

Responding to the avian influenza pandemic threat

Recommended strategic actions

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Purpose

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. 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*.² 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.

Opportunities to intervene

As the present situation continues to evolve towards a pandemic, countries, the international community, and WHO have several phase-wise opportunities to intervene, moving from a pre-pandemic situation, through emergence of a pandemic virus, to declaration of a pandemic and its subsequent spread. During the present pre-pandemic phase, interventions aim to reduce the risk that a pandemic virus will emerge and gather better disease intelligence, particularly concerning changes in the behaviour of the virus that signal improved transmissibility. The second opportunity to intervene occurs coincident with the first signal that the virus has improved its transmissibility, and aims to change the early history of the pandemic. The final opportunity occurs after a pandemic has begun. Interventions at this point aim to reduce morbidity, mortality, and social disruption.

Objectives

The objectives of the strategic actions correspond to the principal opportunities to intervene and are likewise phase-wise.

Phase: pre-pandemic

- 1. Reduce opportunities for human infection**
 - 2. Strengthen the early warning system**
-

Phase: emergence of a pandemic virus

- 3. Contain or delay spread at the source**
-

Phase: pandemic declared and spreading internationally

- 4. Reduce morbidity, mortality, and social disruption**
- 5. Conduct research to guide response measures**

¹ http://whqlibdoc.who.int/hq/2005/WHO_CDS_CSR_GIP_2005.5.pdf.

² http://whqlibdoc.who.int/hq/2005/WHO_CDS_CSR_GIP_2005.4.pdf.

Strategic actions

The document describes strategic actions that can be undertaken to capitalize on each opportunity to intervene. Given the many uncertainties about the evolution of the pandemic threat, including the amount of time left to prepare, a wise approach involves a mix of measures that immediately address critical problems with longer-term measures that sustainably improve the world's capacity to protect itself against the recurring pandemic threat.

Background

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. 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. 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.

Situation assessment

1. 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.

2. 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.

3. 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.

4. 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.

5. 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.

6. 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.

1. Reduce opportunities for human infection

The risk that a pandemic virus will emerge depends on opportunities for human exposure and infections. These opportunities will persist as long as the H5N1 virus continues to circulate in animals. Control of the disease in animals is the principal way to reduce opportunities for human infection and thus reduce opportunities for a pandemic virus to emerge. Prevention of behaviours that expose humans to the virus is a second way.

Hopes that the virus could be rapidly eliminated from poultry have not been realized, and the situation has grown increasingly worrisome. The virus, in its highly pathogenic form, is now endemic in many parts of Indonesia and Viet Nam and in some parts of Cambodia, China, Thailand, and possibly also the Lao People's Democratic Republic. Factors responsible for persistence of the virus are not fully understood. The dynamics of H5N1 behaviour in animals are likewise poorly understood and unpredictable. Domestic ducks are now known to be able to excrete large quantities of highly pathogenic virus without showing clinical signs. Mammalian species not thought to be susceptible to infection have recently developed disease. Complete eradication of H5N1 in Asia is probably precluded by its presence in wild bird populations; control of infection in wild birds is not a feasible option.

Despite these difficulties, control of the disease in poultry remains a feasible objective and a high priority. Food and Agriculture Organization (FAO) and the World Organisation for Animal Health (OIE) have issued detailed technical recommendations³ and a draft global strategy⁴ for control in affected Asian nations. Some of the recommended measures call for significant changes in traditional farming systems and most will take some time to implement. The worrisome situation in poultry has increased the probability that a pandemic virus will emerge, and this could happen in a much shorter time-frame than that needed for control.

As the vast majority of human cases have occurred in rural areas, advice to farmers and their families on how to avoid exposure is a second way to reduce the risk that a pandemic virus will emerge. This option has likewise become more difficult. The fact that domestic ducks can act as a “silent” reservoir has removed the warning signal of a risk, especially for rural farmers and their families, and increased opportunities for unwitting human exposure. Outbreaks in poultry may be “silent” for a second reason. Persistence of the virus in poultry has severely strained economies in affected nations. An inability adequately to compensate farmers for lost birds reduces the incentive to report outbreaks, particularly in rural areas where the true risk of human exposure resides.

³ <http://www.fao.org/ag/againfo/subjects/en/health/diseases-cards/27septrecomm.pdf>.

⁴ http://www.fao.org/ag/againfo/resources/documents/empres/AI_globalstrategy.pdf.

Strategic actions

– **Support the FAO/OIE control strategy**

The FAO/OIE technical recommendations describe specific control measures and explain how they should be implemented. The global strategy, developed in collaboration with WHO, takes its urgency from the risk to human health, including that arising from a pandemic, posed by the continuing circulation of the virus in animals. The strategy adopts a progressive approach, with different control options presented in line with different disease profiles, including such factors as poultry densities, farming systems, and whether infections have occurred in commercial farms or small rural holdings. The proposed initial focus is on Viet Nam, Thailand, Cambodia, and Indonesia, the four countries where human cases of infection with H5N1 avian influenza have been detected.

Clear and workable measures are proposed for different countries and situations within countries. Vaccination is being recommended as an appropriate control measure in some, but not all, epidemiological situations. Other measures set out in the strategy include strict biosecurity at commercial farms, use of compartmentalization and zoning concepts, control of animal and product movements, and a restructuring of the poultry industry in some countries. The strategy notes strong political will to tackle the problem. Nonetheless, time-frames for reaching control objectives are now being measured in years.

In July 2005, OIE member countries approved new standards, recognized by the World Trade Organization, specific to avian influenza and aimed at improving the safety of international trade of poultry and poultry products. The new standards cover methods of surveillance, compulsory international notification of low- and highly-pathogenic strains of avian influenza, the use of vaccination, and food safety of poultry products. Compliance with these standards should be given priority in efforts to strengthen early detection, reporting, and response in countries currently affected by outbreaks of H5N1 avian influenza.

– **Intensify collaboration between the animal and public health sectors**

WHO will appoint dedicated staff to increase the present exchange of information between agricultural and health sectors at the international level. Increased collaboration between the two sectors serves three main purposes: to pinpoint areas of disease activity in animals where vigilance for human cases should be intensified, to ensure that measures for controlling the disease in animals are compatible with reduced opportunities for human exposure, and to ensure that advice to rural communities on protective measures remains in line with the evolving nature of the disease in animals.

WHO will undertake joint action with FAO and OIE to understand the evolution of H5N1 viruses in Asia. Achieving this objective requires acquisition and sharing of a full inventory of H5N1 viruses, from humans, poultry, wild birds, and other animals, and sequences.

WHO will stress the importance of controlling the disease in rural areas. Measures to control the disease in animals of necessity consider how best to regain agricultural productivity and international trade, and this objective is reflected in the FAO/OIE strategy. While elimination of the virus from the commercial poultry sector alone will aid agricultural recovery, it may not significantly reduce opportunities for human exposure, as the vast majority of cases to date have been

associated with exposure to small rural flocks. No case has yet been detected among workers in the commercial poultry sector. The FAO/OIE strategy fully recognizes that control of disease in rural “backyard” flocks will be the most difficult challenge; strong support from the health sector, as expressed by WHO, helps gather the political will to meet this challenge. In addition, it is imperative that measures for controlling disease in rural flocks are accompanied by risk communication to farmers and their families.

A joint FAO/OIE/WHO meeting, held in Malaysia in July 2005,⁵ addressed the links between animal disease and risks of human exposures and infections, and defined preventive measures that should be jointly introduced by the animal and public health sectors. Priority was given to interventions in the backyard rural farming system and in so-called wet markets where live poultry are sold under crowded and often unsanitary conditions.

WHO, FAO, and OIE have jointly established a Global Early Warning and Response System (GLEWS) for transboundary animal diseases. The new mechanism combines the existing outbreak alert, verification, and response capacities of the three agencies and helps ensure that disease tracking at WHO benefits from the latest information on relevant animal diseases. The system formalizes the sharing of epidemiological information and provides the operational framework for joint field missions to affected areas.

– **Strengthen risk communication to rural residents**

WHO will, through its research networks and in collaboration with FAO and OIE, improve understanding of the links between animal disease, human behaviours, and the risk of acquiring H5N1 infection. This information will be used as the basis for risk communication to rural residents.

Well-known and avoidable behaviours with a high risk of infection continue to occur in rural areas. Ongoing risk communication is needed to alert rural residents to these risks and explain how to avoid them. Better knowledge about the relationship between animal and human disease, obtained by WHO in collaboration with FAO/OIE, can be used to make present risk communication more precise and thus better able to prevent risky behaviours.

– **Improve approaches to environmental detection of the virus**

WHO, FAO, and OIE will facilitate, through their research networks, the rapid development of new methods for detecting the virus in environmental samples. The purpose of these methods is to gain a better understanding of conditions that increase the risk of human infection and therefore favour emergence of a pandemic virus. Such knowledge underpins the success of primary prevention of a pandemic through disease control in animals. It also underpins advice to rural residents on behaviours to avoid. Reliance on routine veterinary surveillance, which is weak in most risk-prone countries, has not produced an adequate understanding of the relationship between animal and human disease. For example, in some cases, outbreaks in poultry are detected only after a human case has been confirmed. In other cases, investigation of human cases has failed to find a link with disease in animals.

⁵ <http://www.fao.org/ag/againfo/subjects/documents/ai/concmalaysia.pdf>.

2. 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.

Strategic actions

– 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.

Because of its high pathogenicity, H5N1 can be handled safely only by specially trained staff working in specially equipped laboratories operating at a high level of biosecurity. These facilities do not presently exist in the majority of affected countries. As an alternative, laboratory capacity can be enhanced by strengthening the existing system of national influenza centres or by providing mobile high-containment laboratories. Supportive activities include training in laboratory methods needed for H5N1 diagnosis, distribution of up-to-date diagnostic reagents, and coordination of work between national laboratories and epidemiological institutions.

An infrastructure needs to be developed to complement national testing with rapid international verification in WHO certified laboratories, especially as each confirmed human case yields information essential to risk assessment. The capacity to do so already exists. WHO offers countries rapid administrative support to ship samples outside affected countries. Such forms of assistance become especially critical when clusters of cases occur and require investigation.

– **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.

– **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.

– **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.

Identification of risk groups guides preventive measures and early interventions. Provision of high-quality data on clinical course, outcome, and treatment efficacy meets an obvious and immediate need in countries with human cases. Answers to

some key questions – the efficacy of antiviral drugs, optimum dose, and prescribing schedules – could benefit health services elsewhere once a pandemic is under way.

– **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.

– **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.

– **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.

3. Contain or delay spread at the source

Several international consultations on pandemic influenza have asked WHO to explore establishment of an international stockpile of antiviral drugs for strategic use near the start of a pandemic. Experts have suggested that aggressive measures, centred on the prophylactic use of antiviral drugs, might contain a pandemic at its source or at least slow its spread, thus gaining time to put emergency measures in place and augment vaccine supplies. Based on results from mathematical modelling, the theoretical window of opportunity for taking such action closes quickly. According to these studies, 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. The studies provide some guidance on the quantities of antiviral drugs needed for the strategy to work. They also point out the necessity of combining mass administration of drugs with other measures, including area quarantine.

While the proposal is attractive, the success of such an intervention depends on several assumptions: (1) the first viruses that show an ability to sustain transmission among humans will not yet be highly transmissible; (2) the emergence of such viruses will be geographically circumscribed; (3) the first clusters of human cases caused by the virus will be rapidly detected and reported, and the viruses will be rapidly identified and characterized; (4) antiviral drugs will be rapidly mobilized from the stockpile, made available to the affected population, and administered to sufficiently large numbers of people; and (5) movement of people in and out of the area will be effectively restricted. Given the unpredictable behaviour of influenza viruses, it is impossible to know in advance if the first two assumptions will be borne out in reality when a pandemic virus emerges. The remaining assumptions imply excellent surveillance and logistics capacity in the initially affected areas, combined with an ability to enforce movement restrictions.

As no effort has ever been made to alter the natural course of a pandemic by intervening at its source, the success of this strategy in halting a pandemic or delaying its spread cannot be assured. However, drugs in the stockpile can also be used for treatment purposes. Having an international stockpile available at the start of a pandemic would thus help ensure that people initially affected and initially in greatest need would benefit from treatment with antiviral drugs.

Strategic actions

– **Establish an international stockpile of antiviral drugs**

WHO will establish an international stockpile of antiviral drugs for rapid response at the start of a pandemic. The stockpile is a strategic option that serves the interests of the international community as well as those of the initially affected populations. Issues that need to be addressed include logistics associated with deployment and administration, and licensing for use in individual countries. Mechanisms for using an international stockpile need to be defined more precisely in terms of epidemiological triggers for deploying the stockpile and time-frames for emergency delivery and administration. WHO is working closely with groups engaged in mathematical modelling and others to guide the development of early containment strategies.

While pursuit of this option thus has no guarantee of success, it nonetheless needs to be undertaken as it represents one of the few preventive options for an event with predictably 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. Should early containment fail to completely halt spread of the virus, a delay in wide international spread would gain time to intensify preparedness. It can be expected that most governments will begin introducing emergency measures only when the threat of a pandemic is certain and immediate. A lead time for doing so of one month or more could allow many health services to build surge capacity and make the necessary conversion from routine to emergency services.

– **Develop mass delivery mechanisms for antiviral drugs**

Several WHO programmes, such as those for the emergency response to outbreaks of poliomyelitis, measles, epidemic-prone meningitis, and yellow fever, have acquired considerable experience in the urgent mass delivery of vaccines in developing countries. Less experience exists for the mass delivery of antiviral drugs, where administration is complicated by the need for drugs to be taken over several days and the need for different dosing schedules according to therapeutic or prophylactic use. WHO will develop and pilot test delivery mechanisms for antiviral drugs in collaboration with national health authorities and industry. Studies will assess coverage rates that could be achieved, taking into account compliance rates, and ways to support this intervention with other measures, such as area quarantine.

– **Conduct surveillance of antiviral susceptibility**

Using its existing network of influenza laboratories, WHO will establish a surveillance programme for antiviral susceptibility testing, modelled on a similar programme for anti-tuberculosis drugs. Use of an international stockpile to attempt to halt an outbreak will involve administration of drugs to large numbers of people for several weeks. A mechanism must be in place to monitor any resulting changes in virus susceptibility to these drugs. The development of drug resistance would threaten the effectiveness of national stockpiles of antiviral drugs established for domestic use. The work of WHO collaborating centres for influenza and reference laboratories for H5N1 analysis can be coordinated to include antiviral susceptibility testing.

4. Reduce morbidity, mortality and social disruption

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. Vaccines are universally considered the first line of defence. Because their supply will be inadequate in every country at the start of a pandemic, antiviral drugs assume a critical early role. Authorities in all countries will need to make the most of non-pharmaceutical measures to reduce morbidity, mortality, and social disruption. The problems of inadequate supplies of vaccine and inequitable access to them need to be addressed with particular urgency.

While neither the timing nor the severity of the next pandemic can be predicted, history shows that these events consistently bring an explosive surge in the number of illnesses and deaths sufficient to temporarily paralyse public services and economic productivity. 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 labour force, with capacity temporarily reduced in such essential public services as health care, law enforcement, transportation, utilities, and telecommunications.

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 the source fail, health authorities will have at least some opportunities to intervene to forestall spread internationally, within a country, and within an affected community. Actions aimed at delaying spread must, however, take place rapidly. The three pandemics of the previous century encircled the globe in 6 to 9 months. Since the last one occurred in 1968, the volume of international air travel has increased exponentially. The better hygiene, nutritional status, and drugs for treating the secondary complications of influenza, seen today in many parts of the world, can be expected to mitigate some of the health consequences of a pandemic, but need to be weighed against the likelihood that international spread will be more rapid.

Once a pandemic has begun, political leaders will be under great pressure to protect their citizens. Countries with pandemic response plans, ideally rehearsed in advance, will be in the best position to make decisions and take actions rapidly, as described in Annex 1. In addition, countries should ensure that legislation is in place that allows authorities to introduce and enforce extraordinary measures.

Strategic actions

– Monitor the evolving pandemic in real time

Many characteristics of a pandemic that will guide the selection of response measures will become apparent only after the new virus has emerged and begun to cause large numbers of cases. WHO, assisted by virtual networks of experts, will monitor the unfolding epidemiological and clinical behaviour of the new virus in real time. This monitoring will give health authorities answers to key questions about age groups at greatest risk, infectivity of the virus, severity of the disease, attack rates, risk to health care workers, and mortality rates. Such monitoring can

also help determine whether severe illness and deaths are caused by primary viral pneumonia or secondary bacterial pneumonia, which responds to antibiotics, and thus guide the emergency provision of supplies. Experts in mathematical modelling will be included in the earliest field assessment teams to make the forecasting of trends as reliable as possible.

– **Introduce non-pharmaceutical interventions**

Answers to these questions will help officials select measures – closing of schools, quarantine, a ban on mass gatherings, travel restrictions – that match the behaviour of the virus and thus have the greatest chance of reducing the number of cases and delaying geographical spread. WHO has produced guidance on the use of such measures at different stages at the start of a pandemic and after its international spread.

– **Use antiviral drugs to protect priority groups**

WHO recommends that countries with sufficient resources invest in a stockpile of antiviral drugs for domestic use, particularly at the start of a pandemic when mass vaccination is not an option and priority groups, such as frontline workers, need to be protected.

– **Augment vaccine supplies**

WHO, in collaboration with industry and regulatory authorities, has introduced fast-track procedures for the development and licensing of a pandemic vaccine. Strategies have also been developed that make the most of scarce vaccine antigen and thus allow more quantities of vaccine to be produced despite the limits of existing plant capacity. The status of activities to expedite vaccine development and augment supplies is described in Annex 2. Once a pandemic is declared, all manufacturers will switch from production of seasonal vaccines to production of a pandemic vaccine. Countries need to address liability issues that could arise following mass administration of a pandemic vaccine and ensure adequate warehousing, logistics, and complementary supplies, such as syringes.

– **Ensure equitable access to vaccines**

The present strong interdependence of commerce and trade means that the international community cannot afford to allow large parts of the world to experience a pandemic unprotected by a vaccine. The humanitarian and ethical arguments for providing such protection are readily apparent. As a matter of urgency, WHO must build a political process aimed at finding ways to further augment production capacity dramatically and make vaccines affordable and accessible in the developing world. WHO will also work with donor agencies on the latter issue.

– **Communicate risks to the public**

As soon as a pandemic is declared, health authorities will need to start a continuous process of risk communication to the public. Many difficult issues – the inevitable spread to all countries, the shortage of vaccines and antiviral drugs, justification for the selection of priority groups for protection – will need to be addressed. Effective risk communication, supported by confidence in government authorities and the reliability of their information, may help mitigate some of the social and economic disruption attributed to an anxious public. Countries are advised to plan in advance. A communication strategy for a pandemic situation should include training in outbreak communication and integration of communicators in senior management teams.

5. Conduct research to guide response measures

- **Assess the epidemiological characteristics of an emerging 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. Such data will support urgent decisions about target groups for vaccination and receipt of antiviral drugs. They can also be used to support forecasts on local and global patterns of spread as an early warning that helps national authorities intensify preparedness measures. WHO will identify epidemiological centres for collecting these data and establish standardized research protocols.

- **Monitor the effectiveness of health interventions**

Several non-pharmaceutical interventions have been recommended to reduce local and international spread of a pandemic and lower the rate of transmission. While many of these interventions have proved useful in the prevention and control of other infectious diseases, their effectiveness during a pandemic has never been comprehensively evaluated. More information is needed on their feasibility, effectiveness, and acceptability to populations. WHO will establish study sites and develop study protocols to evaluate these interventions at local, national, and international levels. Comparative data on the effectiveness of different interventions are also important, as several measures are associated with very high levels of social disruption.

- **Evaluate the medical and economic consequences**

WHO will establish study sites and develop protocols for prospective evaluation of the medical and economic consequences of the pandemic so that future health interventions can be adjusted accordingly. In the past, such evaluations have been conducted only after a pandemic had ended. Their value as a policy guide for the allocation of resources has been flawed because of inadequate data.

Annex 1: Strategies for improving national preparedness

– Assist developing countries planning to manufacture their own vaccines

Support is urgently needed for some risk-prone countries which are developing influenza vaccines or establishing influenza vaccine manufacturing capacities. WHO will coordinate the provision of international expert advice, as already requested, to support such national efforts. A WHO working group will be established to provide direct ad hoc advice to governments in line with national needs, priorities, and capacities. Tasks of the working group will include evaluation of opportunities to transfer manufacturing technology to developing countries and the development of pilot projects. The objective is to increase vaccine production capacity in an efficient and economically meaningful way, thus expanding access to both seasonal vaccines (in line with national priorities for the control of infectious diseases) and pandemic vaccines.

– Support national pandemic preparedness planning

Tools are needed for global assessment of national preparedness status. Countries continue to request WHO support in assessing their preparedness plans, but there is no regional or global tool for evaluating the actual status of preparedness in individual countries and pinpointing weaknesses that need to be addressed. Such a tool can be used to coordinate bilateral and multilateral support for improved preparedness in developing countries. The preparation by WHO of template pandemic plans will give many developing countries a head start. Some initial regional training courses and meetings have been used to evaluate national preparedness status, and this opportunity needs to be extended.

– Develop model pandemic response exercises

Several countries have already conducted table-top exercises to rehearse their pandemic response plans. These exercises have been regarded as eye-openers, resulting in recognition of precise critical weaknesses in day-to-day operations and the formulation of precise recommendations for their correction. Valuable as they are, such exercises are costly. WHO recommends establishment of a group of experts with experience in these exercises to develop model table-top exercises that can be shared among countries. Such a mechanism will also ensure that lessons learned during one country's exercise could benefit others.

Annex 2: Strategies for expediting the development of a pandemic vaccine

1. Shorten the time between emergence of a pandemic virus and the start of commercial production

– **Develop global standards to ensure the quality, safety and efficacy of influenza vaccines**

WHO standards give national regulatory authorities and manufacturers international norms for ensuring the quality, safety and efficacy of vaccines, thus bringing uniformity to international vaccine supplies. In particular, the requirements for a vaccine effective against H5N1 introduce a need for international norms governing biosafety requirements for vaccine production. To support the release of vaccine lots worldwide, international reference reagents, supplied through WHO, are needed to calibrate regional, national and manufacturing standards. Global standards are also needed to cover the proposed use of novel cell lines to streamline vaccine production.

– **Resolve outstanding laboratory and safety issues**

WHO has identified a number of technical and regulatory issues that require resolution. These include specifications for accelerated safety testing of candidate vaccines, laboratory methods for testing adjuvanted vaccines, and standardized markers of protection for clinical evaluations. WHO should bring together regulators, vaccine developers and manufacturers to develop consensus on these issues.

– **Harmonize regulatory pathways for licensure of pandemic influenza vaccines**

Greater international consistency in licensing requirements for a pandemic vaccine, including the studies required for marketing authorization, would facilitate international access to vaccines by expediting their availability in non-manufacturing countries. WHO can facilitate discussions among regulatory authorities to develop harmonized procedures for vaccine registration.

– **Address safety issues associated with vaccine use**

The short production cycle for influenza vaccines inevitably limits safety studies prior to licensing, creating a need for safety monitoring during vaccine use. The detection of safety problems will necessitate rapid research, which can be coordinated by WHO across countries, using population-based databases.

– **Support production strategies that economize on the use of antigen**

Finite capacity to produce the antigen content of vaccines is a critical limiting factor. Strategies for producing vaccines that are effective, yet use less antigen can profoundly increase manufacturing capacity. Clinical trials are needed to establish optimal antigen content; coordination of research is required to develop complementary protocols and facilitate rapid sharing of preclinical and clinical data.

2. Increase the supply of influenza vaccines

- **Find ways to bridge the gap between current vaccine production capacity and the expected demand during a pandemic**

Ways must be found to ensure that countries without domestic manufacturing capacity will have access to affordable vaccines in adequate quantities. Several approaches are being pursued, including antigen sparing strategies, technology transfer, and cell-culture and recombinant vaccine development. Increasing the demand for seasonal vaccines expands overall manufacturing capacity. The comparative effectiveness and implementation costs for the various approaches have not been reviewed. An action plan, with specific recommendations for countries with and without vaccine production capacity, is urgently required.

- **Involve vaccine manufacturers from all countries**

Some countries, including the Republic of Korea and the Russian Federation, have manufacturing capacity but have not yet participated in WHO-coordinated activities.

- **Support efforts in developing countries, including through the use of technology transfer, for vaccine development and production**

Such support is urgently needed for high-risk countries, including Thailand and Viet Nam, which are developing influenza vaccines or establishing influenza vaccine manufacturing capacities. Specific activities are outlined in Annex 1.

- **Enhance utilization of seasonal influenza vaccines in high risk groups, in line with WHO targets (50% coverage in 2006 and 75% in 2010)**

Achievement of this goal requires global leadership in assessing and communicating progress in influenza coverage in countries having national policies for influenza vaccination and, elsewhere, in vulnerable groups. Other activities include the development of recommendations to augment vaccine coverage in target groups, support for the implementation of national vaccination programmes, and the acquisition of better epidemiological and economic data on the burden of seasonal influenza in developing countries.