Regulations also provide for a dialogue among affected countries, the international community, and WHO, whereby countries agree to meet certain requirements and timeframes and, when unable to do so, can request specific technical support from WHO and collaboration and assistance, including the mobilization of financial support, from the international community. The strengthening of surveillance and response capacity to enable countries to respond to the pandemic threat would also strengthen capacity to defend the world against many other emerging and epidemic-prone diseases. In this regard, general requirements set out in Annex 1 of the Regulations, pertaining to core capacity requirements for surveillance and response, can be used as guidance for countries requesting or providing assistance in the present situation.

Expected results

1. Countries are able to detect, investigate, manage, and report cases.
2. WHO supports outbreak investigation and response with GOARN teams, when requested.
3. WHO supports field investigations with guidelines and training in their use.
4. A global laboratory system, complemented by regional and sub-regional networks, supports diagnostic confirmation of cases and analyses of viruses.
5. Voluntary compliance with relevant provisions of the International Health Regulations (2005) improves the exchange of information and the sharing of patient specimens.
6. Epidemiological information is routinely exchanged between the veterinary and public health sectors.
7. Using information from all these sources, WHO continuously assessed the pandemic threat and informs the world accordingly.

3. Intensify rapid containment operations

Goal

To ensure rapid detection and investigation of clusters of cases, closely related in time and place, and immediate international intervention aimed at preventing the emergence of a fully transmissible pandemic virus or delaying its international spread.

Strategic approach

- Quickly assess situations that potentially signal the start of efficient and sustained human-to-human transmission of the virus.
- Should assessment indicate that human-to-human transmission is occurring, Intervene immediately, using rapid-response field teams and global and regional stockpiles of antiviral drugs and other supplies.
- Develop an operational protocol, supported by standard operating procedures, to support this intervention.
- Develop a communications protocol to support this intervention, encourage compliance, and minimize the stress experienced by the affected population.

Rationale

Clusters of cases, closely related in time and place and involving chains of transmission that are sustained over time, are considered one key signal that transmission of the virus among humans has increased. Recent studies[3,4], based on mathematical modelling, suggest that rapid intervention, involving the mass prophylactic administration of antiviral drugs and several other measures, near the start of a pandemic might contain the pandemic or at least delay its international spread, provided several demanding conditions are met. Following a donation by industry, WHO will have a dedicated stockpile of antiviral drugs (oseltamivir) sufficient for 3 million treatment courses by June 2006. Drugs in the stockpile are strictly reserved for early intervention in the area where the first signs of increased human-to-human transmission emerge. According to results from mathematical models, antiviral prophylaxis would need to reach 80% of the initially affected population within around three weeks following symptom onset in the first people infected with an emerging pandemic virus. Other measures, including restrictions on the movement of people in and out of the affected area, would also need to be implemented quickly and effectively.

The success of this strategy, which has never been tested, depends on several assumptions: (a) the first viruses that show an ability to sustain transmission among humans will not yet be highly transmissible; (b) the emergence of such viruses will be geographically circumscribed; (c) the first clusters of human cases caused by the virus will be rapidly detected and reported; (d) antiviral medications will be rapidly mobilized from the stockpile, made available to the affected populations, and administered to sufficiently large numbers of people; and (e) movement of people in and out of the area will be effectively restricted. The first two assumptions depend on the behaviour of the virus and cannot be known prior to its emergence. The

[3] Ferguson NM et al. Strategies for containing an emerging influenza pandemic in Southeast Asia. Nature 2005; 437: 209–214.
[4] Longini IM et al. Containing pandemic influenza at the source. Sciencexpress/www.sciencexpress.org / 3 August 2005: 1–5.

remaining assumptions imply excellent surveillance and logistics capacity in the initially affected areas, combined with an ability to enforce movement restrictions and ensure population compliance with drug administration regimens.

While the success of this intervention in forestalling the start of a pandemic or delaying its spread cannot be guaranteed, the strategy nonetheless needs to be pursued as it represents one of the few preventive options for an event with potentially severe consequences for every country in the world. It is also the best guarantee that populations initially affected will have access to drugs for treatment. Moreover, the preparatory work for launching such an intervention can strengthen the interaction of WHO and the international community with priority countries in ways leading to better cooperation, better evidence on the ground, and better capacity within the country, also for responding to other emerging diseases. The prospect of immediate assistance in the treatment of cases and prevention of further spread can be a powerful incentive for priority countries to be more vigilant in their surveillance for cases and more transparent in their sharing of information and patient specimens.

Should early containment fail to prevent a pandemic virus from emerging, a delay in wide international spread would gain time to intensify preparedness. It can be expected that most governments will begin introducing certain emergency measures only when the occurrence of a pandemic becomes certain and immediate. A lead time for doing so of one month or more, as predicted by mathematical models, could allow many health systems to build surge capacity and make the necessary conversion from routine to emergency services.

During the November 2005 meeting, participants asked that a small group of experts be convened immediately to work out an operational protocol for rapid intervention, using the WHO stockpile, near the start of a pandemic. This proposal was accepted. Operational needs to be addressed in the protocol include (a) clear identification of goals, responsibilities and roles; (b) full participation of the Ministry of Health in the affected country; (c) clear definition of what constitutes efficient and sustained human-to-human transmission of the virus; (d) standard operating procedures for managing movement of the drugs within the affected area; (e) a plan for public communications explaining why the drugs are being administered, how they should be taken, and what to do if side effects occur; (f) standard operating procedures for surveys, possibly supported by laboratory testing, aimed at determining how the drugs are being used and whether the intervention is containing the outbreak; and (g) plans for additional measures, such as quarantine, enforcement of quarantine, and provision of food and other essential supplies to the quarantined area. An operational protocol for rapid containment is available at: http://www.who.int/csr/disease/avian_influenza/guidelines/draftprotocol/

Expected results

1. A global stockpile of antiviral drugs exits to support rapid intervention near the start of a pandemic.
2. An operational protocol, supported by standard operating procedures, exists to guide rapid deployment of the stockpile.
3. WHO identifies the data needed to trigger a rapid containment operation and countries are able to provide these data.
4. Strategies for rapid containment are a component of national preparedness plans.

4. Build capacity to cope with a pandemic

Goal

To ensure that all countries have formulated and tested pandemic preparedness plans and identified gaps in core capacities, and that WHO is fully able to perform its leadership role during a pandemic.

Strategic approach

- To provide generic guidance on the content and structure of a response plan.
- To assist individual countries, particularly those with limited resources, in the development of plans.
- To test plans in individual countries, regions, and internationally in order to identify gaps in core capacities.
- To enable WHO and its regional and country offices to carry out greatly expanded functions, around the clock, in leading and coordinating the global response to a pandemic.

Rationale

Vaccines and antiviral drugs are the two most important medical interventions for reducing morbidity and mortality during a pandemic, but will not be available in adequate supplies in any country at the start of a pandemic and for many months thereafter. Authorities in all countries will need to make the most of non-pharmaceutical measures to reduce morbidity, mortality, and social and economic disruption.

Based on past experience, pandemic influenza will not affect all countries or all parts of a country at the same time. If efforts to contain an emerging virus at its source fail, health authorities will have at least some opportunities to intervene to forestall spread internationally, within a country, and within an affected community. Once a pandemic has begun, political leaders will be under great pressure to protect their citizens. Countries with pandemic response plans, ideally tested in advance, will be in the best position to make decisions and take actions rapidly. In addition, countries should ensure that legislation is in place that allows authorities to introduce and enforce extraordinary measures.

While neither the timing nor the severity of the next pandemic can be predicted, history shows that these events consistently bring an abrupt surge in the number of illnesses and deaths. All governments need to be prepared to convert health services, including emergency and intensive care units and morgue capacity, to cope with a sudden and large increase in demand. Another consequence will be increased absenteeism in all sectors of the work force. All governments likewise need to have plans in place to ensure continuity of essential services and certain commercial undertakings, such as those responsible for the food supply. Core capacities that may be needed during a pandemic include an ability to rapidly increase the number of hospitals beds, to find additional staff, to procure and distribute essential medical supplies, and to maintain the continuity of essential services.

The effectiveness of several non-pharmaceutical interventions (school closure, quarantines, restrictions on travel, personal measures) will depend on the characteristics of the pandemic virus (virulence, attack rate, groups at highest risk, patterns of transmission), which cannot be known in advance and will need to be evaluated as the pandemic evolves. WHO has plans in place to undertake this activity in real time, supported by virtual networks of international experts in epidemiology, virology, clinical medicine, and outbreak modelling. For example, should schools play a role in disseminating the disease into the broader community, as has happened in past pandemics, the temporary closing of schools could be recommended as a means of slowing spread. Any measure that flattens the peak incidence of cases will relieve some of the burden on health services and reduce some of the social and economic disruption that can be expected to accompany high rates of worker absenteeism.

Expected results

1. WHO provides technical guidance on the health component of pandemic preparedness plans.
2. Countries test their preparedness plans; gaps in health system capacity are identified and options for reducing these gaps are pursued.
3. WHO has the capacity to conduct real-time surveillance, risk assessment, risk communication, and information management during a pandemic.

5. Coordinate global scientific research and development

Goal

To ensure that pandemic vaccines and antiviral drugs are rapidly and widely available after the start of a pandemic and that scientific understanding of the virus evolves quickly.

Strategic approach

- Identify priority research areas and encourage public- and private-sector funding.
- Obtain more data on the use of both classes of antiviral drugs and on virus susceptibility to these drugs, and (for oseltamivir) on optimum doses and duration of administration for both treatment and prophylaxis in children and adults.
- Establish partnerships with governments, regulatory authorities, academic institutes, and industry to find ways, facilitated by WHO, to increase vaccine manufacturing capacity quickly and in ways that ensure equitable access.
- Assist developing countries embarking on the development, regulatory approval, and production of pandemic vaccines.
- Accelerate research and development for new vaccines conferring long-lasting protection against multiple influenza virus strains.
- Use institutions within the WHO Global Outbreak Alert and Response Network and laboratories within the WHO influenza surveillance network to ensure that scientific knowledge about an evolving pandemic is generated and communicated in real time.

Rationale

Vaccines are potentially the most effective intervention for reducing morbidity and mortality during a pandemic. If available early enough and in sufficient quantities, they can provide population-wide protection against infection. Antiviral drugs can also offer protection against infection; at present, they are the only interventions available for direct treatment of infection. Antiviral drugs have an especially critical supporting role to play at the start of a pandemic, when no country will have a pandemic vaccine and frontline workers and others will need protection in order to ensure the continuity of essential services. The administration of antiviral drugs, for prophylactic purposes, to large numbers of people throughout the duration of potential exposure to a pandemic virus is unrealistic for two main reasons: the quantity of drugs required would be prohibitively large and costly, and the risk of rapid development of drug resistance would be greatly increased.

Antiviral drugs. As noted during the November 2005 meeting, only a small number of antiviral drugs are presently available and supplies, while growing, remain limited. Experience with other diseases has demonstrated the dangers of relying on a few drugs for a disease that affects large numbers of people. Access in developing countries to affordable drugs in sufficient quantities remains a major concern. For oseltamivir, the manufacturing technology is not easily transferred to other production facilities, but strategies for doing so are being explored as a matter of

urgency; particular attention is being given to the option of manufacturing oseltamivir in developing countries.

Pandemic vaccines. At present 90% of the global manufacturing capacity for all influenza vaccines is concentrated in Europe and North America in countries that account for only 10% of the world's population. The present maximum manufacturing capacity – at around 420 million doses of trivalent vaccine per year – falls far below the expected demand during a pandemic. Moreover, the manufacturing process is relatively fragile and technical problems, such as batch failure or difficulties in complying with established Good Manufacturing Practices, can significantly disrupt supply.

The objective is to provide as many people as possible with immunological protection before they are exposed to a pandemic virus. The challenge is threefold: to produce an adequate supply of vaccines of assured quality to meet global needs shortly after the start of a pandemic, to provide for equitable access, and to ensure sufficient capacity to deliver the vaccines to all communities. To meet these challenges, research is needed to accelerate the development of new vaccines and promote the discovery of new technologies that could radically increase vaccine supplies, facilitate vaccine delivery, or induce broad-spectrum protection against both seasonal and pandemic influenza.

Finite capacity to produce antigen (the component of the vaccine that elicits the immune response) for the current inactivated vaccines is a critical limiting factor. Strategies for producing vaccines that are effective, yet use less antigen, can profoundly increase manufacturing capacity. Adjuvants added to vaccine formulation to boost the immune response are one such strategy in an advanced stage of development. In addition, current manufacturing involves growth of influenza virus in fertilized chicken eggs, which prohibits a rapid scaling up of production should a pandemic occur. New production systems relying on cell culture rather than on eggs, or on recombinant technologies, are urgently needed. Although some of these technologies are being developed by industry, support from the public sector could accelerate their application.

The time between assessment of a candidate vaccine and its marketing authorization can be shortened through the coordination of research to develop standard assessment protocols and the sharing of preclinical and clinical data. WHO is coordinating this work. Workshops on regulatory preparedness were convened by WHO, in collaboration with major regulatory agencies, during the first half of 2006. The outcome of the workshops is expected to streamline the work needed to license new vaccines and introduce greater consistency in the various regulatory requirements in the interest of expediting vaccine exportation to non-manufacturing countries. An additional meeting, held in May 2006, was convened to develop a global action plan for increasing access to a pandemic vaccine.

During the November 2005 meeting, participants asked that better use be made of vaccine manufacturing capacity in developing countries. In particular, support is urgently needed for several developing countries that have embarked on the development of a pandemic vaccine or are establishing facilities for vaccine manufacturing. WHO has undertaken the evaluation of options, including opportunities to transfer manufacturing technology, assessment of the feasibility of converting existing manufacturing facilities for other vaccines to produce a pandemic vaccine, and the development of pilot projects. In exploring these options,

the objective is to increase vaccine production capacity in an efficient and economically meaningful way, thus expanding access to both seasonal and pandemic vaccines.

Another option currently being explored involves the development of new influenza vaccines that confer broad protection against several strains of influenza virus, including virus strains responsible for seasonal epidemics as well as candidate pandemic viruses. Such vaccines would confer broad and long-lasting immunity, thus obviating the need for annual revaccination and the related expense, while also providing the first opportunity to protect populations before a pandemic begins. While conceptually appealing as a rational public health approach, this strategy remains largely at the exploratory stage.

Increased use of vaccines for seasonal influenza, in line with WHO targets for population coverage, is the most certain and sustainable way to increase manufacturing capacity for a pandemic vaccine, as the same facilities are used for both. The resulting expansion in manufacturing capacity is, however, gradual, and it is by no means certain that the H5N1 virus will allow this luxury of time. Industry estimates that a significant increase in vaccine manufacturing capacity would take around 4 to 5 years to achieve.

Research during a pandemic. At the start of a pandemic, policy-makers will face an immediate need for epidemiological data on the principal age groups affected, modes of transmission, and pathogenicity. Modelling studies will be needed to project the patterns and dynamics of international spread. Rapid gathering of clinical data will be needed to establish management protocols, especially if the virus causes unusually severe illness. Studies of the virus will be useful in tracking possible changes in its virulence and predicting the severity of illness during the second or possibly a third wave of international spread. Pharmacovigilance studies will also be needed to evaluate any novel medical interventions introduced in response to a pandemic. WHO will establish virtual networks of experts to gather these data in real time and use them when issuing advice to the international community.

Expected results

1. WHO establishes a global agenda for public health research in the areas of risk reduction, diagnostics, clinical management, and prophylaxis, and coordinates related research.
2. WHO coordinates a global action plan to expedite the availability of pandemic vaccines and address the issue of equitable access.
3. WHO provides technical guidance on the use of antiviral drugs and non-pharmaceutical measures during a pandemic.
4. WHO has networks in place to monitor adverse events associated with the use of pharmaceutical measures during a pandemic.