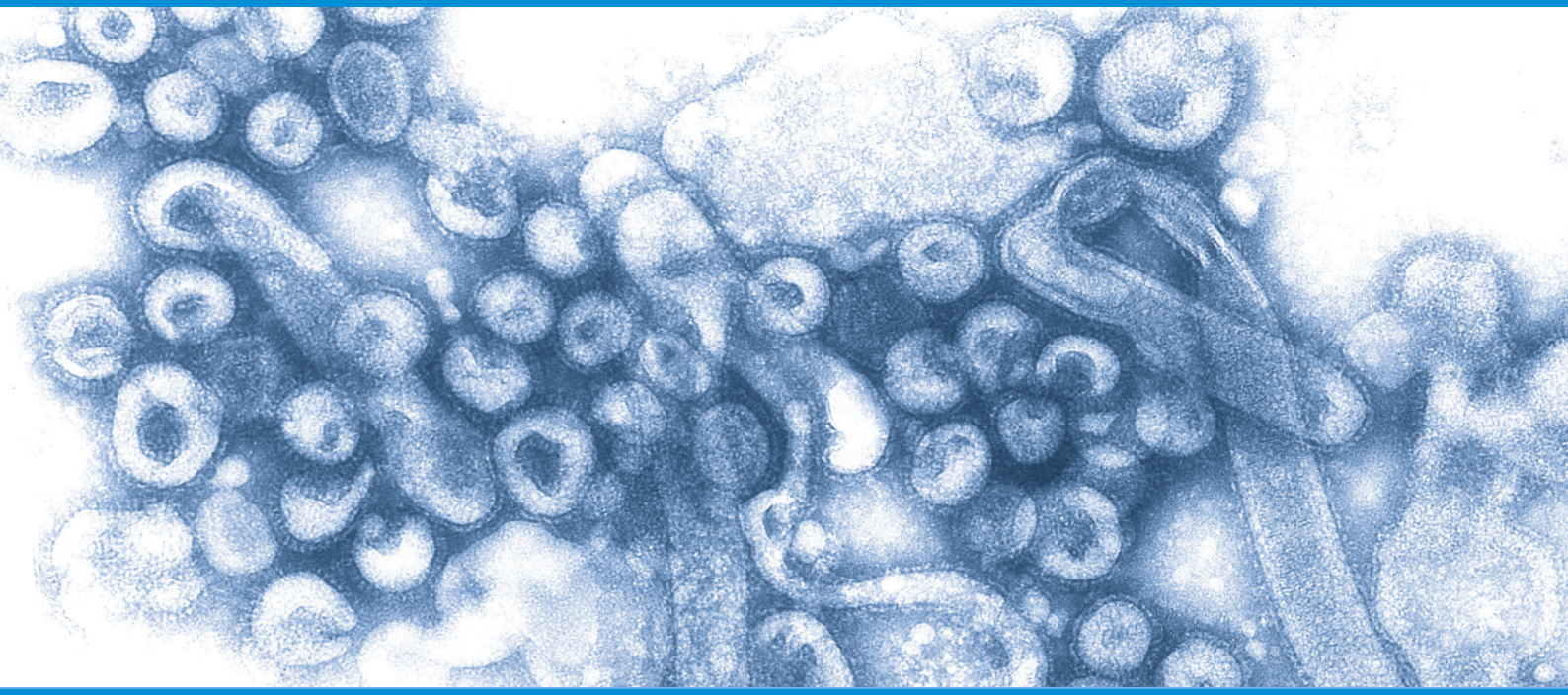
Avian influenza: assessing the pandemic threat



World Health Organization

JANUARY 2005 – WHO/CDS/2005.29

Avian influenza: assessing the pandemic threat

World Health Organization

For further information:
Global Influenza Programme
World Health Organization
E-mail: whoinfluenza@who.int

Cover: micrograph provided by
Drs K. Gopal Murti and Robert Webster
of St Jude Children's Research Hospital
of Memphis, Tennesse, USA

Dr LEE Jong-wook

Director-General
World Health Organization

Foreword

Influenza pandemics are associated with high morbidity, excess mortality, and social and economic disruption. There were three such pandemics in the twentieth century: in 1918, 1957, and 1968. During 2004, the world moved closer to a further pandemic than it has been at any time since 1968.

In the past, pandemics have announced themselves with a sudden explosion of cases which took the world by surprise. This time, we have been given a clear warning. During 2004, large parts of Asia experienced unprecedented outbreaks of highly pathogenic avian influenza, caused by the H5N1 virus, in poultry. The virus crossed the species barrier to infect humans, with a high rate of mortality. Monitoring of the evolving situation, coordinated by WHO, has produced many signs that a pandemic may be imminent. This time, the world has an opportunity to defend itself against a virus with pandemic potential before it strikes.

Preparedness for a pandemic presents a dilemma: what priority should be given to an unpredictable but potentially catastrophic event, when many existing and urgent health needs remain unmet? In such a situation, it is useful to put together all the known facts that can help us to see where we stand, what can happen, and what must be done. That is the purpose of this publication.

The H5N1 virus has given us not only a clear warning but time to enhance preparedness. During 2004, concern about the threat of a pandemic set in motion a number of activities, coordinated by WHO, that are leaving the world better prepared for the next pandemic, whenever it occurs and whichever virus causes it. Nonetheless, our highly mobile and interconnected world remains extremely vulnerable. No one can say whether the present situation will turn out to be another narrow escape or the prelude to the first pandemic of the 21st century. Should the latter event occur, we must not be caught unprepared.

Contents

Introduction

This publication evaluates the present pandemic threat on the basis of what we know about pandemics, influenza A viruses, and the H5N1 virus in particular. It draws together some current facts and figures, evidence from the past, and some best-guess speculations useful in assessing the present situation and understanding its multiple implications for human health. Basic information on human cases detected to date is set out in tabular form.

The publication has four chapters. Chapter 1 traces the evolution of the outbreaks of highly pathogenic H5N1 avian influenza, in humans and poultry, during 2004. For avian influenza viruses, this was an historically unprecedented year. Never before had so many countries been so widely affected by avian influenza in poultry in its most deadly form. Never before had any avian influenza virus caused such extremely high fatality in humans, taking its heaviest toll on children and young adults in the prime of life. The chapter also describes some disturbing new findings about the evolution of the virus that suggest a deepening threat. These changes have made surveillance for human cases, especially in rural areas, far more difficult.

Chapter 2 looks at past pandemics as a basis for assessing what may be on its way. It gives particular attention to patterns of international spread, population groups at special risk, and the effectiveness of the different public health and medical interventions that were applied. One conclusion is clear: past pandemics have been as unpredictable as the viruses that caused them. While the number of deaths has varied greatly, these events do have two consistent features. First, they always cause a sudden and sharp increase in the need for medical care, and this has great potential to overwhelm health services. Second, they always spread very rapidly to every part of the world.

The threat of H5N1 to human health, both immediately and in the future, is closely linked to the outbreaks of highly pathogenic avian influenza in poultry, as described in chapter 3. This chapter explains the disease and summarizes the history of past outbreaks in order to place the present situation in perspective and assess its implications for public health. In poultry, the H5N1 outbreaks have been a catastrophe for agriculture. They have affected the very backbone of subsistence farming in rural areas where large numbers of people depend on poultry for livelihood and food, and this, too, is of public health concern.

Against this background, the final chapter looks at the many activities set in motion during 2004 to improve pandemic preparedness and prevent further human cases. These activities range from intensified surveillance and faster reporting, through molecular characterization of viruses, to work on the development of a pandemic vaccine. WHO, including its outbreak response teams and staff in regional and country offices, has contributed directly to all these activities and helped them to move forward. The chapter also describes the role of antiviral drugs before and at the start of a pandemic, and provides advice on the use of non-medical interventions, such as quarantine and travel restrictions. On the positive side, the chapter shows how concern about the pandemic threat is leaving the world permanently better prepared to respond to any future pandemic caused by any influenza virus.

1 The H5N1 outbreaks in 2004: a pandemic in waiting?

Since 1959, human infections with avian influenza viruses have occurred on only 11 occasions. Of these, 6 have been documented since 2003.

At some unknown time prior to 1997, the H5N1 strain of avian influenza virus began circulating in the poultry populations of parts of Asia, quietly establishing itself. Like other avian viruses of the H5 and H7 subtypes, H5N1 initially caused only mild disease with symptoms, such as ruffled feathers and reduced egg production, that escaped detection. After months of circulation in chickens, the virus mutated to a highly pathogenic form that could kill chickens within 48 hours, with a mortality approaching 100%. The virus first erupted in its highly pathogenic form in 1997, but did not appear again. Then, towards the end of 2003, H5N1 suddenly became highly and widely visible.

The first report of something unusual came from the Republic of Korea in mid-December 2003. Veterinarians were concerned about the sudden death of large numbers of chickens at a commercial poultry farm near the capital city of Seoul. On 12 December, the country's chief veterinary officer sent an emergency report to the World Organisation for Animal Health (OIE) in Paris. The initial diagnosis was highly pathogenic avian influenza – a disease never before seen in the country. Both the origin of infection and mode of spread were listed as "unknown". By 16 December, the disease had spread to another two farms, and laboratory tests had identified the causative agent: the H5N1 strain.

That finding grabbed the immediate attention of health experts. Of all viruses in the vast avian influenza pool, H5N1 is of particular concern for human health for two reasons. First, H5N1, though strictly an avian pathogen, has a documented ability to pass directly from birds to humans. Second, once in humans, H5N1 causes severe disease with very high mortality. These two features combine to make H5N1 of concern for a third and greater reason: its potential to ignite an especially severe pandemic.

Cumulative human cases of avian influenza since 1959

Virus	Cases	Deaths
H5N1	70	**43**
all other avian influenza viruses	101	**1**

The 1997 outbreak in Hong Kong SAR

The first documented occurrence of H5N1 infection in humans involved 18 cases, of which 6 were fatal. Ages ranged from 1 to 60 years, with more than half of cases occurring in children aged 12 years or younger.

In severe cases, disease features included primary viral pneumonia and multiple organ failure.

Cases occurred in two waves: 1 case in May and 17 during November and December.

Molecular studies showed that viruses from humans and poultry were virtually identical, indicating that the virus jumped directly from birds to humans. Most human cases could be traced to direct contact with poultry.

The absence of disease in two high-exposure groups – poultry workers and cullers – indicates that H5N1 did not cross easily from birds to humans.

Antibodies to the H5 virus subtype were found in blood samples taken from family members and health care workers in close contact with patients. Very limited human-to-human transmission may have occurred, but was of low efficiency and did not cause symptoms or disease.

The outbreak ended after all of Hong Kong SAR's 1.5 million poultry were slaughtered within three days (29–31 December).

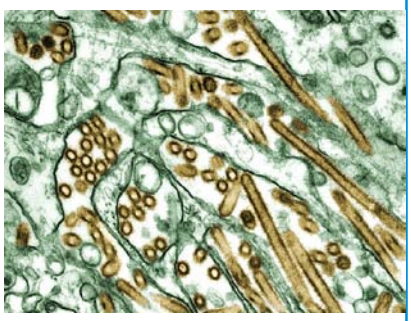
Historically, human infections with avian influenza viruses have been extremely rare. Most of these viruses have caused only mild illness in humans, often in the form of viral conjunctivitis, followed by full recovery. H5N1 has been the exception. In the first documented instance of human infection, the virus caused 18 cases, of which 6 were fatal, in China, Hong Kong Special Administrative Region (Hong Kong SAR)* in 1997. The cases coincided with outbreaks of highly pathogenic H5N1 in poultry on farms and in live markets. Many experts believe that the destruction, within three days, of Hong Kong SAR's entire poultry population of 1.5 million birds averted a pandemic by immediately removing opportunities for further human exposure. That action was subsequently vindicated by evidence that the virus had begun to mutate in a dangerous way.

A striking feature of the Hong Kong SAR outbreak was the presence of primary viral pneumonia in severe cases. When pneumonia occurs in influenza patients, it is usually a complication caused by a secondary bacterial infection. In the H5N1 cases, pneumonia was directly caused by the virus, did not respond to antibiotics, and was frequently rapidly fatal. With one exception, none of these patients had underlying disorders that could explain the severe course of the disease.

In February 2003, H5N1 again caused human cases, this time in a Hong Kong SAR family with a recent travel history to southern China. The 33-year-old father died, but his 9-year-old son recovered. A second child, an 8-year-old girl, died of a severe respiratory illness in mainland China; she was not tested and the cause of her illness will never be known. That small but ominous event convinced many experts that the virus was still circulating in mainland China – a part of the world long considered the epicentre of influenza virus activity and the birthplace of pandemics.

The Hong Kong SAR experience of 1997 clearly demonstrated the pandemic potential of H5N1 and made it a prime suspect to watch. It also altered understanding of how a new pandemic virus might emerge. Apart from being highly unstable and prone to small mutational errors, influenza viruses have a segmented genome, consisting of eight genes, that allows easy swapping of genetic material – like the shuffling of cards – when a host is coinfected

* References to Hong Kong SAR include mentions of the territory before 1997.



H5N1: a virus with proven pandemic potential
(Source: CDC Public Health Image Library).

with two different viruses (Box 1). The pandemics of 1957 and 1968 are known to have been caused by new viruses, containing both human and avian genes, that emerged following a reassortment event in which viruses from the two species coinfected the same cell and exchanged genes. Prior to 1997, pigs were thought to be the obligatory mixing vessel for reassortment of viruses, as they possess receptors for both avian and human influenza viruses on the cells of their respiratory tract. The Hong Kong SAR event, however, demonstrated that humans could be directly infected with a purely avian influenza virus, such as H5N1, and thus also serve as the mixing vessel for the exchange of virus genes. That finding gave human infections with H5N1 added significance as a warning signal that a pandemic might be imminent.

A rapid escalation of concern

5 January 2004
Viet Nam alerts WHO to an unusual cluster of very severe respiratory disease in children at a hospital in Hanoi.

8 January
H5N1 is found in dead chickens in the southern part of Viet Nam.

11 January
H5N1 – a purely avian virus – is detected in samples from fatal cases in Hanoi.

12 January
Japan announces detection of H5N1 in poultry, becoming the third affected country in Asia.

14 January
WHO sends an emergency alert, placing its partners in the Global Outbreak Alert and Response Network (GOARN) on stand-by.

19 January
The first GOARN team arrives in Viet Nam, where five fatal cases have now been confirmed.

23 January
Thailand reports H5N1 in humans and poultry.

High alert

In January 2004, WHO officials were understandably on high alert for any signs that H5N1 might again cross the species barrier to cause disease in humans. On 5 January, Vietnamese health authorities informed the WHO office in Hanoi of an unusual cluster of severe respiratory disease in 11 previously healthy children hospitalized in Hanoi. Of these patients, 7 had died and 2 were in critical condition. Treatment with antibiotics produced no response, and a viral cause was suspected. Infection with the SARS virus was considered but did not seem likely. For unknown reasons, SARS tended to spare children, rarely causing severe illness, and was never considered a paediatric disease. WHO was asked to assist in the Hanoi investigation, and arrangements were made for testing of patient specimens at WHO reference laboratories.

Concern intensified on 8 January, when Viet Nam confirmed that large die-offs of poultry at two farms in a southern province were caused by highly pathogenic H5N1. At that time, the northern part of the country was not known to be experiencing outbreaks in poultry, and no epidemiological evidence suggested a link between the unidentified disease in Hanoi and exposure to poultry infected with H5N1. Nonetheless, the level of suspicion was high and concern remained great.

Box 1. **Influenza A viruses: sloppy, capricious, and promiscuous**

Influenza viruses are grouped into three types, designated A, B, and C. Viruses of the C types are common but usually cause no symptoms or only very mild respiratory illness. They are not considered of public health concern. Type B viruses cause sporadic outbreaks of more severe respiratory disease, particularly among young children in school settings. Both B and C viruses are essentially human viruses; C viruses are stable, but A and B viruses are prone to mutation.

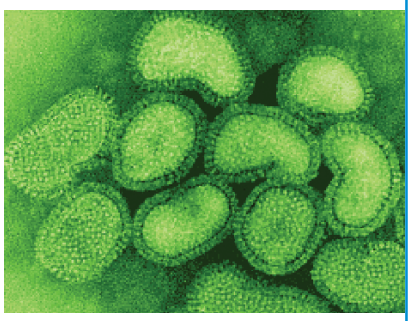
Of greatest concern are the influenza A viruses. They have characteristics that make influenza A one of the most worrisome of all the well-established infectious diseases. These viruses mutate much more rapidly than type B viruses, and this gives them great flexibility. In addition to humans, they infect pigs, horses, sea mammals, and birds. They have a large number of subtypes, all of which are maintained in aquatic birds, providing a perpetual source of viruses and a huge pool of genetic diversity. As a result of their unique features, influenza A viruses regularly cause seasonal epidemics in humans that take a heavy toll in morbidity and excess mortality, especially when pneumonia is a complication. At recurring yet unpredictable intervals, influenza A viruses cause pandemics.

Scientists describe these viruses as sloppy, capricious, and promiscuous. Their labile and unpredictable nature is notorious. As they lack a proof-reading mechanism, the small errors that occur when the virus copies itself are left undetected and uncorrected. As a result, influenza A viruses undergo constant stepwise changes in their genetic make-up. This strategy, known as antigenic drift, works well as a short-term survival tactic for the virus: the speed with which slight variations develop keeps populations susceptible to infection. Though small, the changes are sufficient to evade the defences of the immune system. Populations protected, whether because of previous infection or vaccination, against one virus strain will not be protected when the next slightly different virus arrives. A new vaccine* must therefore be produced for each winter season in temperate climates, when epidemics of influenza almost always occur. Influenza viruses circulate year-round in tropical and subtropical areas.

As yet another feature, the genetic content of these viruses is neatly segmented into eight genes. This facilitates the most greatly feared event: the swapping of gene segments during coinfection with human and avian influenza viruses, creating a new virus subtype that will be entirely or largely unfamiliar to the human immune system. If this new "hybrid" virus contains the right mix of genes, causing severe disease and allowing easy and sustainable human-to-human transmission, it will ignite a pandemic. This strategy, known as antigenic shift, works well as a long-term survival tactic: immunologically, a new virus subtype starts from scratch and is guaranteed a very large population of susceptible hosts.

Pandemics are rare but recurring events, invariably associated with great morbidity, significant mortality, and considerable social and economic disruption. Population vulnerability, combined with the highly contagious nature of influenza viruses, means that all parts of the world are rapidly affected, usually within less than a year.

* *Vaccines for seasonal influenza are trivalent vaccines. They confer protection against two influenza A viruses and one influenza B virus circulating in a given season.*



Influenza viruses are highly unstable, genetically labile, and well adapted to elude host defences.

The situation altered dramatically on 11 January, when a WHO reference laboratory announced detection of H5N1 in specimens from 2 of the fatal cases in Hanoi. Confirmation of H5N1 in a third fatal case was received the following day. That same day, in another ominous development, Japan reported a large outbreak of highly pathogenic avian influenza, caused by the H5N1 strain, at a single poultry farm in Kyoto prefecture. In Viet Nam, the extent of poultry outbreaks was rapidly becoming apparent: within three weeks following the initial report, more than 400 outbreaks were detected throughout the country, affecting at least 3 million poultry. An agricultural nightmare had begun.

The confirmation of human cases gave the outbreaks in poultry a new dimension. They were now a health threat to populations in affected countries and, possibly, throughout the world. All prerequisites for the start of a pandemic had been met save one, namely the onset of efficient human-to-human transmission. Should the virus improve its transmissibility, everyone in the world would be vulnerable to infection by a pathogen – passed along by a cough or a sneeze – entirely foreign to the human immune system.

Prerequisites for the start of a pandemic

Research has identified three prerequisites for the start of a pandemic.

1. A novel virus subtype must emerge to which the general population will have no or little immunity.
2. The new virus must be able to replicate in humans and cause serious illness.
3. The new virus must be efficiently transmitted from one human to another; efficient human-to-human transmission is expressed as sustained chains of transmission causing community-wide outbreaks.

Pandemic alert: the response plan

Fully aware of these risks, WHO activated its pandemic preparedness plan, alerted its network laboratories, and placed response teams on standby. WHO also mapped out a response plan with three objectives: to avert a pandemic, to control the outbreak in humans and prevent further cases, and to conduct the research needed to monitor the situation and improve preparedness, including the immediate development of a pandemic vaccine.

To meet the first two objectives, the foremost need was to reduce opportunities for human exposure by eliminating the virus from its poultry host. Fortunately, the measures for doing so were being vigorously implemented in line with recommendations issued by OIE and the Food and Agricultural Organization of the United Nations (FAO). These called for the immediate culling of infected or exposed birds, quarantine and disinfection of farms, control of animal movements, and implementation of strict biosecurity

The naming of influenza viruses

Influenza A viruses get their names from two sets of protein spikes that jut from the outer surface of the virus. The haemagluttinin, or HA, spike governs virus binding and entry into cells, where copies of the virus are produced. There are 15 HA subtypes, designated H1 to H15. Immunity to an HA subtype – whether conferred by vaccination or previous exposure to that subtype – protects against infection, but only for that subtype.

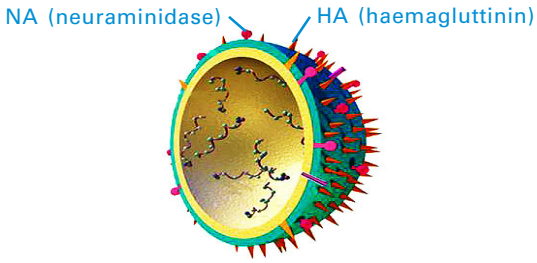
The neuraminidase, or NA, spike governs the release of newly formed virus from infected cells into the host's body. There are 9 NA subtypes, designated N1 to N9. Immunity to an NA subtype reduces the amount of virus released from a cell, resulting in less severe disease.

All 15 HA subtypes and 9 NA subtypes have been detected in free-flying birds. They provide a huge – and highly mobile – pool of genetic diversity.

An individual virus strain is identified by the subtypes of HA and NA protein spikes on its surface. It is named by the letters H and N, each followed by the number of the subtype.

For pandemics, a novel HA subtype is decisive, as it determines population susceptibility. To date, only subtypes H1, H2, and H3 are known to have circulated in humans for at least a century.

As a virus from the H5 subtype will be foreign to the immune system of everyone alive today, vulnerability to an H5N1-like pandemic virus would be universal.



measures on farms. WHO added to these measures by recommending that poultry cullers wear protective clothing and take antiviral drugs as a precaution. Vaccination against normal seasonal influenza was also recommended as a way to reduce chances that this high-risk group might be coinfected with an avian and a human virus, this giving the viruses an opportunity to exchange genes.

In pursuing the third objective, researchers could draw on a growing body of knowledge about pandemic viruses in general and H5N1 in particular that arose following the close call of 1997. This intensified research had done much to characterize H5N1 at the molecular level, track its evolution in avian species, improve understanding of its pathogenicity in humans, and define its pandemic potential. By the third week of January, laboratories in the influenza network had determined that the 2004 virus had mutated considerably since the Hong Kong SAR cases in 1997 and 2003. Work done to prepare a vaccine against an H5N1-like pandemic virus would have to start again from scratch. H5N1 viruses from 2004 also showed resistance to one of only two classes of antiviral drugs available to prevent severe disease. Fear increased that, should a pandemic begin quickly, the world would be caught short with little in the way of medical tools to fight back.

The next major blow came on 23 January, when Thailand announced its first human cases of H5N1 in two young boys. A large outbreak at a poultry farm, affecting nearly 70 000 birds, was announced on the same day. During the remaining days of January, a small but steady number of human cases, most of which were fatal, continued to be reported from both Viet Nam and Thailand. These cases occurred against a backdrop of poultry outbreaks that seemed to worsen as each day passed. During the last week of January, Thailand reported 156 outbreaks in 32 provinces affecting 11 million birds.

Response teams for the WHO Global Outbreak Alert and Response Network (GOARN) were immediately despatched to both Viet Nam and Thailand to support the work of local health officials. WHO also issued a series of guidelines to facilitate heightened surveillance and case detection, laboratory diagnosis according to international standards, and infection control to prevent amplification of cases in health care settings.

Countries with outbreaks largely confined to commercial farms faced the best prospects for successful control.

Among the January cases, two sisters in Viet Nam became the focus of intense investigation when evidence suggested they might represent the first instance of human-to-human transmission (Box 2). While no firm conclusions could be reached, the possibility could not be ruled out that the women, both of whom died from confirmed H5N1 infection, acquired the virus from their brother, who also suffered from a fatal respiratory infection but was not tested.

Outbreaks in poultry: historically unprecedented

Prior to the outbreaks of 2004, highly pathogenic avian influenza was considered a rare disease in poultry.

Near the end of January, the situation in poultry exploded. Outbreaks in the Republic of Korea, Viet Nam, Japan, and Thailand were followed by reports of the same disease in Cambodia, Lao People's Democratic Republic, Indonesia, and China. Most of these countries had never before experienced outbreaks of highly pathogenic avian influenza caused by any strain.

Of these countries, Japan and the Republic of Korea were the most fortunate, as their outbreaks remained largely confined to commercial farms where outbreaks are readily detected and conditions are compatible with rapid implementation of control measures. Thailand and Viet Nam were the most severely affected; outbreaks rapidly extended to all parts of both countries, including large rural areas where nearly every household kept a flock of free-ranging chickens and ducks. China experienced outbreaks in more than half of its 31 provinces and municipalities. In that country, home to more than 13 billion chickens, of which 60% are raised on small farms, compulsory vaccination was introduced to supplement standard control measures. From the outset, neither Cambodia nor Lao People's Democratic Republic was in a position to conduct similarly aggressive control campaigns, as neither country had sufficient surveillance systems or resources. In Indonesia, health authorities and facilities were fully occupied by a large outbreak of dengue fever that began at the start of January. That outbreak, which continued through April, caused more than 58 000 cases and 650 deaths, and left few resources in reserve to deal with an animal disease.

More than 120 million birds died or were destroyed within three months. (Sources, top: WHO/ Huang Liang-China Daily; bottom: AP)

By the start of February, it was clear that the H5N1 outbreaks in poultry were historically unprecedented. Prior to the Asian outbreaks, highly pathogenic avian influenza was considered a rare disease. Beginning in 1959, when the disease was first recognized, only 21 outbreaks occurred worldwide prior to 2004, with the majority in Europe and North America. Of these, only seven resulted in significant spread to numerous farms, and only one spread to other countries.

Never before had highly pathogenic avian influenza caused outbreaks in so many countries at once. Never before had the disease spread so widely and rapidly to affect such huge geographical areas. Never before had it caused such enormous consequences for agriculture – from large commercial farms to the roots of rural subsistence agriculture. In several affected countries, 50% to 80% of poultry are raised in small rural households where they provide a source of income, around 30% of total dietary protein, and an "insurance policy" for raising cash when medicines need to be purchased.

In an historically unprecedented situation, anything can happen. During the second phase, many things did.

In the Asian outbreaks, more than 120 million birds died or were destroyed within three months. That figure is higher than the combined total from all previous large outbreaks of highly pathogenic avian influenza recorded throughout the world over four decades.

The massive control efforts had an impact, and the outbreaks declined sharply during March except in Thailand, where sporadic outbreaks continued to be reported through April. Predictably, new human cases dwindled then ceased, with the last occurring in mid-March in Viet Nam. From January through March, Viet Nam and Thailand together reported 35 cases, of which 24 were fatal (Tables 1 and 2). These figures made the outbreak in humans almost twice the size of that in 1997, and far more deadly.

In an historically unprecedented situation involving a virus as mutable as influenza, anything can happen. And, as the second phase would prove, many things did.

Thousands of poultry workers, often inadequately protected, experienced intense exposures to the virus, giving it ample opportunities to reassort (Source: AP).

The second phase: more cases – and more surprises from the virus

Virus activity for H5N1 is known to peak from November through March. As spring turned to summer, the worst seemed to be over. Two questions hung in the air. First, had the massive control efforts managed to eliminate the virus? Past experience argued strongly against that prospect. Even under far more favourable circumstances, with outbreaks concentrated in a few commercial farms in a small geographical area, complete elimination of the virus typically required two to three years. More likely, H5N1 was merely quiescent, or possibly still active in rural areas where deaths in small backyard flocks were likely to escape detection.

The second question was more puzzling: why had H5N1 failed to reassort? It had certainly had ample opportunities to do so. Virological surveillance demonstrated the co-circulation of normal human influenza strains during peak H5N1 activity. Many thousands of workers, often inadequately protected, had experienced intense exposures during culling operations. The answer might lie in sheer statistical luck – not many human cases had been reported. Many experts believed, however, that numerous other cases, too mild to be detected, were almost certainly occurring, thus expanding opportunities for coinfections.

Though the outbreaks in poultry were much smaller, human cases again occurred.

Events beginning in July answered the first question decisively and rendered the second temporarily irrelevant. Fresh outbreaks were reported in Cambodia, China, Indonesia, Thailand, and Viet Nam. In late August, Malaysia – a country spared during the first wave – reported its first poultry outbreaks. Compared with the first wave, these outbreaks were much smaller, affecting less than 1 million poultry during the summer and autumn of 2004. They also proved remarkably tenacious. Several countries, on the verge of declaring themselves free of H5N1 outbreaks, suffered setbacks when the virus cropped up in yet another flock or farm.

Despite the much smaller areas and numbers of birds affected, human cases again occurred. From August through October, 9 cases, of which 8 were fatal, were reported in Thailand (5) and Viet Nam (4). Most cases occurred in rural areas, suggesting a community-wide threat to health in large and remote areas. In

The July 2004 outbreaks in poultry

Country	No. of birds affected[a]
Cambodia	23
China	8 000
Indonesia	2 500
Thailand	123 000
Viet Nam	17 000

[a] As reported to OIE.

Recent events indicate that the virus is expanding its mammalian host range. In October 2004, H5N1 caused a large and deadly outbreak in captive tigers – a species not considered susceptible to disease from any influenza A virus.

September, Thailand reported its first probable case of human-to-human transmission in a family cluster. That finding initiated a massive door-to-door search, involving around 1 million volunteers. No further clusters suggesting continuing transmission were detected.

The newly reported cases brought the total since January, in the two countries, to 44, of which 32 were fatal. When these cases are viewed together, two features are striking: the overwhelming concentration of cases in previously healthy children and young adults, and the very high mortality. No scientific explanation for this unusual disease pattern is presently available. Nor is it possible to calculate a reliable case-fatality rate, as mildly symptomatic disease may be occurring in the community, yet escape detection.

Although the second wave of outbreaks has been far less conspicuous, it has demonstrated several unusual features. These suggest that the virus may be evolving in ways that increasingly favour the start of a pandemic.

Although the second wave of outbreaks has been far less conspicuous in the numbers of humans and animals affected, it has demonstrated several unusual features. These features, confirmed by findings from recent epidemiological and laboratory studies, suggest that the virus may be evolving in ways that increasingly favour the start of a pandemic.

Evidence strongly indicates that H5N1 is now endemic in parts of Asia, having established a permanent ecological niche in poultry. The risk of further human cases will continue, as will opportunities for a pandemic virus to emerge. Studies comparing virus samples over time show that H5N1 has become progressively more pathogenic in poultry and in the mammalian mouse model, and is now hardier than in the past, surviving several days longer in the environment. Evidence further suggests that H5N1 is expanding its mammalian host range. For example, the virus has recently been shown to cause severe disease and deaths in species, including experimentally infected domestic cats and naturally infected captive tigers, not previously considered susceptible to disease caused by any influenza A virus. The outbreak in tigers, which began on 11 October in Thailand, had a second disturbing feature. Altogether, 147 tigers in a population of 418 developed high fevers, usually progressing to severe pneumonia, as a result of H5N1 infection. Preliminary investigation found no evidence of tiger-to-tiger transmission. As infection was linked to the feeding of chicken carcasses, the amount of infected chicken moving in the food supply must have been great to have caused disease in so many large animals.

New evidence suggests that domestic ducks are now excreting H5N1 in its highly lethal form without showing signs of illness. This "silent" role of domestic ducks may help explain why some recent human cases cannot be linked to contact with diseased poultry.

Another surprising finding is the detection of H5N1, in its highly pathogenic form, in dead migratory birds. Wild waterfowl are the natural reservoir of all influenza A viruses and have historically carried low-pathogenic viruses, in evolutionary equilibrium, without showing symptoms or succumbing to disease. Although more evidence is needed, the finding suggests that the role of migratory waterfowl in the evolution and maintenance of highly pathogenic H5N1 may be changing. The international threat from infected wild birds was vividly demonstrated in mid-October, when airport authorities in Belgium detected two smuggled mountain hawk eagles carried on a flight from Thailand. Both birds tested positive for H5N1 in its highly pathogenic form.

Another disturbing finding is the detection of H5N1 in dead migratory birds. Wild waterfowl are the natural reservoir of all influenza A viruses and do not normally develop any symptoms.

Of greater concern, asymptomatic domestic ducks have recently been shown experimentally to excrete H5N1 in its highly pathogenic form, suggesting an important silent role in maintaining transmission. As these ducks can excrete large quantities of lethal virus without the warning signal of visible illness, it has become difficult to give rural residents realistic advice on how to avoid exposure. The role of domestic ducks may help to explain why several recent human cases could not be traced to contact with diseased poultry. It is also highly likely that apparently healthy ducks play a role in maintaining transmission by silently seeding outbreaks in other poultry.

The present concentration of poultry outbreaks in rural areas, where most households maintain free-ranging flocks and ducks and chickens mingle freely, is of particular concern, especially as many households depend on these birds for income and food. Such outbreaks may escape detection, are difficult to control, and increase the likelihood of human exposures, which may occur when children play in areas shared by poultry or when families slaughter or prepare birds for consumption.

Taken together, these changes in the ecology of the disease and behaviour of the virus have created multiple opportunities for a pandemic virus to emerge. No one knows whether the present window of opportunity to intensify preparedness will remain open or close abruptly. Experts readily agree, however, that H5N1 has demonstrated considerable pandemic potential. With the virus now endemic, the probability that this potential will be realized has increased.

Changes in 2004: an evolving virus

H5N1 has found a new ecological niche in poultry in parts of Asia.

The virus is now more deadly in poultry and in the mammalian mouse model.

New animals – cats and tigers – are becoming infected for the first time, suggesting the virus is expanding its host range.

Domestic ducks are excreting large quantities of virus without showing symptoms.

Viruses from 2004 survive longer in the environment than viruses from 1997.

The virus is killing at least some wild migratory birds.

These changes have created multiple opportunities for a pandemic virus to emerge.

Assessment of the threat

As virus activity peaks from November through March, further evolution of the situation in early 2005 can be anticipated. In December, Viet Nam reported its largest outbreaks in poultry since September. A third wave of human cases, again in young and previously healthy children and adolescents, began during the last days of December. Good surveillance in the Republic of Korea detected low-pathogenic avian influenza, caused by H5N2, in December. The situation in other countries of concern is uncertain because of the absence of high-quality surveillance. It is clear, however, that the full epidemiological potential of H5N1 is still unfolding.

Once again, many questions hang in the air. Why has H5N1 failed to reassort? Why have human cases occurred in only two countries? Have cases occurred elsewhere, yet slipped through the surveillance net? Or are the viruses in Thailand and Viet Nam somehow different from those causing outbreaks elsewhere, perhaps intrinsically more apt to infect humans? Although these questions have prompted investigations, no clear answers have as yet emerged. Nor is it known with certainty why H5N1 causes such severe disease in children and young adults, with death frequently following multi-organ failure in addition to severe respiratory disease.

Recent publications have suggested some similarities between H5N1 and the virus responsible for the 1918 pandemic.

The fact that H5N1 has not yet reassorted prompts consideration of the second mechanism by which a pandemic virus can emerge: adaptive mutation. This mechanism involves stepwise changes, which occur as the virus mutates during infection of humans or other mammals, that gradually allow the virus to improve its transmissibility among humans. Adaptive mutation would likely be expressed in a series of independent chains of very limited human-to-human transmission.

The pandemics of 1957 and 1968 are known to have been caused by the exchange of genes between avian and human influenza viruses. The 1918 pandemic, however, is believed by many experts to have begun following adaptive mutation of an avian virus which acquired, following stepwise changes during subsequent human infections, the adaptations needed to sustain efficient human-to-human transmission. Recent publications have suggested other similarities between H5N1 and the 1918 virus in the severity

With the virus now entrenched in rural areas, the rapid elimination of the disease in poultry no longer appears feasible.

of disease, its concentration in the young and healthy, and the occurrence of primary viral pneumonia in the absence of secondary bacterial infection. The present high lethality of H5N1 would probably not be retained in an H5N1-like pandemic virus, as an avian influenza virus is expected to lose pathogenicity when it acquires the improved transmissibility needed to ignite a pandemic. More certain – and more relevant to preparedness planning – is the fact that no virus of the H5 subtype has probably ever circulated among humans, and certainly not within the lifetime of today's world population. Population vulnerability to an H5N1-like pandemic virus would be universal.

No virus of the H5 subtype has probably ever circulated among humans. Population vulnerability to an H5N1-like virus would be universal.

Many experts regard pandemic influenza as the most significant global public health emergency caused by a naturally occurring pathogen. While the timing of this event cannot be predicted, rapid international spread is certain once a virus with the appropriate characteristics emerges. In the previous century, pandemics travelled from continent to continent along sea lanes, with global spread complete within six to eight months. As demonstrated by SARS, spread along the routes of international air travel could shorten this time considerably. The speed of international spread has no direct effect on mortality, but could compromise response capacity should large parts of the world experience almost simultaneous outbreaks. Many of the public health interventions that successfully contained SARS will not be effective against a disease that is far more contagious, has a very short incubation period, and can be transmitted prior to the onset of symptoms.

With the virus now endemic in poultry and expanding its avian and mammalian host range, the objective of averting a pandemic by eliminating further opportunities for human exposure no longer appears feasible. A second opportunity to avert a pandemic could arise if the virus gradually improves its transmissibility among humans through adaptive mutation. Clusters of cases would be indicative, and sensitive surveillance might detect them. It is not known, however, whether rapid intervention with a pandemic vaccine – if available in time – and antiviral drugs – if quantities are sufficient – could successfully interrupt transmission, as this has never been attempted.

The entrenched presence of H5N1 in rural areas and its newfound silent reservoir in apparently healthy domestic ducks greatly

complicate efforts to prevent further human cases. They also create uncertainty about the ability of surveillance systems to provide an early warning at the start of improved human-to-human transmission, should this occur gradually. In the alternative scenario, in which a fully transmissible pandemic virus emerges following a reassortment event, the resulting explosion of cases would be difficult for any surveillance system to miss.

Box 2. **Investigations of human-to-human transmission**

Suspicions that human-to-human transmission may have taken place usually arise when cases occur close together in time and place among persons, such as family members or health care workers, known to have had close contact with a case.

Such clusters of cases have been detected on several occasions during the 2004 outbreaks. All such instances involved family members. To date, no H5N1 cases have been detected in health care workers despite several instances of close, unprotected contact with severely ill patients.

Investigations of human-to-human transmission involve extensive detective work to gather data on individual cases, giving particular attention to dates, times, places, and potential sources of exposure. All possible exposures are considered, systematically evaluated, and gradually narrowed down to the most plausible.

Sources of information range from face-to-face interviews to sampling of animals and environmental areas, to analysis of viruses and hospital records.

Suspicions that human contact was the source of exposure are raised when dates of onset between two cases with close contact fall within the incubation period and no alternative source of exposure appears plausible. In most such investigations, the final conclusion is a judgement call based on the weight of evidence from all available sources.

Whenever possible, viruses are isolated from cases, sequenced, analysed, and compared. For a disease such as avian influenza, the most conclusive evidence would come when two human cases have identical viruses that differ from those circulating in animals. Such a finding literally catches the virus red-handed.

Evidence that a virus has acquired human genes would be an alarming finding, as it suggests reassortment or adaptive mutation towards a more readily transmissible form. At the same time, evidence that a virus remains purely avian does not exclude the possibility that it was transmitted from one human to another, as purely avian H5N1 has amply demonstrated its ability to infect humans.

Table 1. Human cases, Viet Nam

First phase

No.	Sex	Age	Province	Onset	Outcome
1	female	12 years	Ha Nam	25.12.03	died 30.12.03
2	male	10 years	Bac Ninh	29.12.03	died 11.01.04
3	female	30 years	Ha Nam	1.01.04	died 9.01.04
4	male	5 years	Nam Dinh	23.12.03	died 8.01.04
5	female	8 years	Ha Tay	11.01.04	died 17.01.04
6	female	8 years	Ho Chi Minh City	13.01.04	recovered
7	male	13 years	Ho Chi Minh City	14.01.04	died 22.01.04
8	female	23 years	Thai Binh	10.01.04	died 23.01.04
9	female	30 years	Thai Binh	10.01.04	died 23.01.04
10	male	19 years	Bac Giang	11.01.04	recovered
11	female	20 years	Bac Ninh	9.01.04	recovered
12	male	18 years	Lam Dong	25.01.04	died 2.02.04
13	female	16 years	Soc Trang	21.01.04	died 3.02.04
14	female	17 years	Tay Ninh	12.01.04	died 27.01.04
15	female	6 years	Dong Nai	24.01.04	died 3.02.04
16	male	24 years	Lam Dong	29.01.04	died 3.02.04
17	male	23 years	Lam Dong	28.01.04	recovered
18	male	28 years	Binh Phuoc	29.01.04	died 9.02.04
19	male	22 years	Ho Chi Minh City	31.01.04	recovered
20	male	15 years	Thanh Hoa	9.02.04	recovered
21	male	4 years	Lam Dong	5.02.04	died 18.02.04
22	female	16 months	Dong Nai	14.02.04	recovered
23	male	12 years	Tay Ninh	10.03.04	died 15.03.04

Second phase

24	male	4 years	Ha Tay	19.07.04	died 2.08.04
25	female	1 year	Ha Tay	27.07.04	died 4.08.04
26	female	25 years	Hau Giang	31.07.04	died 6.08.04
27	male	14 months	Hanoi	28.08.04[a]	died 5.09.04

Third phase

28	female	16 years	Tay Ninh	24.12.04	died 8.01.05
29	male	6 years	Dong Thap	30.12.04[a]	died 30.12.04
30	male	9 years	Tra Vinh	2.01.05[a]	died 4.01.05
31	female	18 years	Tien Giang	1.01.05	died 19.01.05
32	female	35 years	Tra Vinh	6.01.05	died 17.01.05
33	female	18 years	Hau Giang	1.01.05[a]	died 10.01.05

[a] Date of hospitalization
Average age: 15 years

Table 2. Human cases, Thailand

First phase

No.	Sex	Age	Province	Onset	Outcome
1	male	7 years	Suphanburi	3.01.04	died 3.02.04
2	male	6 years	Kanchanaburi	6.01.04	died 25.01.04
3	male	6 years	Sukhothai	7.01.04	died 27.01.04
4	female	58 years	Suphanburi	19.01.04	died 2.01.04
5	male	6 years	Kanchanaburi	24.01.04	died 2.02.04
6	male	13 years	Chaiyaphum	29.01.04	died 13.02.04
7	male	2 years	Suphanburi	25.01.04	recovered
8	female	27 years	Uttaradit	20.01.04	recovered
9	male	5 years	Khon Kaen	21.01.04	died 3.02.04
10	female	46 years	Lopburi	3.02.04	recovered
11	male	31 years	Nakhon Ratchasima	13.02.04	recovered
12	female	39 years	Ayadhaya/Patumthani[a]	1.03.04	died 12.03.04

Second phase

13	male	18 years	Prachin Buri	31.08.04	died 8.09.04
14	female	32 years	Kamphaeng Phet	16.09.04	recovered
15	female	26 years	Nonthanburi	11.09.04	died 20.09.04
16	female	9 years	Phetchabun	23.09.04	died 3.10.04
17	female	14 years	Sukhothai	8.10.04	died 19.10.04

[a] Patient lived in Ayadhaya but spent her weekends in Patumthani.
Average age: 20 years

2 Lessons from past pandemics

Pandemics are remarkable global events. They spread to all parts of the world very quickly and cause illness in more than 25% of the total population.

Explosive and unusually deadly outbreaks of influenza have occurred throughout recorded history, probably originating in the earliest cities where humans lived crowded together in close proximity to domestic animals. True pandemics, characterized by sharp increases in morbidity and mortality and rapid spread throughout the world, have been reliably documented since the 16th century. Since then, each century has seen an average of three pandemics occurring at intervals ranging from 10 to 50 years.

The speed with which pandemics can encircle the globe is well illustrated by historical accounts taken from times when international travel was far slower than today. For example, the pandemic of 1580, which began in Asia, spread to all continents in just over a year; the whole of Europe was engulfed in less than six months.

Pandemics are always remarkable global events. Caused as they are by a highly contagious virus to which populations have little if any immunity, they benefit from almost universal susceptibility to infection. This gives them their distinctive features: they spread to all parts of the world very quickly, usually within less than a year, and cause illness in more than a quarter of the total population. It is this abrupt upsurge in illness, outstripping response capacity, that makes pandemics so disruptive, in addition to the excess mortality they invariably cause.

The pandemics of past centuries have typically hit world populations like the epidemiological equivalent of a flash flood. They have started abruptly without warning, swept through populations with ferocious velocity, and left considerable damage in their wake. They could not be stopped, but peaked rapidly and then subsided almost as abruptly as they began. Recovery was, however, impeded

The second wave, which began almost simultaneously in France, Sierra Leone, and the USA, saw explosive outbreaks with a 10-fold increase in deaths.

by the tendency of pandemics to recur in second and sometimes third waves, often causing more severe disease. Subsequent waves often began simultaneously in several different parts of the world, intensifying the abrupt disruption at the global level.

The three pandemics of the 20th century are the best documented in terms of their origins (Box 3), patterns of international spread, and impact. They provide a useful basis for preparedness planning as they illustrate both worst- and best-case scenarios, show the many different turns a pandemic can take, and allow assessment of some control interventions.

1918–1919

Estimated deaths
(in millions)

1918 pandemic	40
World War I	8.3

Of all pandemics, the one that began in 1918 – in a world wearied by war – is generally regarded as the most deadly disease event in human history. Not only did it kill upwards of 40 million people, but it did so in less than a year. For comparison, total military deaths on all fronts during the first world war have been estimated at 8.3 million over four years.

The beginnings were inauspicious. The first simultaneous outbreaks were detected in March 1918 in Europe and in different states within the USA. The infection then travelled back and forth between Europe and the USA via ships carrying troops and then, by land and sea, to Asia and Africa. That first wave, which took place in the spring and summer, was highly contagious but not especially deadly; its significance as a warning signal was missed. When the second wave began near the end of August, no country was prepared.

The first wave was highly contagious but not especially deadly, and its significance as a warning signal was missed. When the deadly lethal wave arrived, no country was prepared.

The experience was unprecedented. That second wave, which began almost simultaneously in France, Sierra Leone and the USA, saw explosive outbreaks characterized by a 10-fold increase in the death rate. The disease had features that were not seen before and, fortunately, have not been seen since. Deaths from influenza, whether during seasonal epidemics or pandemics, usually occur at the extremes of the lifespan – in the very young or very old. “Spanish flu” preferred the prime of life, causing most

Spanish flu caused a form of viral pneumonia that could kill the perfectly fit within 48 hours or less.

deaths in young and healthy persons in the age range of 15 to 35 years. In a complete reversal of previous patterns, 99% of deaths occurred in people younger than 65 years.

As expected, many of the deaths in 1918 were from pneumonia caused by secondary bacterial infections. But Spanish flu also caused a form of primary viral pneumonia, with extensive haemorrhaging of the lungs, that could kill the perfectly fit within 48 hours or less. The disease was so severe and its clinical course so unfamiliar that influenza was not even considered when the first cases appeared. Doctors suspected cerebrospinal meningitis or, more grimly, a return of the Black Death.

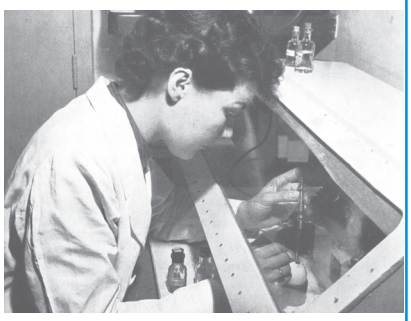
The disease was so severe and the symptoms so unfamiliar that some doctors initially feared a return of the Black Death.

Health authorities were at a loss. Antibiotics, which could have prevented many deaths from bacterial pneumonia, had not yet been discovered. An effective vaccine was out of the question: the first isolation of an influenza virus from humans would not take place until 1933. With no medical tools available, control efforts turned to the more prosaic measures of isolation, quarantine, good personal hygiene, use of disinfectants, and the prevention of public gatherings. These measures were imposed with varying degrees of severity and different levels of public support. Many populations began wearing gauze masks in public either voluntarily or under penalty of law. In some countries, people caught coughing or sneezing, unprotected, in public were fined or jailed. Public institutions, including schools, were often closed and public gatherings banned.

Quarantine and isolation were widely imposed, but probably did little to stop the contagion. Predictably, quarantine could delay spread somewhat but, having no impact on population susceptibility, could do nothing to reduce the numbers who would eventually fall ill. Australia was the notable exception. By maintaining a strict maritime quarantine, that country managed to stave off arrival of the epidemic until the start of 1919. By that time, the virus has lost some of its lethality, and Australia experienced a milder, though somewhat longer, period of influenza activity than elsewhere. Though less lethal, the virus retained its preference for the young and healthy, with 60% of deaths occurring in persons aged 20 to 45 years.

Why "Spanish" flu?

The designation of the 1918 pandemic as "Spanish" flu is a misnomer, as no evidence suggests the pandemic originated in that country or was more severe there than elsewhere. The first cases were detected in Europe and the USA. As Spain was neutral during the first world war, its media covered the epidemic there without restraint. The popular association of the 1918 pandemic with Spain (in name only) is thought to have arisen from that high-profile news coverage.



In 1957, the WHO global influenza network was 10 years old. Its laboratories played an essential role in rapidly isolating the virus and alerting the world to the onset of a pandemic.

During the course of the pandemic, an estimated 25% to 30% of the world population fell ill. The pace of spread and the rate of death outstripped response capacity at every level – from hospital beds to burial space, from medical supplies to coffins. No part of the world was spared. Densely populated India suffered more than 10 million deaths. In the more sparsely populated countries of sub-Saharan Africa, the epidemic moved easily from port cities to the remote hinterlands, killing 1.5 to 2 million people within a few weeks. There, as elsewhere, efforts to dampen spread through quarantines and the closing of markets made very little difference. Globally, the demographic effect was enormous; in many areas, life expectancy dropped by 10 years and more.

1957–1958

Within a week, network laboratories had analysed the virus and identified it as a completely new virus subtype. Using radio and telegraph despatches, WHO alerted the world.

The pandemic that began in 1957 was caused by a milder virus than the one responsible for the 1918 pandemic. In addition, the world was much better prepared to cope. Modern virology had arrived and knowledge about influenza viruses was progressing rapidly. Vaccines for seasonal epidemics had been developed and had already proven their value as the most effective method for prevention; where used, they reduced the incidence of seasonal influenza by two thirds or more. Antibiotics were available to treat complications, including bacterial pneumonia. The WHO Global Influenza Surveillance Network – a virological monitoring and early warning system – was 10 years old (Box 4). The 1957 pandemic was its first major test; it performed admirably.

At the start of May, WHO received news of extensive influenza epidemics in Hong Kong and Singapore. Subsequent information revealed that epidemics had begun at the end of February in a single province of China, spread throughout the country in March, and reached Hong Kong SAR in the middle of April. By mid-May, the virus had been isolated by laboratories in Japan and Singapore. Within a week, laboratories in the WHO network had analysed the virus and identified it as a completely new virus subtype. Using radio and telegraph despatches, WHO alerted the world to the onset of a pandemic, allowing health services to brace themselves for an upsurge of cases and deaths. Samples of the virus were immediately distributed to vaccine manufacturers throughout the world.

Box 3. **The origin of pandemic viruses**

A pandemic virus can emerge via two principal mechanisms: reassortment and adaptive mutation.

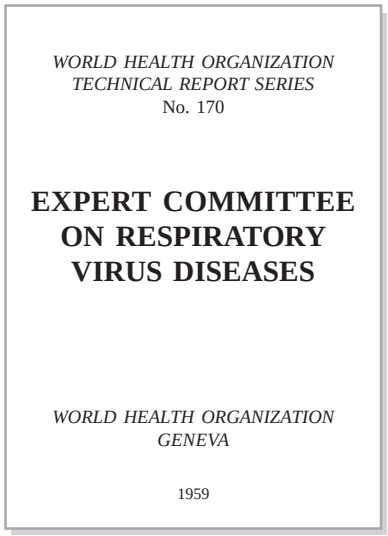
The organization of the influenza virus into eight gene segments facilitates reassortment, which occurs when two different viruses (such as avian H5N1 and human H3N2) infect the same cell and exchange some of their gene segments. If the resulting new virus can infect humans, cause serious disease, and spread easily from person to person in a sustainable way, it will ignite a pandemic.

Genetic and biochemical analysis of viruses from the 1957 and 1968 pandemics has identified them as reassortants of human and avian viruses. During a pandemic, the causative virus achieves dominance over all other circulating influenza viruses in humans. After the pandemic, the virus continues to circulate for decades, causing severe illness, until it is replaced by the next pandemic strain. The 1957 virus (the H2N2 strain) obtained three of its genes from an avian virus and the remaining five genes from the circulating human H1N1 strain, which caused the 1918 pandemic. The 1968 virus (the H3N2 strain) also took three genes from an avian donor and the remaining five from the circulating human H2N2 strain, responsible for the previous pandemic. Both pandemics began with an explosion of human cases. Neither has been convincingly linked to influenza outbreaks in birds or other animals. For both events, experts have long assumed that pigs, which have both human and avian receptors on the cells lining their respiratory tract, served as the mixing vessel for the swapping of gene segments.

Adaptive mutation is the second mechanism by which a pandemic virus can emerge. This mechanism involves stepwise changes in the virus, which occur during sequential infection of humans or other mammals, whereby an avian virus gradually acquires the changes needed to improve its transmissibility among humans. Experts have postulated that the essential changes involve adaptation of receptors specific to binding sites in bird cells to receptors that bind more easily to human cells. Only a few changes are needed; once in a new mammalian host, avian influenza viruses evolve very rapidly.

As the deadly 1918 pandemic occurred before the advent of modern virology, knowledge about the virus has emerged slowly – pieced together from "seroarchaeology" – and remains incomplete. Efforts to characterize the virus have relied on stored tissue samples taken from United States soldiers and United Kingdom civilians who succumbed to the disease, and on samples retrieved from bodies of fatal cases preserved in the Alaskan permafrost. Evidence to date suggests that the virus may have evolved through adaptive mutation of an avian virus, though considerable debate centres on whether this happened fairly rapidly or took place over a number of years. Investigations have, however, failed to find the tell-tale sequence of amino acids that distinguish highly pathogenic avian viruses and are thought to confer their unique ability, at least in birds, to cause severe systemic disease in addition to severe respiratory illness. Studies to date have not been able to determine what made the virus so deadly or why it preferentially affected the young and healthy.

The 1918 virus – the H1N1 strain – was detected as a cause of severe disease in pigs during the second phase of the pandemic, which began in the autumn of 1918. It will probably never be known whether pigs played a role in emergence of the virus or – more likely – were merely the incidental victims of a virus already spreading rapidly and widely in humans.



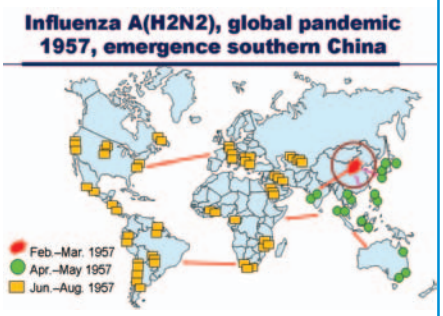
WHO convened an expert panel in 1958 to consider lessons from the pandemic. The report of that meeting gives a good picture of the epidemiology of a pandemic.

This time, pathways of international spread were tracked by the network of laboratories, and the event was accompanied by a flurry of epidemiological, clinical, and virological studies. In 1958, WHO convened a panel of experts to discuss this work and assess what had been learned from the pandemic. The result is a good picture of how a pandemic – probably much more representative than that of 1918 – affected health, globally and within individual countries.

The speed of international spread was characteristically swift. Less than six months after the disease reached Hong Kong SAR, every part of the world had experienced cases. Within individual countries, however, the pattern of spread differed in striking ways. In tropical countries and Japan, introduction of the virus was followed almost immediately by a succession of outbreaks, quickly resulting in a general community-wide epidemic. In Japan, for example, influenza entered the country at the end of April, spread immediately, peaked in June, and disappeared after mid-July. In contrast, both Europe and the USA experienced a grace period of at least six weeks before epidemics occurred following the introduction of cases. Epidemiologists believe that an almost silent "seeding" of the population occurred during these weeks. The reasons for the delayed epidemics remain obscure but are thought to be associated with climate and the timing of school holidays. In Europe and the USA, for example, the epidemics exploded coincident with the opening of schools in September but peaked rapidly. By December, the worst was over, at least for the first wave.

During the first wave, cases were concentrated in school-aged children. This was attributed to their close contact in crowded settings, and not to a special vulnerability.

Once epidemics began, patterns of morbidity were remarkably similar throughout the world. As with the initial wave in 1918, large numbers of cases occurred and the outbreaks were frequently explosive, but fatalities were much lower. Mortality showed a more characteristic pattern, similar to that seen in seasonal epidemics, with most excess deaths confined to infants and the elderly. During the first wave, cases of illness were concentrated in school-aged children; this was attributed to their close contact in crowded settings, and not to a particular age-related vulnerability. In general, close contact and crowding of persons together, as also seen in military barracks, favoured the spread of infection. In most countries, a second wave followed disappearance of the first from one to three months later, causing very high rates of illness and increased fatalities. Unlike the first wave, which affected mostly school-aged children, the second wave was concentrated in the elderly, which helps to explain the increased mortality.



Like other pandemics, the one in 1957 rapidly spread around the world.

Total excess mortality globally has been estimated at more than 2 million deaths.

As is 1918, many countries observed a subset, though smaller, of fatal cases of pneumonia with no evidence of bacterial infection. At autopsy, examination of lung material indicated death resulting from primary viral pneumonia, with findings similar to those observed in 1918. In 1957, however, most such fatalities occurred in persons with underlying disease, and not in the previously healthy.

Quarantine measures were applied in several countries and were generally found to be ineffective, managing at best to postpone the onset of an epidemic by a few weeks to two months.

Vaccines were available in August in the USA, in October in the United Kingdom, and in November in Japan. The quantities, however, were too small for widescale use. Moreover, as the disease was so much milder than in 1918, health authorities decided against an expansion of vaccine production to the scale needed for population-wide vaccination. Then, as now, the greatest problem was inadequate manufacturing capacity. Countries with domestic capacity were able to produce enough vaccine, early enough, to protect priority groups only. No country had sufficient production capacity to cover its entire population, much less to export vaccines elsewhere.

Quarantine measures were applied in several countries and were generally found to be ineffective, managing at best to postpone the onset of an epidemic by a few weeks to two months. The WHO expert panel found that spread within some countries frequently followed public gatherings, such as conferences and festivals, with infection dispersed as participants returned home. The banning of public gatherings and the closing of schools were considered the only measures that could dampen the spread of pandemic influenza. Even the most extreme option – severe restrictions on international travel and trade – was thought to bring nothing more than a few weeks of freedom from a disease whose international spread might be forestalled, but never stopped.

For health authorities, the biggest challenge presented by the 1957 pandemic was the provision of adequate medical and hospital services. Measures to delay the speed of spread and thus flatten the peak occurrence of cases were considered justified if they allowed the maintenance of medical and other essential services.

Viruses causing past pandemics

1889–1891	H3N8
1918–1919	H1N1
1957–1958	H2N2
1968–1969	H3N2

1968–1969

The pandemic that began in 1968 was even milder than that in 1957, but brought its own set of special epidemiological surprises. The first hint of a pandemic came from a newspaper story, published in the United Kingdom in mid-July, describing a widespread outbreak of acute respiratory disease in south-eastern China. That same month, the disease spread to Hong Kong SAR, where it reached maximum intensity within two weeks, causing half a million cases. Within days, Hong Kong SAR scientists isolated the virus and distributed it to network laboratories for analysis. The virus was rapidly identified as a novel subtype and, on 16 August, WHO issued a warning of possible worldwide spread, predicting a pattern similar to that seen in 1957, when the virus likewise spread from a focal point within mainland China.

Initial international spread did resemble that seen during 1957, but there the resemblance ended. Nearly everywhere, clinical symptoms were mild and mortality low. In most countries, the disease spread slowly rather than in the highly visible pattern of explosive outbreaks seen in previous pandemics. In some countries, the impact on absenteeism and on deaths rates was slight or absent altogether. The USA was the notable exception, and the epidemiology of the disease there was one of the most striking features of the pandemic.

The epidemic in the USA began in September in California, carried there by troops returning from Viet Nam, and spread eastwards to affect the whole of the country by late December. A significant increase in deaths from influenza-related pneumonia occurred during the first two weeks of January, with deaths concentrated in the elderly. Altogether, around 34 000 excess deaths, mostly in the elderly, occurred in the USA. In striking contrast, Canada experienced a relatively slight increase in disease incidence and practically no excess deaths. A similar picture was seen in most parts of Europe, where symptoms were mild and excess deaths negligible. In the United Kingdom, for example, the epidemic began in December 1968, progressed at a leisurely pace until early April 1969, and was associated with no sudden or excessive demands on general medical practitioners or hospital services. Deaths from influenza-like illness and pneumonia were actually lower than the year before.

Why was the 1968 pandemic so mild?

The mildness of the 1968 pandemic, caused by the H3N2 strain, is thought to result, in part, from protection against severe disease conferred by the pandemic of 1957.

As that pandemic was caused – just 11 years previously – by the H2N2 strain, the N2 subtypes were the same. The short time between the two pandemics means that large populations exposed in 1957 would still be alive and protected from severe illness by their previous exposure. In addition, the fact that the 1889 pandemic, caused by the H3N8 strain, shared the same HA (H3) subtype may have protected a subgroup of the elderly from infection.

Once again, vaccine arrived too late. Though vaccine manufacturing began within two months of virus isolation, only 20 million doses were ready when the epidemic peaked in the USA.

Although good mortality estimates are not available, global excess mortality was probably around 1 million. Many efforts have been made to explain the relative mildness of this pandemic. As the virus was genetically similar to viruses from previous pandemics, including the one as recent as 1957, at least some segments of the world population probably had partial protection either against infection or from severe disease. The occurrence of major epidemics at different times in different parts of the world was another fortunate, but curious feature. Several tropical countries experienced epidemics only at the beginning of 1969. For unknown reasons, Japan experienced numerous imported cases at the start of the pandemic, but was spared a major epidemic until mid-January 1969. Once again, however, too little vaccine arrived too late. Though vaccine manufacturing began within two months of virus isolation, only 20 million doses were ready when the epidemic peaked in the USA.

Lessons from the three pandemics of the last century

1 Pandemics behave as unpredictably as the viruses that cause them. During the previous century, great variations were seen in mortality, severity of illness, and patterns of spread.

2 One consistent feature important for preparedness planning is the rapid surge in the number of cases and their exponential increase over a very brief time, often measured in weeks. The severity of illness caused by the virus, which cannot be known in advance, will influence the capacity of health services, including hospitals, to cope, but a sudden sharp increase in the need for medical care will always occur.

3 Apart from the inherent lethality of the virus, its capacity to cause severe disease in non-traditional age groups, namely young adults, is a major determinant of a pandemic's overall impact. Milder pandemics are characterized by severe disease and excess deaths at the extremes of the lifespan (the very young and the elderly).

4 The epidemiological potential of a virus tends to unfold in waves. Age groups and geographical areas not affected initially are likely to prove vulnerable during the second wave. Subsequent waves have tended to be more severe, but for different reasons. In 1918, the virus mutated, within just a few months, into a far more virulent form. In 1957, schoolchildren were the primary vectors for spread into the general community during the first wave. The second wave reached the elderly, a group traditionally at risk of severe disease with fatal complications.

5 Virological surveillance, as conducted by the WHO laboratory network, has performed a vital function in rapidly confirming the onset of pandemics, alerting health services, isolating and characterizing the virus, and making it available to vaccine manufacturers.

6 Over the centuries, most pandemics have originated in parts of Asia where dense populations of humans live in close proximity to ducks and pigs. In this part of the world, surveillance for both animal influenza and clusters of unusual respiratory disease in humans performs an important early warning function.

7 Some public health interventions may have delayed the international spread of past pandemics, but could not stop them. Quarantine and travel restrictions have shown little effect. As spread within countries has been associated with close contact and crowding, the temporary banning of public gatherings and closure of schools are potentially effective measures. The speed with which pandemic influenza peaks and then disappears means that such measures would probably not need to be imposed for long.

8 Delaying spread is desirable, as it can flatten the epidemiological peak, thus distributing cases over a longer period of time. Having fewer people ill at a given time increases the likelihood that medical and other essential services can be maintained and improves capacity to cope with a sharp increase in demand for care.

9 The impact of vaccines on a pandemic, though potentially great, remains to be demonstrated. In 1957 and 1968, vaccine manufacturers responded rapidly, but limited production capacity resulted in the arrival of inadequate quantities too late to have an impact.

10 Countries with domestic manufacturing capacity will be the first to receive vaccines.

11 The tendency of pandemics to be most severe in later waves may extend the time before large supplies of vaccine are needed to prevent severe disease in high-risk populations. The interval between successive waves may, however, be as short as a month.

12 In the best-case scenario, a pandemic will cause excess mortality at the extremes of the lifespan and in persons with underlying chronic disease. As these risk groups are the same as during seasonal epidemics, countries with good programmes for yearly vaccination will have experience in the logistics of vaccine administration to at least some groups requiring priority protection during a pandemic. While such a strategy can reduce excess mortality, sudden and large increases in morbidity, and a correspondingly high demand for medical care, should nonetheless be anticipated.

Box 4. **The WHO global influenza programme: a network of flu "detectives"**

Influenza surveillance is the oldest disease control programme at WHO. It was established in 1947 because of two concerns: the inevitable recurrence, at unpredictable intervals, of highly disruptive pandemics, and the significant health and economic impact of seasonal epidemics, which occur nearly every year. The objective at the outset was to obtain an ongoing representative picture, at the global level, of how the virus is changing and what these changes mean for human health. The programme was set up as a network of laboratories commissioned to study circulating influenza viruses, collected from around the world, and document changes in the viruses' genetic make-up.

Within four years, the network included 60 laboratories in 40 countries. At that time, when the world was far less mobile and interdependent than now, public health authorities recognized influenza as a disease that cannot be mitigated without an international collaborative effort having a broad geographical scope. From its earliest years on, the network has operated as a model of international scientific collaboration to safeguard public health: virus strains are made freely available to other laboratories and to manufacturers the moment any unusual characteristics are detected.

Today, the WHO Global Influenza Surveillance Network consists of 113 national influenza centres located in 84 countries, and four WHO collaborating centres for influenza reference and research, located in London (England), Atlanta (USA), Melbourne (Australia), and Tokyo (Japan). A fifth collaborating centre, located in Memphis, USA, performs specialized work on iinfluenza viruses in animals. The national centres collect influenza viruses circulating in different parts of the world. These are then sent to the four collaborating laboratories for in-depth investigations. Apart from providing a composite global picture of changing influenza activity, this work allows WHO to issue advice, twice each year, on the composition of influenza vaccines considered most likely to confer protection against seasonal epidemics in both the northern and southern hemispheres. The WHO network has thus contributed greatly to the understanding of influenza epidemiology and assists manufacturers both by ensuring that influenza vaccines contain the most appropriate viruses and by providing them with high-yielding "seed" virus for vaccine production.

In a given year, around 200 000 samples are collected by the national centres, of which some 6 500 are sent to the four collaborating centres for in-depth analysis. Each year, the United States Centers for Disease Control and Prevention (CDC) prepares a kit of reagents to assist the global network in determining the types of viruses in circulation. The results are reported directly to WHO. The four collaborating centres also store virus samples for historical comparisons and provide diagnostic support for countries experiencing unusual influenza cases, such as those caused by H5N1. At present, eight network laboratories perform confirmatory diagnostic work on H5N1 viruses. Sequencing of 2004 viruses and comparisons with historical samples from previous outbreaks have yielded valuable clues about the evolution of the virus and the significance of possible instances of human-to-human transmission. Although all this work takes place quietly behind the scenes and receives little attention, it is universally regarded as a model of efficient surveillance and of effective international collaboration.

In responding to the H5N1 outbreaks, WHO has also drawn considerable support from a second network of laboratories and scientists conducting work on animal influenza.

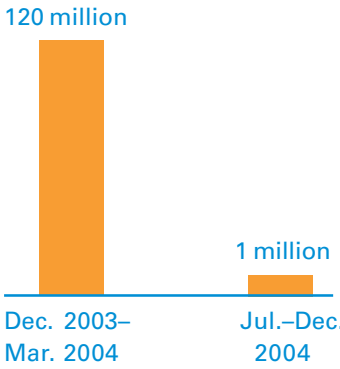
3 Understanding the outbreaks in poultry

Opportunities for both the occurrence of further human cases and the emergence of a pandemic virus are intrinsically linked to the presence of the H5N1 virus in poultry. Hopes that a potentially explosive situation might be defused by elimination of the virus – as was done in Hong Kong SAR in 1997 – have dwindled. As 2004 progressed, evidence mounted that the virus has become firmly entrenched in parts of Asia. Time and time again, countries on the verge of declaring outbreaks over have been set back by detection of the disease in yet another farm or flock.

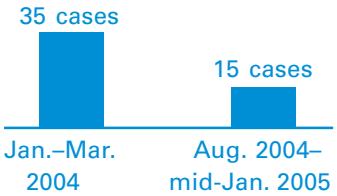
Though far fewer outbreaks, affecting far fewer birds, were detected in the second half of the year, the threat to humans has actually become more dangerous. The virus is no longer causing large and highly conspicuous outbreaks on commercial farms. Nor have poultry workers or cullers turned out to be an important risk group that could be targeted for protection. Instead, the virus has become stealthier: human cases are now occurring with no discernible exposure to H5N1 through contact with diseased or dead birds. This change has created a community-wide risk for large numbers of rural households and – for unknown reasons – most especially for children and young adults. The true magnitude of the threat may well be masked in rural areas where surveillance is poor and respiratory illness, including pneumonia, is common.

True to the nature of influenza A viruses, H5N1 is certain to continue to mutate, though the direction these changes will take cannot be predicted. If the virus continues to expand its avian and mammalian host range, the prospects for eliminating the disease in animals will become even grimmer. An understanding of the H5N1 outbreaks in poultry, and of their unique features when compared with previous outbreaks, adds to the total fund of information useful in assessing the severity of the present situation and its implications for public health.

Outbreaks in poultry



Human cases, Thailand and Viet Nam combined



Previous outbreaks of highly pathogenic avian influenza worldwide

1959	Scotland	H5N1
1963	England	H7N3
1966	Ontario (Canada)	H5N9
1976	Victoria (Australia)	H7N7
1979	Germany	H7N7
1979	England	H7N7
1983–1985	Pennsylvania (USA)[a]	H5N2
1983	Ireland	H5N8
1985	Victoria (Australia)	H7N7
1991	England	H5N1
1992	Victoria (Australia)	H7N3
1994	Queensland (Australia)	H7N3
1994–1995	Mexico[a]	H5N2
1994	Pakistan[a]	H7N3
1997	New S. Wales (Australia)	H7N4
1997	Hong Kong SAR[a]	H5N1
1997	Italy	H5N2
1999–2000	Italy[a]	H7N1
2002	Hong Kong SAR	H5N1
2002	Chile	H7N3
2003	Netherlands[a]	H7N7
2004	Pakistan	H7N3
2004	Texas (USA)	H5N2
2004	British Col. (Canada)[a]	H7N3
2004	South Africa	H5N2

[a] Outbreaks with significant spread to numerous farms, resulting in great economic losses.

The disease in birds: from ruffled feathers to "chicken Ebola"

Avian influenza, previously known as "fowl plague", was first recognized as a serious disease of chickens in Italy in 1878. Decades later, in 1955, studies demonstrated that the disease was caused by influenza A viruses. Since then, influenza A viruses of all subtypes have been detected in more than 90 species of apparently healthy wild birds.

Wild waterfowl, most notably ducks, are by far the most frequent carriers of the largest variety of viruses. It is now recognized that wild waterfowl, gulls, and shorebirds are the natural reservoir of all influenza A viruses. These birds have carried the viruses without developing symptoms – presumably for thousands of years – in a relationship thought to represent optimal adaptation of a virus to its host. This huge, stable, benign, and perpetual reservoir of viruses is also highly mobile. Wild waterfowl can carry viruses over great distances and excrete large quantities in their faeces, yet remain perfectly healthy.

Other bird species, including domestic poultry, are less fortunate. In poultry, avian influenza causes two distinctly different forms of disease – one common and mild, the other rare and highly lethal. Considerable circumstantial evidence indicates that the viruses, in their low-pathogenic form, are introduced into poultry by wild waterfowl. This evidence is further substantiated by the fact that outbreaks are seen most often in poultry having contact with feral birds, often sharing the same water sources.

In the mild form of avian influenza, signs of illness range from ruffled feathers and reduced egg production to typical respiratory symptoms. Outbreaks can be so mild they escape detection unless regular testing for the virus is in place. In contrast, the second and far less common highly pathogenic form is difficult to miss, characterized as it is by sudden onset of severe disease, rapid contagion and a mortality that can approach 100% within 48 hours. In this form, the virus not only affects the respiratory tract, as in the mild form of disease, but also invades multiple organs and tissues, causing massive internal haemorrhaging that has earned it the lay name of "chicken Ebola".

Testing for highly pathogenic avian influenza

The standard method used to determine whether an avian influenza virus is highly pathogenic takes time. The method involves the inoculation of a minimum of eight susceptible 4- to 8-week old chickens with infectious virus. If 75% of the chickens (six of the eight) die within 8 days, the virus strain is considered to be highly pathogenic. Because work with a highly lethal virus is involved, testing must be done in a high-security laboratory.

Some highly pathogenic avian influenza viruses will kill six or more chickens within 48 hours or less. In such cases, conclusive test results become available quickly.

An additional test involves sequencing of the virus. All highly pathogenic avian influenza viruses will show a distinctive sequence of amino acids, located at the so-called HA "cleavage site", known to be associated with high lethality.

H5 and H7 viruses: always cause for alarm

Viruses that can cause highly pathogenic avian influenza are currently restricted to the H5 and H7 subtypes. Some variants within these two subtypes are capable of causing highly lethal disease, but not all will do so, as an intermediate step is required. Highly pathogenic viruses have no natural reservoir. Instead, they emerge by mutation when a virus, carried in its mild form by a wild bird, is introduced to poultry. Once in poultry, the previously stable virus begins to evolve rapidly, and can mutate, over an unpredictable period of time, into a highly lethal version of the same initially mild strain. It is this propensity for rapid mutation from a mild into a lethal form that always makes detection of any H5 or H7 infection in poultry of great concern. If the disease is detected early enough, and aggressive control measures are undertaken, the mild virus can be eliminated before it has an opportunity to mutate into the highly pathogenic form.

Outbreaks of low pathogenic avian influenza have been reported in poultry throughout the world, but the frequency and size of outbreaks have varied with individual countries, regions, and agricultural systems. Prior to 2004, outbreaks of highly pathogenic avian influenza were considered rare. While the 1878 outbreak in Italy, which caused extremely high mortality in chickens, was almost certainly of the highly pathogenic form, the first confirmed outbreak of highly pathogenic avian influenza was reported in 1959. Since then, 24 outbreaks have been recorded worldwide, of which 14 have occurred in the past 10 years. The majority have shown limited geographical spread, a few remained confined to a single farm or flock, and only one spread internationally. All of the larger outbreaks proved notoriously difficult to control, typically requiring two to three years to eliminate the virus. Since 1959, none of the outbreaks has approached the size of the Asian outbreaks of H5N1 in 2004.

Viruses of the H5 and H7 subtypes can rapidly mutate from a mild to a highly lethal form. Their detection in poultry is always of great concern.

The most important control measures are rapid culling of all infected or exposed birds, proper disposal of carcasses, and the quarantining and rigorous disinfection of farms. Restrictions on the movement of live poultry, both within and between countries, are another important control measure. Strict application of these

Strict application of control measures is virtually impossible in rural areas where poultry roam freely.

measures, while feasible on commercial farms, is virtually impossible in rural areas where chickens and ducks roam freely and mingle with wild birds or share water sources with them. Faecal contamination of water supplies is considered a very efficient way for waterfowl to transmit the virus. Moreover, domestic ducks attract wild ducks and provide a significant link in the chain of transmission from wild birds to domestic flocks.

Highly pathogenic avian influenza viruses were probably endemic in Europe and Asia from 1900 to the mid-1930s. Endemicity of these viruses has not been reported since that time. Even in areas where outbreaks have tended to recur, differences in the causative viruses have suggested independent introductions from wild birds, especially as many areas with recurring outbreaks are located along the flight paths of migratory birds.

The 2004 outbreaks: the largest – and most ominous – on record

H5N1 now appears firmly entrenched in parts of Asia. Other unique features of the outbreak suggest that the virus is changing in ominous ways.

Viewed against this historical background, the 2004 outbreaks of highly pathogenic H5N1 avian influenza in Asia are clearly unprecedented in their geographical scale and the endemicity of the virus, which now appears firmly entrenched in parts of Asia. Other unique features of the outbreaks suggest that the complex ecology of influenza viruses may be changing in ominous ways. Domestic ducks are now known to be excreting H5N1 in its highly pathogenic form yet – like wild ducks – appear to be perfectly healthy. They may thus be silently perpetuating transmission of the virus to chickens and other poultry and possibly also to humans. The recent detection of highly pathogenic H5N1 in dead migratory birds – long considered asymptomatic carriers – may suggest another ominous change, but more research is needed before any conclusions can be reached.

The history of all known human infections with avian influenza viruses readily reveals the significance of the 2004 outbreaks for human health (Table 3). They have caused the largest number of severe cases of avian influenza in humans on record. Compared with the Hong Kong SAR outbreak in 1997, the 2004 H5N1 outbreak in humans has also been far more deadly.

WHO advice on the preparation of poultry for consumption

1. **Avoid contamination**

   Separate raw meat from cooked or ready-to-eat foods. Do not use the same chopping board or the same knife for preparing raw meat and cooked or ready-to-eat foods. Do not handle both raw and cooked foods without washing your hands in between and do not place cooked meat back on the same plate or surface it was on before it was cooked.

2. **Cook thoroughly**

   Thorough cooking will inactivate influenza viruses. Either ensure that the poultry meat reaches 70 °C or that the meat is not pink and there are no pink juices.

3. **Be careful with eggs**

   Eggs, too, may carry pathogens, such as the bird-flu virus inside or on their shells. Care must be taken in handling raw eggs and shells. Wash shells in soapy water and wash hands afterwards. Egg yolks should not be runny or liquid. Do not use raw or soft-boiled eggs in foods that will not be cooked.

4. **Keep clean**

   After handling raw or thawed raw poultry or eggs, wash your hands and all surfaces and utensils thoroughly with soap and water.

Chicken and eggs: is there a risk from poultry products?

As a general rule, WHO recommends that all meats, including that from poultry, be thoroughly cooked, so that all parts of the meat reach an internal temperature of 70 °C. This temperature will kill an influenza virus and thus render safe any raw poultry meat contaminated with H5N1 virus.

In countries affected by H5N1 outbreaks, eggs should also be thoroughly cooked, as some studies have detected virus in raw eggs.

To date, epidemiological investigations have not linked any human cases to the consumption of poultry products. Strong evidence does, however, point to a far greater risk: exposure to the virus during the slaughter of infected birds and their preparation for cooking. This risk is compounded by the practice, common among rural subsistence farmers, of killing and eating poultry – even those showing obvious signs of illness – once birds within a flock start to die. In several such instances, the person who slaughtered or prepared an ill bird for consumption developed fatal illness, while family members who participated in the meal did not.

The large outbreak in captive tigers, which occurred in October in Thailand, is thought to be linked to the feeding of contaminated whole chicken carcasses. It this hypothesis is substantiated, it will provide further evidence that contact with raw poultry carcasses can be a significant source of exposure to the virus.

Table 3. **Documented human infections with avian influenza viruses**

Date	Country/ area	Strain	Cases	Deaths	Symptoms	Source
1959	USA	H7N7[a]	1 (46-year-old man)	0	respiratory	overseas travel
1995	United Kingdom	H7N7	1 (43-year-old woman)	0	conjunctivitis	pet ducks (shared lake with migratorybirds)
1997	Hong Kong SAR	H5N1[a]	18	6	respiratory, pneumonia	poultry
1998	China (Guangdong)	H9N2	5	0	unknown	unknown
1999	Hong Kong SAR	H9N2	2 girls (4 years, 13 months)	0	respiratory	poultry for 4-year-old; unknown for 13-month-old
2003 (Feb.)	Hong Kong SAR[b]	H5N1[a]	2 (9-year-old boy, 33-year-old father)	1	respiratory	unknown
2003 (Mar.)	Netherlands	H7N7[a]	89	1 (57-year-old veterinarian)	conjunctivitis (pneumonia, respiratory insufficiency in fatal case)	poultry
2003 (Dec.)	Hong Kong SAR	H9N2	1 boy (5-year-old)	0	respiratory	unknown
2004	Viet Nam	H5N1[a]	33	25	respiratory	poultry
2004	Thailand	H5N1[a]	17	12	respiratory	poultry
2004	Canada	H7N3[a]	2	0	conjunctivitis	poultry

[a] Highly pathogenic for poultry.
[b] Possibly acquired in mainland China.

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.

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.

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

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.

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.

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.

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

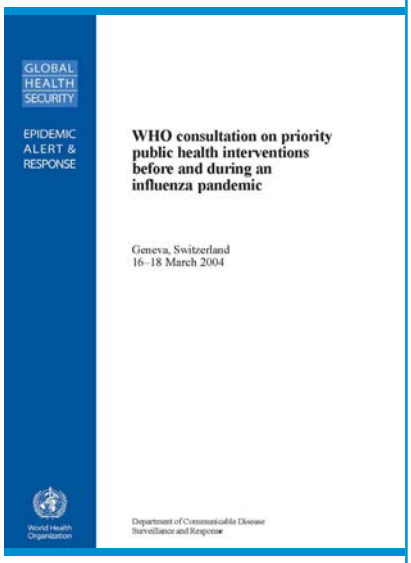
Oseltamivir is effective in the treatment of human infections with H5N1. As the drug must be given within two days after the onset of symptoms, a critical problem is the tendency of patients to be detected late in the course of illness.

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-



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.

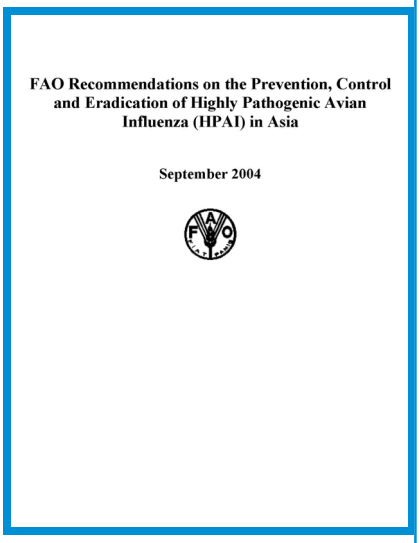
The risk of importing avian influenza into areas affected by the tsunami can be minimized by controlling the movement of poultry from areas where outbreaks are known to be occurring. It is also important to ensure that infected poultry are kept out of the food chain, including emergency food relief activities.

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



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

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.

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

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]				Comments
	pre-pandemic				
	0.1	0.2	0.3	1.0	
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
– 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	may be indicated. Persons on affected conveyance should be traced and similarly advised.
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.
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] 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/