4 Action in the face of an uncertain threat

Countries with H5N1 poultry outbreaks, 2004

Cambodia
China
Indonesia
Japan[a]
Lao People's Democratic Republic
Malaysia[a]
Republic of Korea[a]
Thailand
Viet Nam

[a] Countries considered free of the disease (January 2005) according to OIE criteria.

When the events involving H5N1 infections during 2004 are reviewed, influenza experts can reach only a small number of firm conclusions. The H5N1 virus has demonstrated considerable pandemic potential. The world has moved closer to a pandemic than at any time since 1968. The ecology of the virus has changed in ways that increase opportunities for a pandemic virus to emerge. Based on the recurring pattern of past pandemics, the next one is overdue. Here the certainty ends. The questions of whether H5N1 will improve its transmissibility, and when this might happen, cannot be answered. Influenza viruses have survived for thousands of years because of their inherent ability to change and elude. These properties also defy predictions about the next surprises a highly labile and mutable virus may bring.

Epidemiologists can point to at least three conditions, not anticipated at the start of 2004, that have subsequently become apparent. First, the virus is now firmly entrenched in the poultry populations of parts of Asia. Although most affected countries launched massive campaigns to eliminate the disease in poultry, only a few have been entirely successful. Even in these few instances, the risk that the disease may be reintroduced remains ever-present.

Second, no high-risk group, defined by occupation, exists for the targeting of protective measures. Surprisingly, no cases of H5N1 infection have occurred in poultry workers, cullers, veterinarians, or laboratory workers. Nor have cases been detected in health care workers, despite several instances of close unprotected contact with severely ill patients. Instead, the most vulnerable population has turned out to be rural subsistence farmers and their families, and these people constitute the true risk group.

Rural residents in large areas depend on poultry for livelihood and food.

Third, the health threat for this group has been compounded by the increasing tendency of human cases to occur in the absence of reported outbreaks in poultry. Without the warning signalled by the presence of dead or visibly ill poultry, rural residents – who depend on poultry for livelihood and food – will not be aware of the need to take special precautions when handling, slaughtering, and preparing birds for consumption. Clinicians, too, may be less alert to the possibility of an H5N1 diagnosis when no obvious history of exposure to the virus is apparent.

Regardless of whether H5N1 achieves even greater pandemic potential, the risk of further sporadic cases and occasional family clusters can be expected to continue in rural areas where the virus is now endemic. Any newly emerging virus that disproportionately affects the young and healthy and causes extremely severe disease with very high fatality must remain of great public health concern. Continued vigilance for further cases is essential, as are efforts to adapt preventive advice to the present situation and find effective treatments. At the same time, however, the consequences of a pandemic are potentially so devastating that monitoring of this risk – at levels ranging from field epidemiology to the molecular characteristics of the virus – must likewise remain a priority.

Forecasts and dilemmas

Regardless of the pandemic threat, any newly emerging virus that causes highly fatal disease in the young and healthy must be viewed with great concern.

Although the timing of the next pandemic cannot be predicted, several efforts have been made to estimate its consequences, most conspicuously measured in the projected number of excess deaths. Knowing what to expect is useful for preparedness planning, but the actual consequences of the next pandemic will be greatly influenced by the properties of the virus, which cannot be known in advance.

The mortality of the previous century's three pandemics varied enormously, from less than 1 million to more than 40 million deaths. Best-case scenarios, modelled on the mild pandemic of 1968, project global excess deaths in the range 2 million to 7.4 million. Other estimates that factor in a more virulent virus,

GPHIN: artificial intelligence for disease detection

In 1996, WHO began building up an operational system, supported by a "virtual" architecture, for improving world capacity to recognize and respond to new and re-emerging diseases. The major Ebola outbreak of 1995, which caught the international community unprepared, made earlier detection of outbreaks of utmost importance.

To expedite the gathering of epidemic intelligence, WHO introduced the Global Public Health Intelligence Network (GPHIN) in 1997. This powerful new tool, developed and maintained for WHO by Health Canada, is a customized search engine that continuously scans world Internet communications for rumours and reports of suspicious disease events.

Operating as a sensitive real-time early warning system, GPHIN has brought great gains in time over traditional systems in which an alert is sounded only after case reports at the local level progressively filter to the national level and are then notified to WHO. GPHIN also helped compensate for the reluctance, motivated by economic concerns, of many national authorities to disclose outbreaks promptly and frankly.

similar to that responsible for the deadly 1918 pandemic, estimate much higher numbers of deaths. Both scenarios are scientifically valid. The differences arise from assumptions about the inherent lethality of the virus, which past experience has shown to vary greatly. In the final analysis, it is impossible to predict with any accuracy the impact that the next pandemic will have.

Compared with the situation during past pandemics, the world is now more populous, and the proportion of the vulnerable elderly is larger. Overall nutritional status is better, and medical treatments, especially for the management of severe complications associated with bacterial infections, have greatly improved. Electronic communications have brought much more rapid and comprehensive disease intelligence, and surveillance within countries has improved. International mechanisms have been developed – and severely tested during the SARS outbreak – for mounting a rapid response to emerging disease threats.

Disparities in access to health services are, however, now greater than they were at the start of the previous century. Nor is it known how an influenza pandemic would affect a world in which an estimated 49 million people are infected with HIV; people with compromised immune systems have long been considered at increased risk from serious influenza-related complications during normal seasonal epidemics. Limited epidemiological data from past pandemics suggest that countries where malaria is endemic may experience higher mortality during an influenza pandemic. It is not known, however, whether the excess mortality observed was caused by some interaction between the two diseases or – more likely – occurred because infection with either one of the two diseases increased vulnerability to severe illness and death from the other.

In the midst of all these unknowns, one epidemiological event is certain: health systems around the world will be confronted by a sudden and sharp increase in the demand for health care. The rapid global spread which has historically characterized pandemics will very likely be accelerated in today's highly mobile world. While the speed of international spread has no direct effect on morbidity and mortality, it may compromise response capacity if large populations within a country or geographical region are affected almost simultaneously. That situation would preclude the generous

An avian influenza web site in Indonesia.

assistance so often provided during humanitarian crises in which only a single country or geographical region has been affected and the rest of the world is spared. Judging from past experiences with pandemics, good health systems and standards of care, high levels of sanitation and hygiene, and adequate resources may reduce mortality during a pandemic but cannot protect countries against the arrival and rapid spread of a highly contagious disease caused by a virus that will be largely or entirely foreign to the human immune system.

This mixture of unknowns and certainties creates a familiar but difficult public health dilemma: what priority should be given to preparedness for an inevitably recurring event of unpredictable timing and an outcome that is also unpredictable but could be catastrophic? Public health officials in a number of countries, faced with a chronic shortage of funds, must often regard preparedness for some future emergency as a luxury when viewed against the many other immediate and urgent infectious disease threats competing for resources.

All measures that could mitigate the impact of a pandemic and can be set up in advance are best undertaken now rather than during the chaos of a pandemic.

Many experts are convinced that priorities will shift dramatically, and solutions to many current problems will be found, once a pandemic has been declared and its epidemiological potential begins to unfold. At the same time, preparedness planning cannot wait, especially as several key activities – improvements in surveillance systems, development of a pandemic vaccine – take time. All measures that could mitigate the impact of a pandemic and can be set up in advance are best undertaken now rather than during the chaos of a pandemic. Such measures fall into three main categories: advance warning that the virus is improving its transmissibility, early intervention to halt further adaptation or forestall international spread, and urgent development of a pandemic vaccine.

Once a pandemic begins, governments within individual countries will very likely be preoccupied by the need to take care of their own citizens. Now is clearly the best time for international collaboration. Faced with an infectious disease threat that will inevitably be shared by all, the international community must rely on surveillance systems within affected countries to detect and report human cases, giving particular attention to clusters of cases that may indicate the first signs of efficient human-to-

The special case of pandemic vaccines

1. Adverse events
A pandemic vaccine, which is needed to provide population-wide protection, is produced for administration to large numbers of people in all age groups. Adverse events will inevitably occur, whether caused by the vaccine or coincidental. Liability issues can also arise if a vaccine fails to confer adequate protection.

2. Safety testing
Ideally, safety testing should be exceptionally extensive, but the pressure to manufacture rapidly during a public health emergency is expected to shorten the time available for testing.

3. Demand
The demand for a pandemic vaccine will be far greater than that for seasonal vaccines. Present manufacturing capacity is finite and inadequate and cannot be augmented quickly.

4. Costs
The steps needed to develop and produce a pandemic vaccine are costly. Industry lacks incentives to invest in a product which may never reach the market and thus never bring a financial return.

human transmission. At the same time, the international community must rely on wealthy countries to advance work on the development of a vaccine against a pandemic virus – a complex and costly undertaking.

Vaccines: the first line of defence

Vaccines are universally regarded as the most important medical intervention for preventing influenza and reducing its health consequences during a pandemic. In the past, however, vaccines have never been available early enough and in sufficient quantities to have an impact on morbidity and mortality during a pandemic. Past problems, related to the special nature of pandemic vaccines and the inadequacy of manufacturing capacity, have endured.

From 11 to 12 November 2004, WHO convened a meeting to explore ways to expedite the development of vaccines against a pandemic virus. All the major influenza vaccine manufacturers were represented. The meeting specifically considered what needs to be done, by industry, regulatory authorities, governments, and WHO, to make vaccines available rapidly and in as large a quantity as possible.

Industry has moved forward following the initial H5N1 alert in January 2004. Several manufacturers are fully engaged in work on pandemic vaccine development, and various strategies, both short-term and long-term, are being pursued. As a new vaccine for seasonal influenza is produced almost every year, the steps required for vaccine development, licensing, and production are familiar to both industry and regulatory agencies. Nonetheless, the development and manufacturing of a vaccine against any pandemic virus faces unique and significant challenges, as all these steps must take place under the extreme conditions of an emergency.

The challenges are even more formidable for a highly lethal avian virus like H5N1. Although a few companies are moving towards cell-culture production technologies, fertilized chicken eggs are the standard medium for the growth of virus for use in influenza

Gaining time with a "mock-up" vaccine

A "mock-up" vaccine contains an influenza virus from a subtype, such as H5, known to have pandemic potential. The mock-up vaccine undergoes all safety and efficacy testing required for registration by national licensing agencies.

A dossier for this pandemic-like vaccine, including data on antigen content, immunogenicity, safety, and efficacy, is submitted for regulatory approval prior to the start of a pandemic.

When the actual pandemic virus emerges, a variation of the dossier, with technical data specific to the pandemic virus, is then submitted for final marketing authorization, which is then rapidly granted following a fast-track procedure.

To gain time, several activities can be undertaken now to lay the groundwork for rapid production of vaccines once a pandemic is declared.

vaccines, and will remain so in the near future. Highly pathogenic H5N1 kills chicken embryos and must therefore be modified. The preferred method for doing so uses the technology of "reverse genetics" to remove lethal genes.

Reverse genetics involves patented technologies, and this raises issues of intellectual property rights. Industry knows how to manage these issues, but the consequences of doing so may be reflected in the price of the vaccine. In Europe, a vaccine produced using reverse genetics is considered a "genetically modified organism"; the resulting safety concerns introduce additional biosafety requirements for manufacturing facilities. Upgrading of facilities to meet these higher standards is possible but costly and cannot be done rapidly.

As agreed during the consultation, all of these problems can be solved through a collaborative effort involving governments, industry, and academia. Some solutions depend on public funding; others require research support; still others will benefit from international coordination by WHO. To gain time, several activities can be undertaken now to lay the groundwork for rapid marketing authorization and production of vaccines once a pandemic is declared. These include clinical trials to establish optimal vaccine formulation and the immediate registration of a "mock-up" vaccine. Bulk antigen, protective against the H5 virus subtype, can be produced and stored in advance. Advance stockpiling of a true pandemic vaccine is not possible, as the vaccine must closely match the actual strain of the pandemic virus and must therefore await its emergence.

The greatest problem is inadequate production capacity. Demand will unquestionably outstrip supply, particularly at the start of a pandemic. Better use of seasonal vaccines would increase manufacturing capacity for pandemic vaccines. It also mitigates the considerable health impact of seasonal influenza epidemics – which cause an estimated 250 000 to 500 000 deaths globally each year – and makes the supply of vaccines for this purpose more secure. While this approach is considered the best long-term strategy for expanding the manufacturing base for all influenza vaccines, more immediate solutions are needed.

Fertilized eggs are the standard medium for growing virus for vaccine. H5N1 kills chicken embryos.

During pandemics, more severe disease tends to arrive with the second wave. Should this happen, a few more months could be available to augment vaccine supplies. Each day gained means an additional 5 million doses of vaccine.

High priority has been given to the investigation of strategies that economize on the use of antigen. Inclusion of an adjuvant in the vaccine formulation could enhance the effectiveness of low doses of antigen, thus making the most of limited antigen supplies and limited manufacturing capacity. Intradermal vaccination might extend vaccine supplies several-fold. Such strategies currently represent the best hope that countries without manufacturing facilities will have some access to a pandemic vaccine. At the start of a pandemic, manufacturers will halt production of trivalent seasonal vaccines (protective against three strains) and begin manufacturing of a monovalent vaccine protective against the pandemic virus only, thus greatly increasing the number of doses that can be produced during a given time. Two doses may, however, be needed to elicit a satisfactory immune response in immunologically naive populations.

WHO network laboratories developed a prototype virus, for use as the "seed" for vaccine production, and made it available to manufacturers in April 2004. Small investigational batches of an H5N1 vaccine have been produced in Japan and the USA for use in clinical trials, scheduled to begin in 2005. These trials will gather critical data on efficacy and safety and answer some initial questions about the antigen content and optimal dose needed to confer protection. Further trials will then be needed to assess a wider spectrum of possible formulations. Final vaccine formulation is guided by data from these studies; commercial production of a vaccine protective against an H5N1-like pandemic virus can then follow quickly.

Manufacturing capacity for influenza vaccines is concentrated in Australia, Europe, Japan, and North America, but the need for a vaccine will be global. When a pandemic begins, countries with domestic manufacturing capacity will have a distinct advantage and are expected to reserve scarce supplies for their own citizens. Once domestic needs have been met, surplus capacity can be used to export vaccines to meet international needs. Even so, supplies will be inadequate and cost factors will further limit access.

In the past, more severe disease has tended to arrive with the second wave. Should this happen, a few more months could be available to augment vaccine supplies. Larger quantities of vaccine, supported by well-planned distribution strategies, will

Historically, the distribution of any drug on a mass scale has faced formidable logistic challenges.

save many lives. In any event, all countries must undertake the difficult task of defining population groups that should have first priority for scarce supplies.

Antiviral drugs: different roles at different phases

For the newer drugs, the main constraints are price and very limited supplies. Surge capacity for production is negligible.

Antiviral drugs play two principal roles in the management of seasonal influenza: prophylaxis, aimed at decreasing the likelihood of developing influenza, and treatment, aimed at reducing the severity and duration of influenza. Research has demonstrated their effectiveness when used for both purposes. When used for treatment purposes, these drugs need to be administered shortly after the onset of symptoms. Some currently available drugs are expected to be effective in the treatment of human illness caused by avian influenza.

Of the two classes of antiviral drugs specific for influenza, the oldest and most affordable drugs are the so-called “M2 inhibitors”, amantadine and rimantadine. Apart from their advantageous price, these drugs have a long shelf life – at least two decades and possibly more. Their use, however, faces several problems. In treatment, drug resistance may develop quickly. Their safety in pregnant women is questionable. The dose in elderly patients has to be reduced and close clinical monitoring in certain patient groups is needed. During a pandemic, when health services are challenged by a sudden and sharp surge in the number of patients, such careful monitoring of individual patients may not be possible. Of far greater importance is the fact that studies have already demonstrated that the H5N1 virus is resistant to these drugs; this resistance might be retained in a pandemic virus.

Drugs in the second and newer class, the neuraminidase inhibitors (oseltamivir and zanamivir), have a better safety profile and are less prone to the development of drug resistance. Here, the main constraints are price and supplies. The drugs are much more expensive than the M2 inhibitors and supplies are very limited. Surge capacity for production is negligible.

Some cost comparisons in Viet Nam

Per capita health expenditure
US$ 8

Rapid test to detect influenza A
US$ 8

Test to detect H5 subtype
US$ 30

Treatment course, antiviral drugs
US$ 30–40

Can the spread of a pandemic be delayed?

For the first time in history, the H5N1 situation in Asia has given the world a warning that a pandemic may be imminent. This warning has inevitably sparked questions about whether the right actions, taken at the right time, might do something to alter the historical pattern of rapid international spread.

Such an approach, which aims to forestall international spread and thus gain time to augment vaccine supplies, is linked to assumptions that the first chains of human-to-human transmission might not reach the efficiency needed to initiate and sustain pandemic spread. Should this happen, early detection of tell-tale clusters of cases, followed by aggressive containment measures, including the prophylactic use of antiviral drugs, might hold the disease at bay, thus gaining time to increase preparedness.

Should early containment fail, once a certain level of efficient transmission is reached, no interventions are expected to halt international spread, and priorities will need to shift to the reduction of morbidity and mortality.

Despite these constraints, antiviral drugs have important roles to play, both now and at the start of a pandemic. Under pandemic conditions, their importance is elevated during the first wave of infection when vaccines – unquestionably the most useful medical tool for reducing morbidity and mortality – are not yet available. In the absence of vaccines, antiviral drugs will be the only medical intervention for providing both protection against disease and therapeutic benefit in persons who are ill.

Public health priorities will change as the situation moves from the present incipient pandemic situation, through the phase when human-to-human transmission becomes more efficient, to the onset of a full-fledged pandemic characterized by a rapid increase in the number of cases and the start of international spread. Antiviral drugs have clear but different roles to play at each of these phases. The impact of their use is, however, not equally certain for each phase and, at least in the short term, may be constrained by available supplies and price.

All subtypes of avian influenza are considered susceptible to the newer drugs. In the present situation, one of these drugs, oseltamivir, is being used to treat cases in both Thailand and Viet Nam. Currently available evidence suggests that oseltamivir is effective in the treatment of H5N1 infections in humans. As oseltamivir needs to be administered within two days after the onset of symptoms, a critical problem is the tendency of cases to be detected late in the course of their illness. Many patients are not being treated early enough for the potentially life-saving role of oseltamivir to have an appreciable impact on mortality. Nonetheless, patients with H5N1 infection presenting late in the course of illness are being treated with this drug for compassionate reasons: it may still have a chance of saving a life.

Oseltamivir has a second use in the present situation: to protect clearly defined risk groups. The drug is currently being given, for prophylactic purposes, to health care workers, family members, and close contacts of cases, and this policy is considered to represent wise use of a drug in short supply. When a human case occurs, on-the-spot investigations are undertaken to identify the people who should be targeted for prophylactic treatment. At the same time, these investigations sometimes fail to uncover a direct link between human infection and exposure to dead or

Field investigations are no longer able to link all human cases to direct exposure to sick poultry.

diseased poultry, suggesting that the risk of exposure may be widely diffused within a community or is arising from an inapparent source. In such situations, health officials will have no clear exposure history to guide decisions about who is most at risk and should therefore be targeted for antiviral prophylaxis. It may thus prove very difficult to expand the protection conferred by antiviral drugs to risk groups beyond those people who have had close contact with a patient.

Opportunities for using antiviral drugs

1. Present situation
Drugs are being used to treat patients and prevent infection in close contacts, including health care workers and family members.

2. Start of efficient human-to-human transmission
Drug administration to the entire community where clusters of cases are occurring might stop the virus from further improving its transmissibility or delay international spread.

3. Start of a full-fledged pandemic
Antivirals will have great importance as the only influenza-specific medical intervention for reducing morbidity and mortality.

The second opportunity to use antiviral drugs arises when surveillance indicates that the virus is beginning to improve its transmissibility – the epidemiological trigger for a greatly increased level of alarm. This change will be expressed by evidence that transmission from one person to another is resulting in a chain of transmission. It will most likely be visible as clusters of cases closely related in place and time. Many experts view this event as a unique opportunity to intervene with mass administration of antiviral drugs to protect against influenza in the entire area where cases have occurred. The goals of doing so are twofold. First, community-wide administration of antiviral drugs, aimed at reducing the number of human infections, could give the virus fewer opportunities to further improve its transmissibility either through adaptive mutation during human infections or following the exchange of genes during coinfection with a human and an avian virus. In an ideal situation, such an intervention would forestall the start of a pandemic. Should this fail, the second goal is to delay the start of international spread, thus holding the disease at bay and gaining time to augment vaccine supplies. At present global capacity, each day gained could allow manufacturers to produce an additional 5 million doses of vaccine.

The ability to use this opportunity effectively depends on several unpredictable factors. The question of whether rapid intervention might forestall the emergence of a pandemic virus or at least delay international spread cannot be answered with any certainty. As this preventive approach has never been attempted, there is no experience on which to base estimates of its effectiveness. Rapid intervention also depends on very sensitive surveillance, oriented towards the detection of clusters of cases, and an ability to quickly acquire and administer a substantial supply of drugs. Several epidemiological events will determine whether these requirements can be met. Will the emergence of a pandemic virus

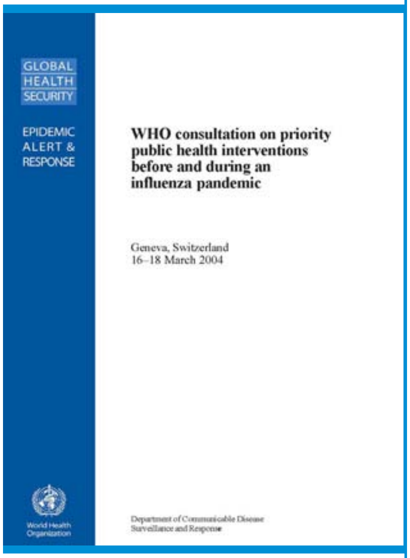
Oseltamivir is effective in the treatment of human infections with H5N1. As the drug must be given within two days after the onset of symptoms, a critical problem is the tendency of patients to be detected late in the course of illness.

announce itself with small and potentially manageable clusters of cases or will it begin with an explosion of rapid and sustainable human-to-human transmission? Will the earliest cases remain confined to a small geographical area or will the onset of a pandemic be detected only after large areas are experiencing cases? None of these important questions can be answered with any certainty. Investigations of recent cases indicate that rural, as opposed to urban, residents are at greatest risk. If only a small area with a sparse population is initially affected, intervention with antiviral drugs may have a more realistic chance of success, especially when considering the limited supplies available and the logistic challenge of quickly reaching larger numbers of people. In Viet Nam, for example, health officials see great value in maintaining a stockpile of oseltamivir sufficient to cover an entire village and ready for rapid mobilization.

The third opportunity arises once a pandemic has been declared, and here the role of antiviral drugs is unquestionable. Pending the availability of vaccines, antiviral drugs will be the principal medical intervention for reducing morbidity and mortality, which becomes the most important priority once a pandemic is under way. Stockpiling drugs in advance is presently the only way to ensure that sufficient supplies are available at the start of a pandemic. Several countries are now stockpiling antiviral drugs, and these advance orders are expected to expand manufacturing capacity for the future. This, in turn, will put the world in a better position to respond to any future pandemic caused by any influenza virus.

Non-medical interventions: balancing impact against costs and social disruption

Given the problems of inadequate vaccine supplies and the uncertain role of antiviral drugs, several efforts have been made to determine whether non-medical interventions could mitigate the initial impact of a pandemic. In March 2004, WHO convened an expert consultation to assess priority public health interven-


GLOBAL HEALTH SECURITY
EPIDEMIC ALERT & RESPONSE

WHO consultation on priority public health interventions before and during an influenza pandemic

Geneva, Switzerland
16–18 March 2004

World Health Organization

Department of Communicable Disease Surveillance and Response

tions, including non-medical interventions, before and during a pandemic. Some main conclusions are summarized below.

A wide range of non-medical interventions – from personal hygiene and the wearing of masks to quarantine, contact tracing, and the screening of travellers – can potentially reduce opportunities for transmission at the start of a pandemic and slow international spread (Tables 4 and 5). Consideration of their use during a pandemic is particularly important, as non-medical interventions will be the principal protective tools pending the augmentation of vaccine supplies. In resource-poor settings, non-medical interventions may be the main line of defence throughout the first wave of a pandemic. The effectiveness of most of these interventions has not, however, been tested under the unique conditions of a pandemic.

An influenza pandemic is a public health emergency that rapidly takes on significant political, social, and economic dimensions. As with other emerging infectious diseases, the course of its evolution is governed by factors – including the properties of a new causative agent – that cannot be known in advance and require some time to understand. Health authorities will need to make a series of emergency decisions in an atmosphere of considerable scientific uncertainty and fragile public confidence.

The effectiveness of many interventions will depend on the behaviour of the virus as determined by its pathogenicity, principal mode of transmission (droplet or aerosol), concentration in different age groups, duration of virus shedding, and susceptibility to antiviral drugs. If, for example, it is known that children are the most severely affected age group, or play a major role in transmission, health authorities will be in a better position to make decisions about the effectiveness of school closure, travel measures (children travel less frequently than adults) and quarantine (children cannot be separated from their parents). Apart from questions of effectiveness, the selection of appropriate measures will be driven by questions of feasibility, and these are closely linked to costs, ease of implementation within existing infrastructures, likely acceptability to the public, and potential to cause social and economic disruption.

GOARN: a strike force of specialized expertise

The Global Outbreak Alert and Response Network (GOARN) was set up in early 2000 to ensure that a "strike force" of specialized staff and technical resources could be rapidly assembled and deployed for emergency investigations and on-the-spot assistance.

This overarching network currently interlinks, in real time, 120 existing networks and institutes which together possess much of the data, laboratory capacity, specialized skills, and experienced personnel needed to act rapidly, on many different fronts, when outbreaks require international support.

The establishment of GOARN solved many long-standing problems. By drawing on the resources and expertise of a broad range of technical partners, the network obviated the need – with all its associated expenses – to maintain a permanent staff of dedicated experts in the face of a danger that emerges only sporadically and unpredictably.

As outbreaks present widely varying demands for their control, GOARN brought much-needed flexibility and a surge capacity that could be tailored to outbreak needs. It also helped ensure that experts from any single country would have frequent opportunities, during international responses, to exercise and sharpen their technical skills.

At the earliest stage of a pandemic, when large numbers of cases are not yet occurring, measures such as simple hand-washing, the use of masks, and voluntary quarantine of patients might help reduce transmission. If only a few countries are affected, travel-related measures, such as exit screening for persons departing from affected areas, might delay international spread somewhat, but cannot stop it. Once efficient and sustained human-to-human transmission has been established, the containment of pandemic influenza is not considered feasible.

When large numbers of cases begin to occur, priorities need to change, moving away from efforts to reduce transmission and international spread and towards the reduction of morbidity and mortality. Several measures, such as contact tracing and follow-up, will no longer be either effective or feasible because of the sheer number of cases. Other measures, such as entry screening at airports and borders, will have no impact.

Non-medical interventions successfully contained SARS within four months following the start of international spread. For several reasons, however, pandemic influenza is considered far more difficult to control than SARS. Influenza A viruses are much more contagious than the SARS coronavirus. The incubation period is shorter and the virus can be spread prior to the onset of symptoms. Fever checks and border screenings will not be able to detect people in the incubation period who have no symptoms but are nonetheless capable of spreading infection. While SARS remained largely confined to hospital settings, pandemic influenza will rapidly and widely spread within the community.

The response to date: a good investment – whatever the future brings

Public health authorities and influenza experts have watched H5N1 with great concern since 1997. Several countries in Asia have lived under the shadow of this virus – with all its consequences for human and animal health and all its social and economic

Cases are being detected more quickly, testing is more rapid, and results are openly shared with WHO.

Countries remain on high alert. WHO epidemiologists in Thailand and Viet Nam are confident that unusual clusters of cases will be detected quickly and reported immediately.

Estimated total gross domestic product losses accruing from poultry farm losses, 2004[a]

Thailand	**US$ 1.2 billion**
Viet Nam	**US$ 0.3 billion**
Asia	**US$ 10–15 billion**

[a] Source: Oxford Economic Forecasting. Estimates for poultry farm losses are based on an assumed quarter-year loss of income. The total GDP losses estimated include Asia-wide multiplier effects from the farm losses. The scaling up of health-risk impacts, from avian influenza in birds to a more generalized problem for livestock and a drop in tourism, could create annual economic losses of as much as US$ 50–60 billion, even if human cases of disease were to remain limited. Escalation of the latter would have yet more serious implications.

costs – throughout 2004. The seriousness with which this threat has been taken by the governments concerned is commendable. In the only two countries with human cases, Thailand and Viet Nam, surveillance for both avian and human disease continues at a very high level. In Viet Nam, where a third wave of human infections began in December 2004, clinicians are increasingly able to recognize likely cases on the basis of clinical features. Cases are being detected more quickly, laboratory testing is more rapid and reliable, and results are being openly shared with WHO.

At the same time, changes in the epidemiology of the virus have made surveillance far more difficult, and human cases are still being detected too late. In the present situation, where outbreaks in poultry are less conspicuous, clinicians need to maintain a high level of suspicion when confronted with cases of severe respiratory illness, even when no exposure history is apparent. Good links and lines of communication between clinical, public health, and veterinary services are a very efficient way to improve the surveillance system. In January 2004, alert clinicians in Hanoi were the first to raise the alarm about a possible new disease, and their suspicions – rapidly communicated to WHO – greatly expedited the international response.

In both Thailand and Viet Nam, the detection of a new human case initiates a series of intense field investigations, including surveillance and testing of family members and community contacts, and sampling of poultry and environmental areas. WHO epidemiologists working in both countries are increasingly confident that any unusual clusters of respiratory disease, possibly signalling the start of efficient human-to-human transmission, will be rapidly detected and immediately reported.

Thailand's determination to mount an aggressive response on all fronts was exemplified during the month of October 2004. Detection of that country's first probable instance of human-to-human transmission prompted the recruitment of around 1 million volunteers who combed the country, door-to-door, searching for outbreaks in poultry and any associated influenza-like illness in humans. For a disease which has caused a comparatively small number of human cases and deaths, such actions indicate a sense of national responsibility to the international community for a domestic health problem that could

Has the tsunami in South-East Asia increased the pandemic threat?

Concerns have been raised about whether the recent tsunami in South-East Asia may have increased the risk of an influenza pandemic. The level of pandemic risk depends on how widespread H5N1 is in domestic poultry, how often the virus is transmitted to humans, and the concurrent circulation of human influenza viruses.

The tsunami itself does not increase the risk that a pandemic virus might emerge, as it did not directly affect areas with the highest prevalence of H5N1 infection in poultry. At the same time, however, any activity that spreads the outbreaks in poultry increases opportunities for human exposure, which is linked to the emergence of a pandemic virus.

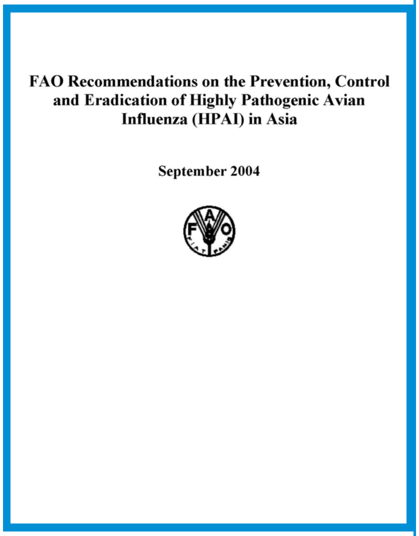
The risk of importing avian influenza into areas affected by the tsunami can be minimized by controlling the movement of poultry from areas where outbreaks are known to be occurring. It is also important to ensure that infected poultry are kept out of the food chain, including emergency food relief activities.

potentially threaten the whole world. It is in the self-interest of all countries to support such efforts. With H5N1 now firmly entrenched in parts of Asia, the struggle against this virus will be long and the consequences – for economies as well as for health and agriculture – are likely to be severe.

The outbreaks in poultry have affected the very backbone of rural subsistence farming in large parts of Asia. Recognition is growing that fundamental changes in agricultural practices may be the only viable long-term solution, and Thai authorities are moving forward in this direction. Apart from being costly to implement, the changes that are needed touch upon traditional farming practices that date back, in some cases, for centuries. In these matters, FAO is playing an instrumental role in providing both expert guidance and direct support to countries.

In January 2005, the Vietnamese government established an interagency working group as part of its intensified response to avian influenza. Members include high-ranking technical experts and senior staff from the ministries of health and agriculture and rural development. Both FAO and WHO are represented. Establishment of the working group acknowledges the direct links between avian outbreaks and human cases and the need for a closely coordinated response. Having such a body of expertise and authority is expected to facilitate the rapid exchange of new findings from both the avian and human fronts and expedite decisions should emergency actions be needed. Specific responsibilities assigned to the group include heightened surveillance, joint field investigations when human cases occur, and pandemic preparedness planning. The working group will also advise the government on priorities for short- and medium-term research that can lead to better understanding of the disease and measures for prevention. One particularly urgent need is to strengthen the advice given to rural residents on how to avoid exposure.

H5N1 causes a disease with many disturbing and unusual features that are poorly understood. The virus has crossed the species barrier twice in the past, in 1997 and 2003, but the cases in 2004 and early 2005 constitute the largest and most deadly human outbreak on record. With the virus now endemic in parts of Asia, sporadic cases and occasional family clusters need to be anticipated. The continuing risk of more cases, combined with


FAO Recommendations on the Prevention, Control and Eradication of Highly Pathogenic Avian Influenza (HPAI) in Asia

September 2004

In September 2004, FAO issued detailed recommendations for addressing the poultry outbreaks in Asia.

The continuing risk of more human cases, combined with the extremely high fatality, makes it imperative to find an effective treatment.

the extremely high fatality, makes it imperative to understand the disease and find an effective treatment. In response to this need, WHO is creating a network of clinical experts to expedite the exchange of experiences with cases, compare results with different treatments, and coordinate urgent research on pathogenicity. The expected outcomes are better diagnostic tools, more specific treatments, and improved infection control. As with any other poorly understood new disease, doctors treating cases benefit from the guidance embodied in collective experience.

Recent work, by industry and academia, on the development of a pandemic vaccine has likewise left the world better prepared for the next pandemic – whenever it comes and whichever virus causes it. Steps taken by some companies during 2004 will expedite the development of a vaccine for any pandemic virus that emerges. New plants meeting higher biosafety requirements have been constructed. New production technologies offering greater flexibility and speed are in the final stages of development. Several vaccine manufacturers have moved forward with the work needed for the generic registration and licensing of pandemic vaccines. Regulatory agencies have established procedures for advance approval of a "mock-up" vaccine and subsequent fast-track marketing authorization once a pandemic is declared. The work of WHO and its network of influenza laboratories quietly underpins all of these activities in ways that range from isolation and characterization of viruses to their transformation into a form ready-made for use by industry.

Preparedness has moved forward on other fronts as well, also in ways that bring permanent improvements in capacity. During 2004, WHO held a series of training courses in Asia and elsewhere designed to give laboratory workers the skills needed to reliably isolate and characterize influenza viruses. This training has made more countries competent, in a self-sufficient way, to monitor circulating influenza viruses and detect unusual variants. Also under pressure of a pandemic threat, regional workshops were held to support the development of pandemic preparedness plans that are appropriate for the capacities and resources available in developing countries. As a further support, WHO has issued a comprehensive checklist of step-wise actions and options to help countries to think through likely events during a pandemic and plan their responses accordingly.

Urgent research needs

1. Understand the potential of H5N1 to reassort

Studies that mimic reassortment are being conducted, under high-security conditions, to determine whether H5N1 readily reassorts.

2. Clarifiy the role of animal influenza in the emergence of pandemic viruses

Data are needed on the prevalence of H5N1 in aquatic birds and pigs. The role of domestic ducks needs to be studied to determine whether they are sustainable reservoirs of highly pathogenic H5N1.

3. Improve clinical knowledge of human disease

Features of human H5N1 infection important for control, but poorly understood, include the incubation period, patterns of virus excretion, factors determining disease outcome, and effectiveness of various treatments.

4. Find ways to economize on antigen content in vaccines

Research is needed to guide vaccine formulations that make the maximum use of limited amounts of antigen and thus extend manufacturing capacity.

The H5N1-related events during 2004 have again created a flurry of research. This work is rapidly improving understanding of the origins of H5N1, the patterns of its evolution, and its behaviour in avian and mammalian species. Work has also been initiated, in high-level biosafety facilities, to determine how readily the H5N1 virus exchanges genes with human influenza viruses. Most importantly, work on currently circulating viruses is allowing virologists to track changes in the present situation and thus issue precise warnings should the threat of a pandemic increase. A tradition of scientific collaboration that dates back to 1947, when the influenza laboratory network was established, has continued to operate efficiently behind the scenes. Viruses from the 2004 outbreaks have been shared with network laboratories, and the resulting studies of these viruses will benefit all countries, now and in the future.

The unpredictable nature of influenza viruses makes it impossible to know whether recent events will turn out to be another close call with a dangerous virus, or the prelude to the first pandemic of the 21st century. Should the latter event occur, the world will find itself warned far in advance, better prepared than at the start of 2004, yet still highly vulnerable.

Table 4. Non-medical interventions at the national level (for persons living or travelling within an affected country)[a]

Measures	Phases[b] pre-pandemic 0.1	0.2	0.3	1.0	Comments
Public health information, communication					
Information for public on risks and risk avoidance (tailored to target population)	Y	Y	Y	Y	
Information for professionals	Y	Y	Y	Y	
Advice on universal hygiene behaviour	Y	Y	Y	Y	
Preparatory information on next phase	Y	Y	Y	Y	
Measures to reduce risk that cases transmit infection					
Confinement					
– confine cases (mild and severe) as appropriate to local situation; provide medical and social care	Y	Y	Y	Y	Need to plan for large numbers of severe cases.
Face masks[c]					
– symptomatic persons	Y	Y	Y	Y	Logistics need to be considered.
– exposed person: undertake risk assessment considering: evidence of human-to-human transmission; closeness of contact; frequency of exposure	C	C	C	C	Consider recommending masks based on risk assessment.
– persons seeking care (respiratory illness) in risk area (waiting room)	Y	Y	Y	Y	Need more data, especially on use by well people.
Measures to reduce risk that contacts transmit infection					
Tracing and follow-up of contacts	Y	Y	Y	N	Not feasible once pandemic starts.
Self-health monitoring and reporting if ill	Y	Y	N	Y	
Voluntary quarantine (home confinement) of healthycontacts; provide medical and social care	N	N	Y	N	Home confinement should also apply to persons undergoing antiviral prophylaxis, as efficacy not known.
Advise contacts to reduce social interaction	N	N	NR	N	Not relevant for contacts in quarantine; see also measures to increase social distance.
Advise contacts to defer travel to unaffected areas	N	Y	NR	Y	Precautionary principle when unclear whether human-to-human transmission is occurring; see also travel measures.
Provide contacts with antiviral prophylaxis[d]	Y	Y	Y	N	Principle of early aggressive measures to avert pandemic.
Measures to increase social distance					
Voluntary home confinement of symptomatic persons	Y	Y	Y	Y	Measures needed to reduce risk of transmission to other household members.
Closure of schools (including pre-school, higher education) in conjunction with other measures (limiting after-school activities) to reduce mixing of children	N	N	C	C	Depends on epidemiological context – extent to which these settings contribute to transmission.
Population-wide measures to reduce mixing of adults (furlough non-essential workers, close workplaces, discourage mass gatherings)[e]	N	N	C	C	Consider in certain circumstances – extent to which unlinked community transmission and transmission in workplaces occurs.
Masks in public places	N	N	N	N	Not known to be effective; permitted but not encouraged.

Measures	Phases[b] pre-pandemic 0.1	0.2	0.3	1.0	Comments
Measures to decrease interval between symptom onset and patient isolation					
Public campaign to encourage prompt self-diagnosis	Y	Y	Y	Y	
Urge entire population (affected area) to check for fever at least once daily	N	N	N	N	
Set up fever telephone hotlines with ambulance response	N	N	C	N	
Set up fever clinics with appropriate infection control	N	N	C	N	
Introduce thermal scanning in public places	N	N	N	N	Not effective based on experience; also requires individual and public health action for identified febrile persons.
Disinfection measures					
Hand-washing	Y	Y	Y	Y	
Household disinfection of potentially contaminated surfaces	Y	Y	Y	Y	
Widespread environmental disinfection	N	N	N	N	
Air disinfection	N	N	N	N	
Measures for persons entering or exiting an infected area within the country					
Advise to avoid contact with high-risk environments (infected poultry farms, live poultry markets)	Y	Y	Y	Y	
Recommended deference of non-essential travel to affected areas	N	N	Y	Y	If significant areas of country remain unaffected.
Restrict travel to and from affected areas	N	N	N	N	Enforcement of travel restrictions considered impractical in most countries but likely to occur voluntarily when risk appreciated by the public.
Cordon sanitaire	N	N	N	N	Enforcement considered impractical.
Disinfection of clothing, shoes, or other objects of persons exiting affected areas	N	N	N	N	Not recommended for public health purposes, but may be required by veterinary authorities to prevent spread of infection in animals.

Y = yes, should be done at this phase; N = no, not necessary at this phase; C = should be considered; NR = not relevant.

[a] This table is being revised in line with recommendations made during a WHO expert consultation held in December 2004.

[b] *Phases*

0.1 = A novel virus subtype is isolated from a single human case. No evidence of further spread or outbreak activity.

0.2 = Two or more human infections with the novel virus subtype are confirmed. No evidence of human-to-human transmission.

0.3 = Human-to-human transmission is confirmed.

1.0 = Onset of pandemic. The new virus subtype causes several outbreaks in at least one country, shows international spread, and causes serious morbidity and mortality in at least one segment of the population.

[c] Quality and type of mask depend on risk group. Cases: surgical mask; health care workers: N95 or equivalent; others: depends on risk.

[d] Implementation depends on adequate supplies and may require a global stockpile with a pre-negotiated targeting and delivery strategy to ensure availability in the area where a potential pandemic virus emerges. Prophylactic use will depend on evidence of effectiveness. Targeted use required because of potential for drug resistance, side-effects and limited supplies. Targeted use might consider: public prevention; protection of health care workers; protection of other essential service providers; individual treatment.

[e] Given a pandemic strain causing significant morbidity and mortality in all age groups and the absence of a vaccine, authorities should seriously consider introducing population-wide measures to reduce the number of cases and deaths. Decisions can be guided by mathematical and economic modelling. If modelling indicates a reduction in the absolute numbers of cases and deaths, decisions to introduce measures, involving multiple government sectors, will then need to balance the protection of priority functions against the risk of social and economic disruption.

Table 5. Non-medical interventions at the international level[a]

Measures	Phases[b] pre-pandemic 0.1	0.2	0.3	1.0	Comments
Public health information, communication					
Information for public on risks and risk avoidance (tailored to target population)	Y	Y	Y	Y	
Information for professionals	Y	Y	Y	Y	
Advice on universal hygiene behaviour	Y	Y	Y	Y	
Preparatory information on next phase	Y	Y	Y	Y	
Measures at borders for persons entering or exiting a country					
Information to travellers					
– outbreak notice	Y	Y	Y	Y	Message must be tailored to phase. While travel would remain matter of personal choice, transparency must be assured in order to allow for informed decision-making. Consequences for the traveller may include personal risk to health and economic harm.
– recommend that travellers to areas experiencing outbreaks of highly pathogenic avian influenza avoid contact with poultry farms and live animal markets	Y	Y	N	N	
– recommend deference of non-essential international travel to affected areas	N	N	Y	Y	
– recommend deference of non-essential international travel from affected areas	*See screening measures*				
Measures at borders for international travellers coming from or going to affected areas					
Health alert notices to travellers to and from affected areas	N	N	Y	Y	WHO negotiates with IATA[c] to ensure that airlines distribute health alert notices; WHO facilitates shared notice formats among countries.
Medical surveillance					
– daily self-checking for fever					
Travellers from affected area	N	N	Y	Y	
Travellers to affected area	N	N	N	Y	
– self-reporting if symptoms appear in travellers from affected areas	Y	Y	Y	Y	Contacts of confirmed cases should be encouraged to monitor health. Quarantine may be indicated. Persons on affected conveyance should be traced and similarly advised.
– advice on how to behave if ill after travel in affected areas (seek health care, give travel history, receive influenza laboratory test); if pandemic virus detected, patient should be isolated and public health officials, including WHO, notified.	Y	Y	Y	Y	
Entry screening for travellers coming from affected areas					Due to lack of proven health benefit, practice should be permitted (for political reasons, to promote public confidence) but not encouraged. Travellers should receive health alert notices instead.
– screening for symptoms (visual detection of symptoms)	N	N	N	N	Entry screening may be considered where host country suspects exit screening (see below) at traveller's point of embarkation is suboptimal.

Measures	Phases[b] pre-pandemic 0.1	0.2	0.3	1.0	Comments
– screening for at-risk travellers (health declaration, questionnaire)	N	N	N	N	
– thermal screening	N	N	N	N	
– medical examination	N	N	N	N	
Entry screening options for geographically isolated infection-free areas (islands)	N	N	Y	Y	Feasible, may prevent entrance of pandemic virus. May also be relevant where country's internal surveillance capacity is limited.
Exit screening for all travellers from areas with human infection	N	N	Y	Y	More feasible than entry screening for detecting early cases.
– screening for symptoms (visual detection of symptoms)	N	N	N	N	Not feasible due to passenger volume.
– screening for at-risk travellers (health declaration, questioinnaire)	N	N	Y	Y	
– thermal scanning or ear-temperature measurement	N	N	Y	Y	Thermal scanning less sensitive and specific but may be more practical than ear-temperature scanning.
– stop list of isolated or quarantined persons	N	N	N	N	May be feasible in certain countries, but generally not encouraged.
– recommend that ill persons postpone travel	Y	Y	Y	Y	
– medical examination for travellers at risk, with fever	N	N	N	N	Not feasible to implement at borders.
Measures for countries with porous borders (including informal or illegal crossing points) adjoining affected areas					
Raise awareness among health care providers and general public to facilitate "informal" surveillance and response measures, such as social distancing, quarantine or isolation	N	N	Y	Y	WHO to post relevant guidelines on web for use by countries in developing posters, mass media messages, and similar measures. Possible benefits include rumour control.
Measures for travellers on board international conveyances from affected areas					
Recommend self-reporting if influenza-like symptoms appear	N	N	Y	Y	
Separate sick travellers (if possible) on board	N	N	Y	Y	On flights from affected areas, masks should be offered to all passengers upon boarding.
Advise health authority at countries of traveller's embarkation, destination and transit that a person on board is ill (airline is responsible for destination only)	Y	Y	Y	Y	Established requirement for destination, but not uniformly observed in practice.
Share epidemiological information for contact tracing with national public health authorities	N	N	Y	Y	Countries to share this information directly with others, as appropriate.

Y = yes, should be done at this phase; N = no, not necessary at this phase; C = should be considered; NR = not relevant.

[a] This table is being revised in line with recommendations made during a WHO expert consultation held in December 2004.

[b] *Phases*
0.1 = A novel virus subtype is isolated from a single human case. No evidence of further spread or outbreak activity.
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0.3 = Human-to-human transmission is confirmed.
1.0 = Onset of pandemic. The new virus subtype causes several outbreaks in at least one country, shows international spread, and causes serious morbidity and mortality in at least one segment of the population.

[c] IATA = International Air Transport Association.

Recent WHO recommendations and reports on H5N1 and avian influenza available on the Internet

Information for the general public

- Avian influenza: frequently asked questions
  http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/
- Avian influenza: fact sheet
  http://www.who.int/mediacentre/factsheets/avian_influenza/en/

Laboratory procedures

- WHO reference laboratories for diagnosis of influenza A/H5 infection
  http://www.who.int/csr/disease/avian_influenza/guidelines/referencelabs/en/
- WHO guidelines for the collection of human specimens for laboratory diagnosis of influenza A/H5 infection
  http://www.who.int/csr/disease/avian_influenza/guidelines/humanspecimens/en/
- Recommended laboratory tests to identify influenza A/H5 virus in specimens from patients with an influenza-like illness
  http://www.who.int/csr/disease/avian_influenza/guidelines/labtests/en/
- Access to influenza A(H5N1) viruses
  http://www.who.int/csr/disease/avian_influenza/guidelines/form/en/index.html

Surveillance for H5N1 in humans

- WHO guidelines for global surveillance of influenza A/H5
  http://www.who.int/csr/disease/avian_influenza/guidelines/globalsurveillance/en/

Influenza surveillance in animals

- WHO manual on animal influenza diagnosis and surveillance
  http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_NCS_2002_5/en/

Prevention

- Guidelines for the use of seasonal influenza vaccine in humans at risk of H5N1 infection
  http://www.who.int/csr/disease/avian_influenza/guidelines/seasonal_vaccine/en/
- WHO interim recommendations for the protection of persons involved in the mass slaughter of animals potentially infected with highly pathogenic influenza viruses
  http://www.who.int/csr/disease/avian_influenza/guidelines/interim_recommendations/en/
- Advice for people living in an area affected by highly pathogenic avian influenza (HPAI) virus
  http://www.who.int/csr/disease/avian_influenza/guidelines/advice_people_ area/en/

Infection control

- Influenza A (H5N1):WHO interim infection control guidelines for health care facilities
  http://www.who.int/csr/disease/avian_influenza/guidelines/infectioncontrol1/en/

Clinical management

- WHO interim guidelines on clinical management of humans infected by influenza A(H5N1)
  http://www.who.int/csr/disease/avian_influenza/guidelines/clinicalmanage/en/

Recent consultations and meetings

- WHO consultation on priority public health interventions before and during an influenza pandemic, March 2004
  http://www.who.int/csr/disease/avian_influenza/consultation/en/
- Vaccines for pandemic influenza: informal meeting of WHO, influenza vaccine manufacturers, national licensing agencies, and government representatives on influenza pandemic vaccines, November 2004
  http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2004_3/en/