

NATIONAL PANDEMIC INFLUENZA PREPAREDNESS AND RESPONSE PLAN UPDATE

December 2006



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INTRODUCTION

The National Pandemic Influenza Preparedness and Response Plan was presented in May 2005. This Plan included a description of the activities to be prepared in order to provide an adequate response in each phase.

Since then, the avian influenza virus H5N1 has been advancing and expanding its geographical distribution, to the extent that in the last year, wild birds and poultry infected with this virus have been detected in Asia, Europe and Africa. Cases in humans have continued to appear, associated with outbreaks in domestic poultry in the vicinity, while no evidence of sustained person-to-person transmission has been found.

In April 2005, the World Health Organization (WHO) presented a Plan defining six phases, the objective of which was to ensure that similar activities would be carried out in all countries in order to address the risks for public health. On publishing the Plan, the World Health Organization declared that the world was in Phase 3 at that time.

As of December 2006, the public health risk remains unchanged: the world continues to be in Phase 3. Nevertheless, although evidence indicates that the person-to-person transmission is inefficient and that only transmissions between close contacts have been detected, the infection in wild birds and domestic poultry has not ceased to progress, with an increase in the number of species affected and in the number of countries where new cases of infected birds have been detected.

Asia continues to be the major reservoir of the H5N1 influenza virus. Infection with this virus has become endemic in the animal population over large areas on this continent, involving a risk for the rest of the world, as this situation increases the likelihood of a mutation of the virus and the ac-

quisition of the capacity of its transmission among humans.

The objective of this document is to provide information on the activities that have been carried out by the Organizational and Coordinating Structure described in the National Plan since its approval.

The Public Health Commission (PHC) has ensured that control measures were adopted in a coordinated manner in all of the Autonomous Communities (AACC). The organization of healthcare services in order to confront a pandemic has been undertaken fundamentally by the health authorities of the Autonomous Communities. Each of them must adapt the response to their resources and organizational structure. In order to harmonize the response as far as possible, the Subcommittee for the Emergency Response of Healthcare Services has facilitated the preparation of protocols on the control of infections in the hospital environment and the clinical management of patients. Moreover, in view of a possible abrupt increase in healthcare demand, the Subcommittee has proposed criteria for establishing a rapid patient triage system and for redirecting patients in order to reduce the risk of transmission of infections. Similarly, the rest of the groups and Subcommittees have drawn up consensus documents on the key aspects of the response, which have driven the development and implementation of the Autonomous Community Plans.

In this update of the National Plan, the activities carried out are presented grouped together along the lines of the four strategic actions proposed in the document "Strategic Action Plan for Pandemic Influenza 2006-2007", recently published by WHO:

1. Reduce human exposure to the H5N1 virus in order to reduce opportunities of infection in humans, with the consequent reduction of the possibility for a pandemic to emerge.

2. Strengthen the early warning systems to ensure that the country is capable of detecting cases quickly, to enable them to be treated and to report them to the relevant international organizations for the performance of an adequate risk assessment. This includes making certain that the specimens are shared with WHO laboratories.
3. Intensify rapid containment operations, which will ensure a rapid investigation of cases and clusters of cases and the management and implementation of measures quickly in order to prevent the transmission of the virus. Prevent an increase in the ability for person-to-person transmission of the H5N1 virus.
4. Develop the capacities for coping with a pandemic and ensure that the pandemic preparedness and response plans are prepared and tested on a national and Autonomous Community level.

This National Plan Update begins by presenting a general overview of the evolution of the outbreak caused by the H5N1 avian virus, the lessons learned from the cases in humans and the evolution of the risk in Europe. This is followed by a description of the activities carried out in the context of the four strategic actions and those to be developed in the near future.

A. AVIAN INFLUENZA A (H5N1) OUTBREAK. ASSESSMENT OF THE RISK TO HUMAN HEALTH

A.1. Evolution of the Avian Influenza A (H5N1) Outbreak

A.2. Characteristics of Human Infection with the H5N1 Virus

- A.2.1 Human infection with avian influenza virus prior to the current H5N1 outbreak
- A.2.2 Clinical characteristics of the H5N1 influenza
- A.2.3 Transmission of the H5N1 avian virus to humans. Factors associated with the risk of human infection

A.3. Assessment of the Risk to Human Health of the H5N1 Virus

A.1. Evolution of the Avian Influenza A (H5N1) Outbreak

Human infections caused by avian influenza viruses have been extremely rare in the course of history, and the majority of such infections have only caused mild illnesses in humans, often in the form of viral conjunctivitis.¹ The H5N1 virus is the exception to the rule.

The first case documented of human infection with this virus occurred in Hong Kong in 1997,² when the virus caused 18 cases, 6 of which were fatal. The cases coincided with highly pathogenic outbreaks of H5N1 in poultry in farms and in live fowl markets. A striking characteristic of this outbreak in Hong Kong was the presence of primary viral pneumonia in the severe cases, which did not respond to the antibiotics administered and often advanced rapidly to a fatal outcome. The age group of the cases ranged from 1 to 60, with more than half of the cases being in children under 12. The cases occurred in two waves: a case was first detected in May and later, in November and December, 17 were detected.

Molecular studies showed that the virus causing the human infection was identical to that of the poultry, indicating that the virus had been transmitted directly from poultry to people. In the majority of the human cases, there was a history of direct contact with domestic poultry. The absence of disease in two highly exposed groups, workers of poultry farms and those involved in the slaughtering of domesticated birds, indicated that the H5N1 virus was not transmitted readily from birds to humans. Antibodies of the H5 virus subtype were found in blood specimens taken from members of the family and healthcare workers in close contact with the patients, which would indicate the existence of person-to-person transmission, even though this was neither efficient nor sustained.³ The outbreak was contained following a rapid and massive culling of all of the poultry infected or at risk and after the implementation of strict biosecurity measures.⁴

Although this was the first time that the H5N1 virus had been detected, a number of investigations have found that this virus was circulating among poultry in China prior to 1997.¹ The H5N1 virus was detected anew in Hong Kong in February 2003, again causing human cases in a Hong Kong family with a recent history of travel to Fujian Province in China. Two cases were confirmed, and one of the patients died.⁵ On this occasion as well, the infection in poultry was controlled following a large-scale bird culling, the adoption of biosecurity measures and a vaccination campaign.

However, months later, at the end of 2003, the H5N1 virus was isolated once again, this time followed by a dramatic spread of the infection in Southeast Asia. Both the commercial movements of domestic poultry and poultry products, as well as the dissemination of the infection by wild birds have been singled out as causes of this spread. The system for raising domestic poultry in Asia, where small backyard flocks account for 70% of the avian population, has contributed to a large extent to the situation that has arisen in these countries.

Since the end of 2003, more than 50 countries on three continents have reported outbreaks of

avian influenza H5N1 to the Organization International des Epizooties (OIE). The virus has become endemic in Southeast Asia.

The evolution of the H5N1 virus and the spread of the outbreak can be divided into three major waves.⁵

FIRST WAVE:

Mid 2003 - March 2004

In the middle of 2003, the H5N1 began to cause outbreaks in Asia, however, they remained undetected or unreported. In December 2003, two tigers and two leopards that had been fed chicken carcasses died in a Thailand zoo. Post-mortem investigations of the tissue samples detected the H5N1 virus. This was the first case reported in which the influenza virus was the cause of death in big cats.

On December 19th 2003, the Republic of Korea confirmed that the death of poultry on three farms in this country was due to the highly pathogenic H5N1 virus. During the following month, January 2004, outbreaks were reported

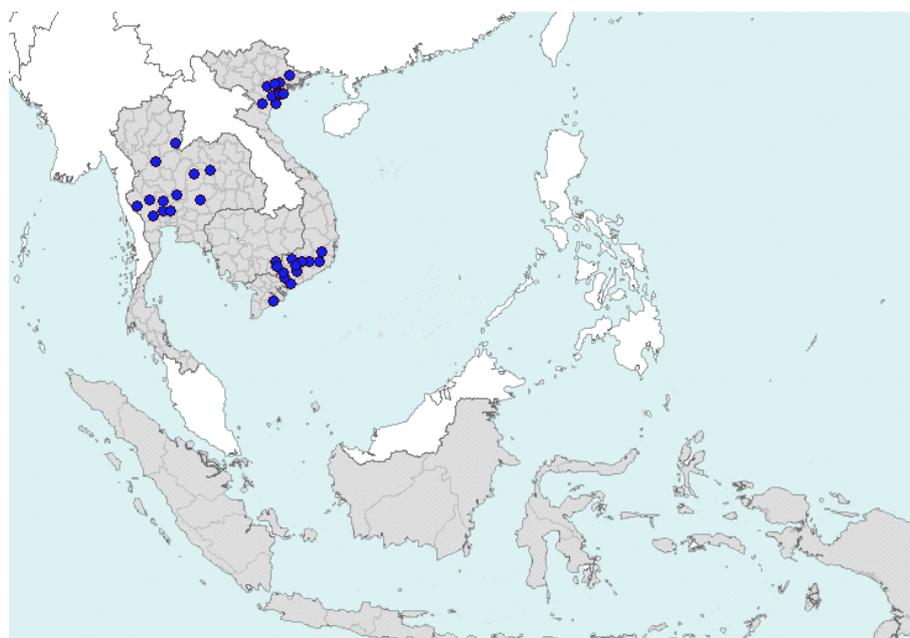
in domesticated birds in Vietnam, Japan, Cambodia and Laos. In February, outbreaks occurred in Indonesia and China.

In parallel with the detection of these outbreaks in poultry, the initial cases of human infection began to be confirmed. In early January 2004, the H5N1 virus was identified in Vietnam as the cause of human cases of severe respiratory disease with a high mortality rate. Also in January, Thailand reported two new cases of human illness caused by H5N1.

By the middle of March 2004, the reports of human cases had ceased, and this first wave ended with a total of 12 cases in Thailand (8 fatal) and 23 cases in Vietnam (16 fatal).

In March 2004, an initial study based on the first 10 cases occurring in Vietnam was published⁶ and concluded that close contact with domesticated birds was the most likely source of infection in the majority of cases. This study also showed that two family clusters had occurred, in which a limited person-to-person transmission could not be ruled out.

Cumulative number of human cases of H5N1. December 2003 – March 2004



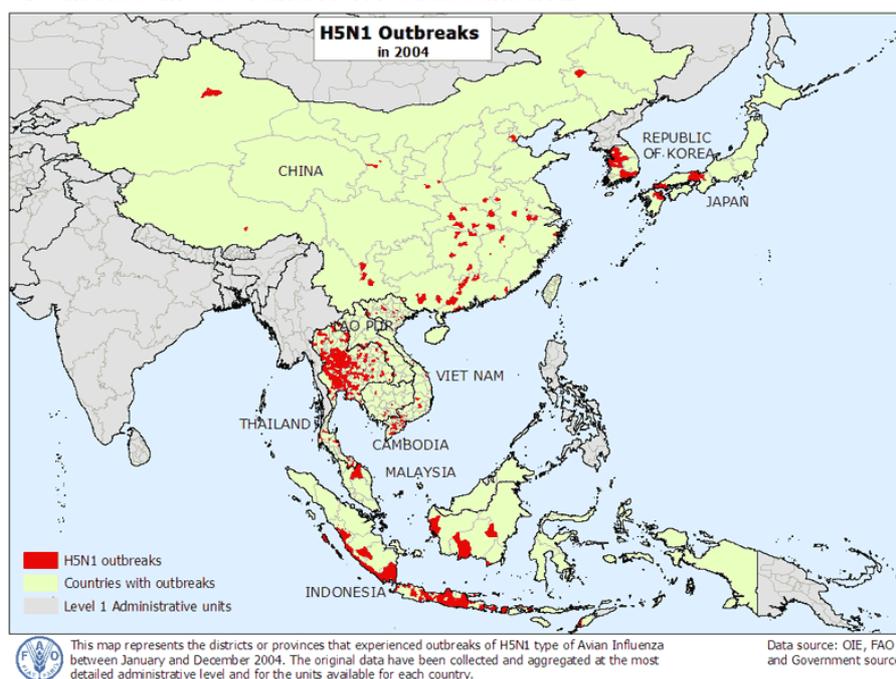
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SECOND WAVE:**June - November 2004**

Starting in June 2004, recurring outbreaks were detected in poultry farms in China, Indonesia, Thailand and Vietnam. In August, Malaysia reported the appearance of H5N1 in

domesticated birds. Two of the countries initially affected, Japan and the Republic of Korea, announced the control of the H5N1 poultry outbreak in July and September, respectively, and were considered disease-free by the OIE.

Countries affected and H5N1 outbreaks in 2004



In October 2004, a major outbreak of H5N1 occurred in tigers in a zoo in Thailand. The tigers had been fed chicken carcasses. The ensuing investigation pointed to the fact that to a certain extent tiger-to-tiger transmission of the virus may have occurred.⁷

Human infection in this wave still remained in Vietnam and Thailand. Vietnam reported 3 new human cases in August and an additional case in September, all fatal, while in this same period, Thailand reported 5 new cases, four of which were also fatal.

In July 2004, an atypical case of infection in Thailand was published⁸ presenting fever and diarrhoea without respiratory symptoms, which suggested that the clinical spectrum may be broader than what was previously thought.

The investigation of the H5N1 virus published during this period revealed the enormous impact of the dominant Z genotype on the poultry of infected farms, concluding that the H5N1 virus had found a new ecological niche in them but was not ready to infect humans efficiently.⁹

A characteristic of the H5N1 virus, which was already coming out in this period of the outbreak, was the ability of some strains of the virus to infect domestic ducks without evidence of illness in them. It has been observed that these animals are able of shedding large quantities of the virus without presenting symptoms of the disease.¹⁰ In endemic countries, the role of domestic ducks in the perpetuation of the transmission cycle has been significant. Subsequent specific studies carried out in Thailand have identified the existence of H5N1 infection

in a percentage that ranges between 20 and 50% of ducks examined in farms without a closed system and have identified this infection as an important risk factor for the appearance of outbreaks in domestic birds.¹¹



The investigations published during these months pointed to an increase in the lethality of the H5N1 virus in mammals and to the infection of wild waterfowl, a species previously considered to be a disease-free reservoir.¹⁰

At that time, Chinese researchers reported preliminary findings of the infection in pigs. There is no evidence to suggest that the infection in these animals is spreading, nor do these findings appear to have epidemiological significance.⁵

Experimental studies which found that the H5N1 virus could infect household cats and that the infection could be transmitted among these animals were also published.¹¹ A number of experimental studies on the transmission of the influenza virus in household cats had already been carried out earlier.¹²

THIRD WAVE:

Part One

(Asia). December 2004 - October 2005

Starting in December 2004, new outbreaks were reported in poultry farms in Thailand, Vietnam, Indonesia, Laos and Cambodia. Malaysia announced that the outbreaks were under control and was declared disease-free.

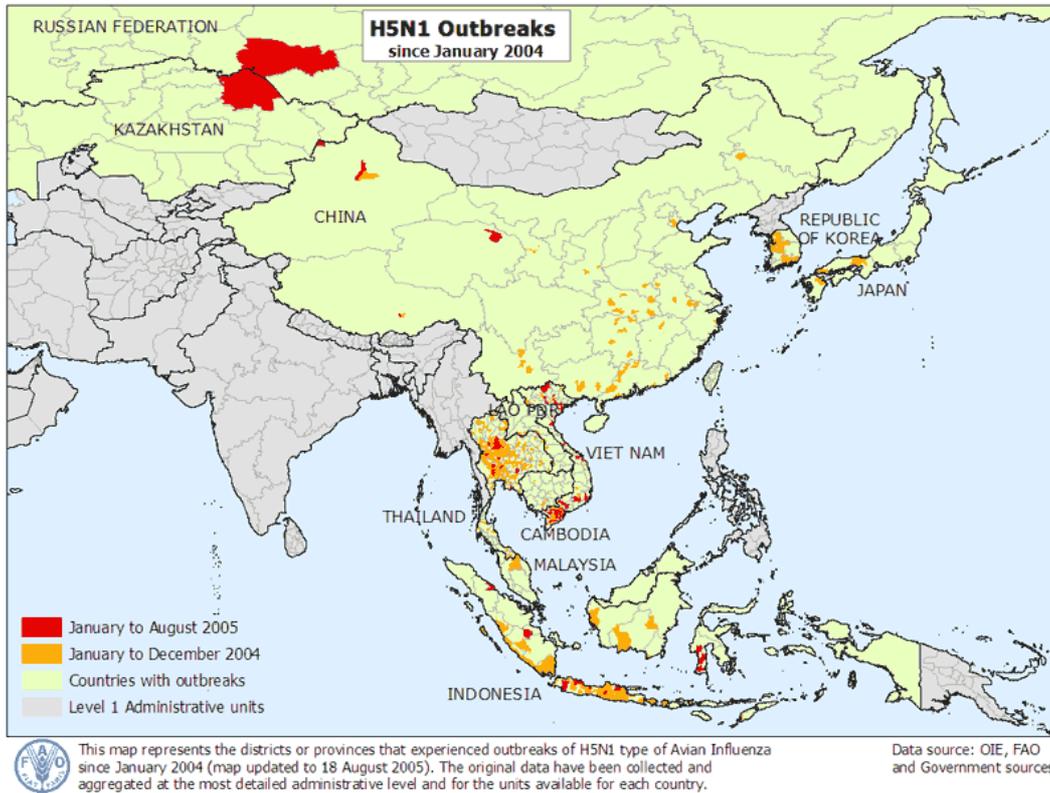
In mid 2005, a turning point was reached in the evolution of the H5N1 outbreak, marked by the particular role taken up by migratory birds in the spread of the disease. The detection of the highly pathogenic H5N1 virus in more than 6000 dead migratory birds in the Qinghai Lake nature reserve in China at the end of April 2005, was an unusual and probably unprecedented event.⁵ A few months later the results of several investigations were published, indicating that this H5N1 outbreak, responsible for the death of wild birds, was caused by a strain that could be more lethal in migratory birds and experimental mice.¹³



By the end of July 2005, the virus had spread from its original focal point in Asia, where it was infecting poultry and wild birds, to the Russian Federation, affecting farms in western Siberia and adjacent parts of Kazakhstan. The outbreaks registered in these countries have been attributed to the contact between domestic and wild birds through shared sources of water. Dead infected migratory birds were found in the vicinity of the farms affected.

In July, China reported outbreaks in the region of Xinjian and, in August, in the region of Tibet, while Mongolia reported the death of 89 migratory birds infected with the H5N1 virus in two lakes.

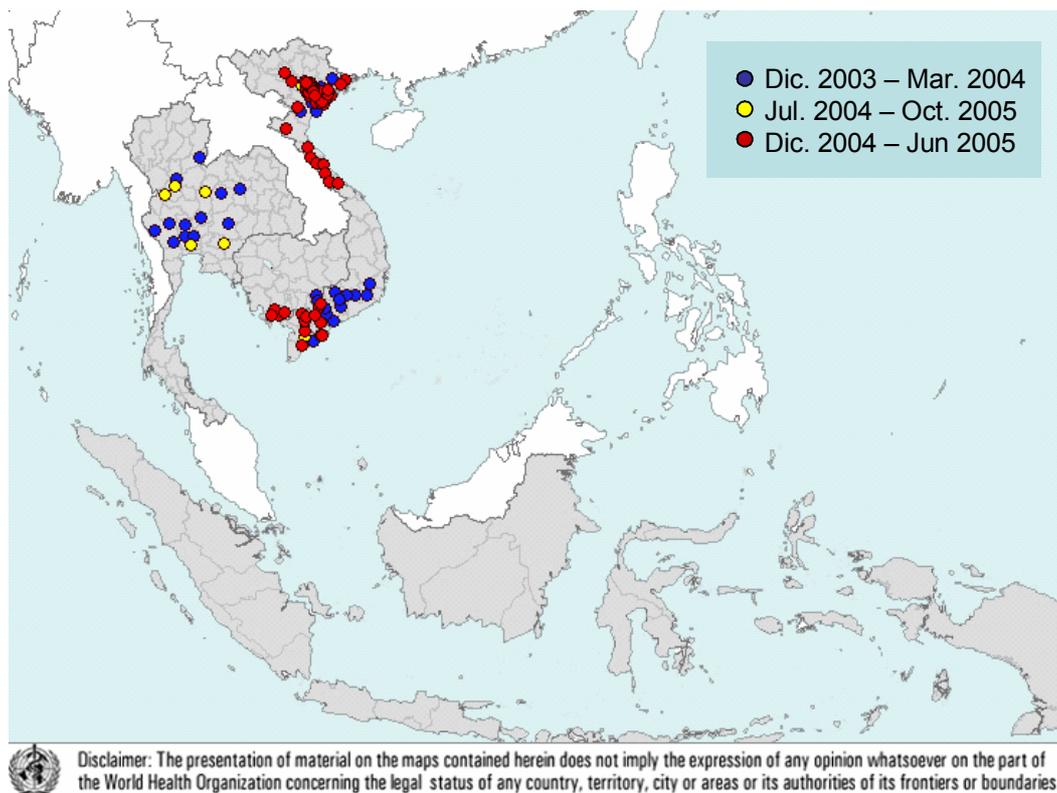
Countries affected and H5N1 outbreaks from January 2004 to August 2005



During this period, Vietnam was the country where the largest number of infected human cases was reported, with a total of 64 cases, 21 of which were fatal. Cambodia and Indone-

sia reported cases in humans for the first time, with four cases in Cambodia, all fatal, and five in Indonesia.

Cumulative human cases of H5N1. December 2003 - June 2005



The isolation of the Quinghai Lake viruses also demonstrates that this virus can be transmitted among migratory geese, giving rise to the possible spread of the virus along the migratory routes.¹⁴ Up to then, the findings of wild birds killed by highly pathogenic influenza viruses were rare and considered isolated cases affecting only a small number of birds. However, since the end of 2005, it appears evident that some H5N1 viruses could quickly travel over long distances by using migratory birds as their vehicle and, although these birds have not been the sole source of the dissemination of the virus, their role in the spread of the infection now appears evident.¹⁵⁻¹⁶

A study was published in January 2005, revealing that a girl infected in Thailand in September 2004 may have transmitted the virus to her mother. The disease was fatal in both cases. This is the first published account of probable secondary human transmission of avian influenza resulting in severe disease.⁷

One month later, retrospective investigations found that at least one of the fatal cases in Vietnam presented a clinical picture of encephalitis and diarrhoea with a normal chest X-ray.¹⁸

In June 2005, research performed by a WHO team reached to the conclusion that the situation of the transmission in humans of the H5N1 virus had improved in Vietnam, and in October, research on the evolution of the human and animal viruses circulating in Asia in 2005 suggested that several amino acids located near the receptor-binding site were changing, thereby affecting the antigenic capacity or its transmissibility.¹⁹

In October 2005, research was published describing the reconstruction of the lethal virus of the 1918 pandemic and concluding that this virus was entirely avian, presenting similarities with the H5N1 virus.²⁰

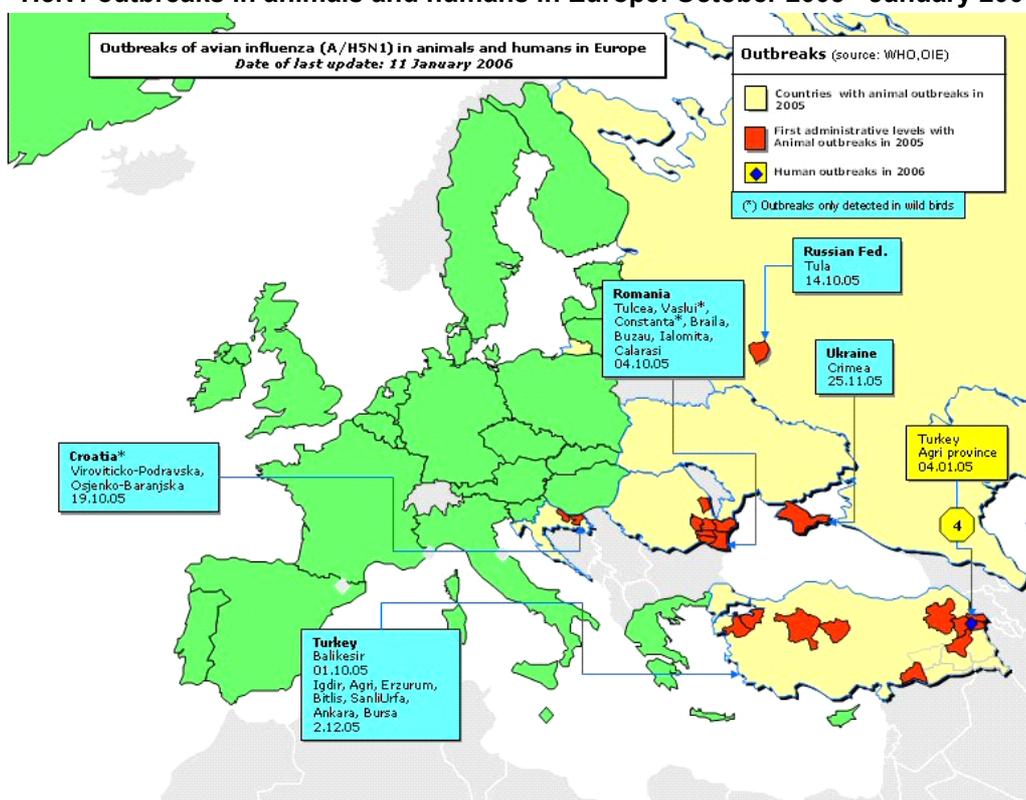
Part Two**(Asia and Eastern Europe).****October 2005 - January 2006**

In October 2005, the presence of the virus was detected in poultry farms in Turkey and Romania. During that same month, Croatia reported the confirmation of H5N1 in wild birds and, in early December 2005, the Ukraine reported its first outbreak in domestic birds.

During the months of October and November, China also reported new outbreaks at poultry farms. In these two months, 25 new outbreaks were reported in 9 provinces, leading to the culling of 20 million birds.

In December 2005 and January 2006, Turkey reported new outbreaks affecting poultry farms in 11 of the 81 provinces. Kuwait detected H5N1 in a single migratory flamingo in November, registering the first case in the Gulf Region.

Also in October 2005, a case of H5N1 was confirmed in an imported parrot, held in quarantine in Great Britain, which had died three days earlier.

H5N1 outbreaks in animals and humans in Europe. October 2005 - January 2006

Three new countries reported cases in humans during this period: China, Iraq and Turkey. Moreover, on October 20th 2005, Thailand reported its first case since October 2004, while Vietnam confirmed its first new case since July 2005.

In November 2005, China reported its first two cases in humans and, in January 2006, Iraq

reported its first case, one month prior to the notification of the outbreak in poultry.

One of the most significant events during this period was the appearance in Turkey of human cases caused by the H5N1 virus, as reported by the national authorities to WHO on January 5th 2006. WHO, the European Commission and the European Centre for Disease

Prevention and Control (ECDC) immediately sent a team of experts to that country in order to assess the situation and provide epidemiological, clinical and laboratory support. In all, the WHO reference laboratory confirmed 12 people infected, with 4 deaths.²¹ All of the cases that occurred in Turkey were concentrated in a period of two weeks.

The average age of the human cases affected was 8, and 80% of the total were children under 14. The results of the studies made in the area indicated that all of the patients had acquired the disease following direct, intense contact with infected poultry. The rapid control of the situation was achieved by the implementation of strict control measures of the outbreaks in poultry, the search, investigation and speedy treatment of the human cases and large-scale information campaigns aimed at the general public as well as social mobilization.

Part Three:

(Western-Central Europe and Africa)

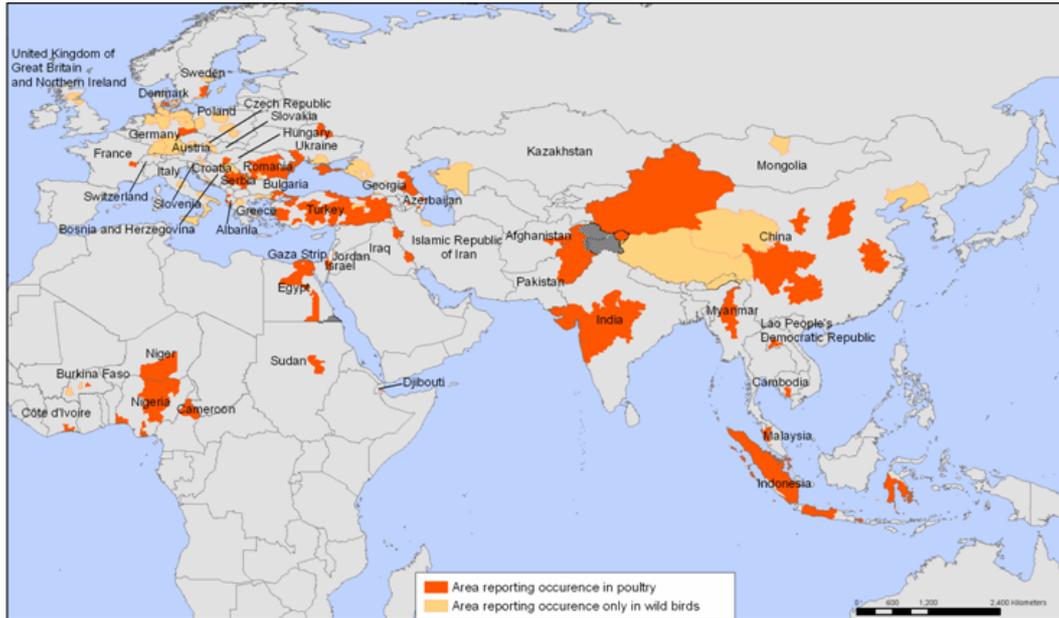
February 2006 - November 2006

The most relevant fact in this period in relation with the evolution of the H5N1 disease is the spread of the infection to the African continent. The virus was reported for the first time on this continent in February 2006, confirming a large focus of infection on industrial poultry farms in Nigeria. In a matter of days the infection

spread to Niger. By November 2006, 8 African countries (Burkina Faso, Cameroon, Egypt, Niger, Nigeria, Sudan, Côte d'Ivoire and Djibouti) had reported outbreaks in domesticated birds to the OIE. The onset and rapid spread of the infection on this continent have been associated with the trade (legal or illegal) of poultry and poultry by-products, combined with poor biosecurity and veterinary structure measures. These areas are particularly relevant because they are the points of connection of migratory bird routes. Moreover, even though the human and bird population density in Africa is less than in Southeast Asia, the production systems and the lack of surveillance systems reveal a number of similarities, with the consequent risk that the infection will become endemic in Africa and human exposure to infected poultry will increase.

Another significant occurrence since February 2006 is the enormous geographical spread of the H5N1 virus, which now affects more than 50 countries, over half of which have been affected for the first time during this period. In addition, new outbreaks of the disease have occurred in countries where the disease had been considered controlled, such as Malaysia, which has confirmed new outbreaks in February 2006 or the Republic of Korea, in November 2006.

Areas reporting H5N1 outbreaks in poultry and wild birds from January to June 2006

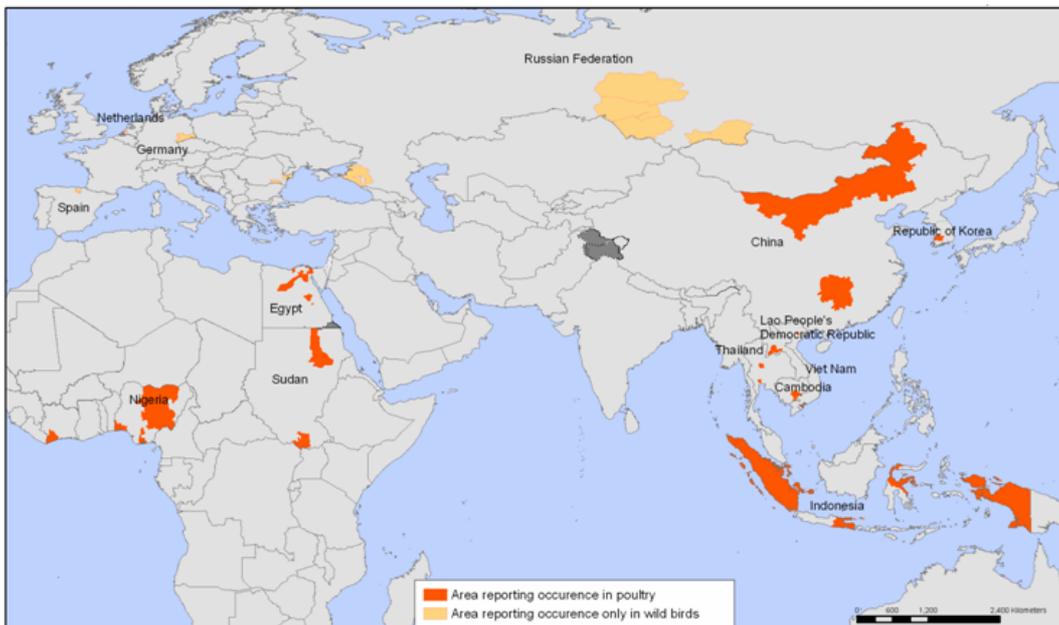


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Data Source: World Organisation for Animal Health (OIE) and national governments
Map Production: Public Health Mapping and GIS Communicable Diseases (CDS) World Health Organization

Areas reporting H5N1 outbreaks in poultry and wild birds from July to November 2006



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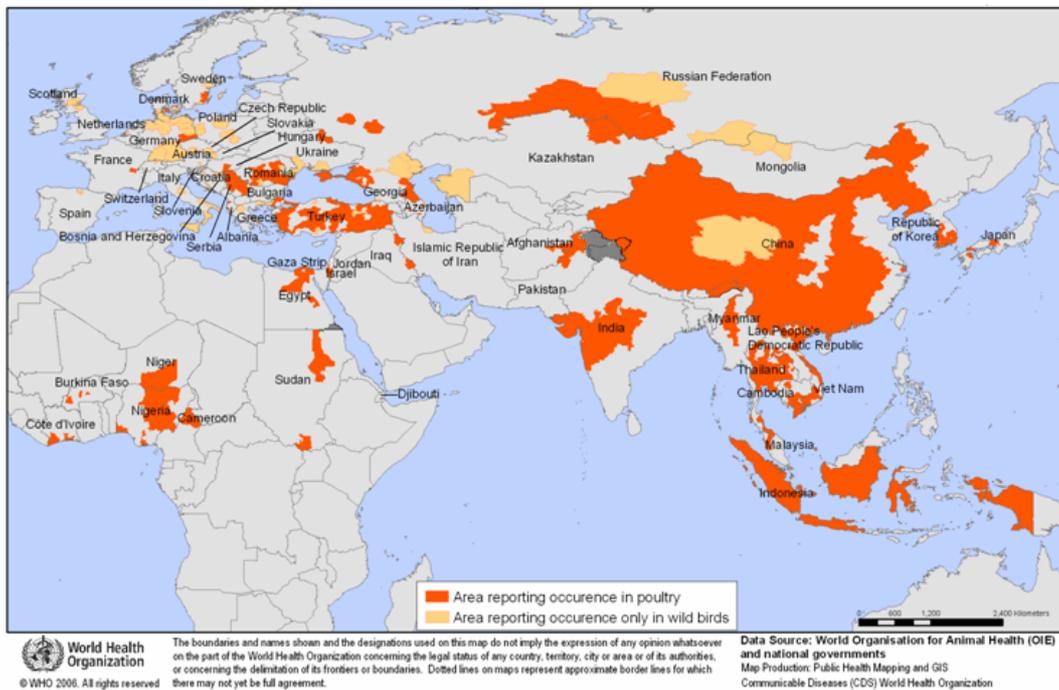
Data Source: World Organisation for Animal Health (OIE) and national governments
Map Production: Public Health Mapping and GIS Communicable Diseases (CDS) World Health Organization

In February 2006, Azerbaijan confirmed the H5N1 virus in migratory birds, and the Russian Federation reported its first H5N1 outbreak on large commercial farms in the region of the Caucasus, close to the Azerbaijan border. More than one half million birds were culled. Also in February 2006, India reported its first foci of affected poultry and, in March, out-

breaks were reported in Pakistan. Iraq reported its first H5N1 outbreak in February 2006.

The most alarming situation in this period arose in Indonesia, where outbreaks were reported in 29 of the country's 33 provinces. In Europe, the country most affected was Romania, with many foci in this period which took months to control.

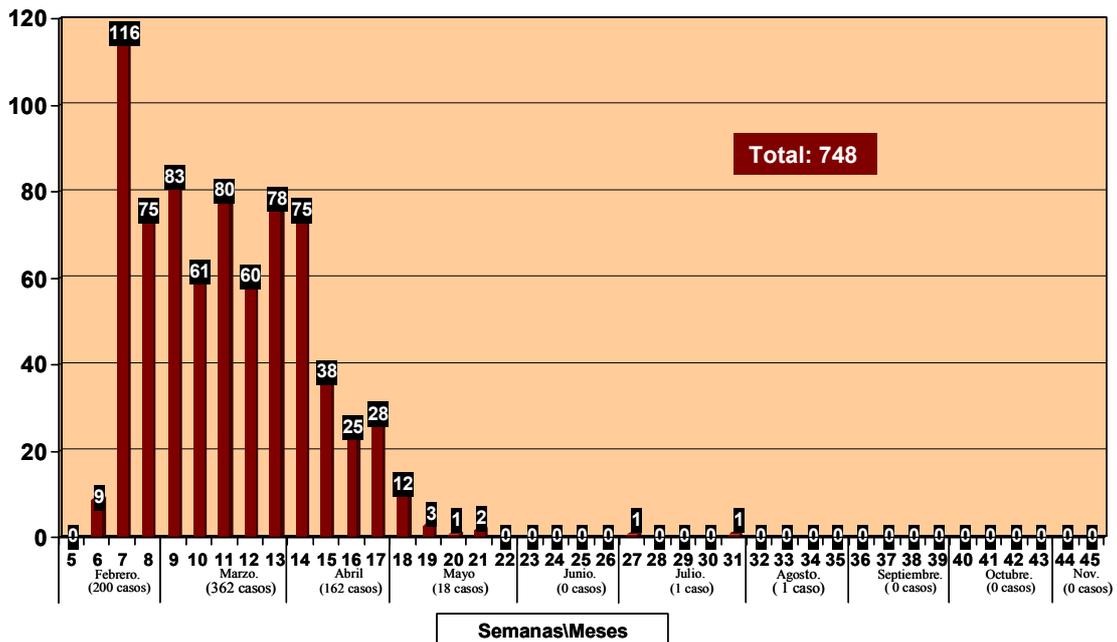
Areas reporting H5N1 outbreaks in poultry and wild birds from 2003 to November 2006



In the European Union, following the confirmation of the first case in wild birds in Greece and Italy on February 11th 2006, cases of this infection in wild or domestic birds have been detected in 15 countries. Nevertheless, the incidence since the end of April has declined considerably. The cases detected in EU countries have affected primarily wild birds, with the exception of foci in domestic birds, highly local-

ized and quickly controlled, in five of these countries: France (the first EU country to report an outbreak in poultry), Germany, Sweden and Denmark and more recently, in June, Hungary. The infection in wild birds in the EU during the spring has been associated fundamentally with the infection of migratory birds originating from Russia and Central Asia.

Cases of avian influenza H5N1 in wild birds in the EU from February 1st to November 9th 2006.



Source: European Commission

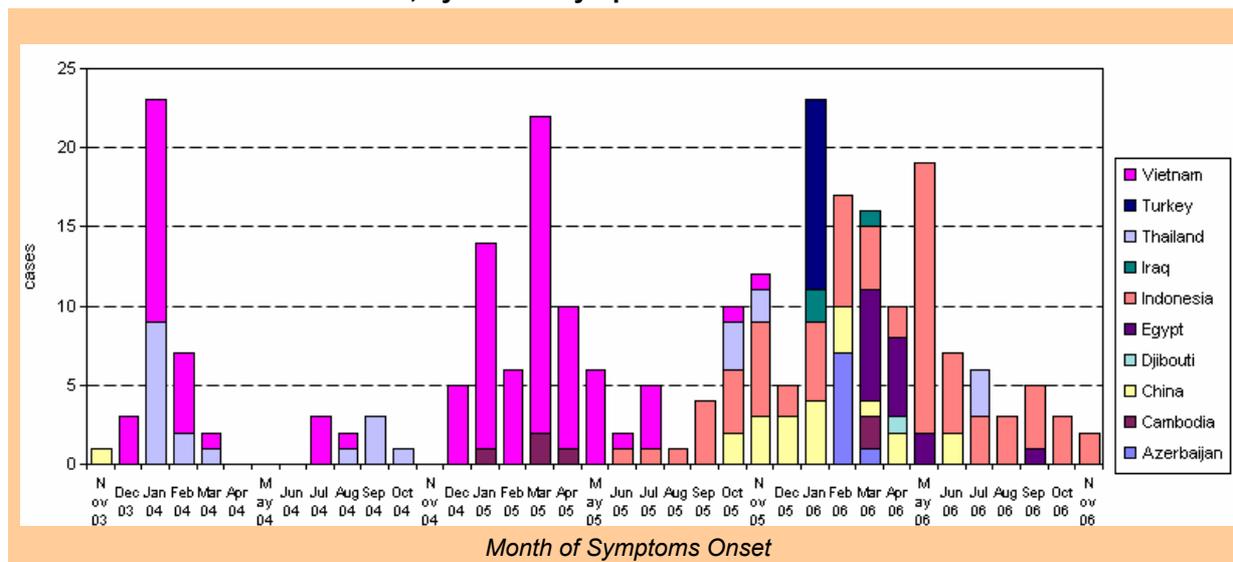
On July 7th 2006, the first case of infection with the A/H5N1 virus in Spain was confirmed in a wild bird. A single case was detected in a wild migratory bird, a great crested grebe (*Podiceps cristatus*), originating from the south of the Peninsula, which was found dead in the Salburua (Alava) wetlands. All preventive measures established in the current protocols to face the confirmation of cases of H5N1 in wild birds were set into motion, which involve control and inspection actions in the animal health domain (censuses of farms, restriction of movements of birds, control of the circulation of by-products, prohibition of fairs and markets, etc...) and, after failing to detect additional positive cases, the end of the outbreak was notified to the OIE on August 29th 2006.

The infection in wild birds and poultry shows that, in Asia, the virus has become endemic in a certain number of the initially affected countries and that, in some places, the spread of the infection is occurring along the routes followed by migratory waterfowl, which can vary slightly depending on weather conditions and/or the scarcity of food. As published by WHO,²² the H5N1 viruses isolated in the wild birds and poultry infected during these months, both in Europe as well as in Asia and Africa,

are almost identical, from a genetic point of view, to those isolated from the Lake Qinghai's migratory birds, which means that this virus is very stable, an unusual circumstance in influenza viruses.

With respect to human infection, during this period, it has also been observed an increase in the number of countries affected as it already occurred in the outbreaks in wild birds and poultry. Up to November 13th 2006, human cases have been reported in ten countries, the majority of which are in Asia: Azerbaijan, Cambodia, China, Egypt, Indonesia, Iraq, Thailand, Turkey, Vietnam and Djibouti. Five of these ten countries (Turkey, Iraq, Azerbaijan, Egypt and Djibouti) have experienced their first cases in 2006. In total, the WHO-confirmed cases as of November 29th 2006 numbered 258, 154 of which were fatal. In 2006, to date, 111 cases have been reported, 76 of which were fatal. The situation of Indonesia stands out particularly, as 40% of the cases occurring in 2006 have been confirmed in that country.²³

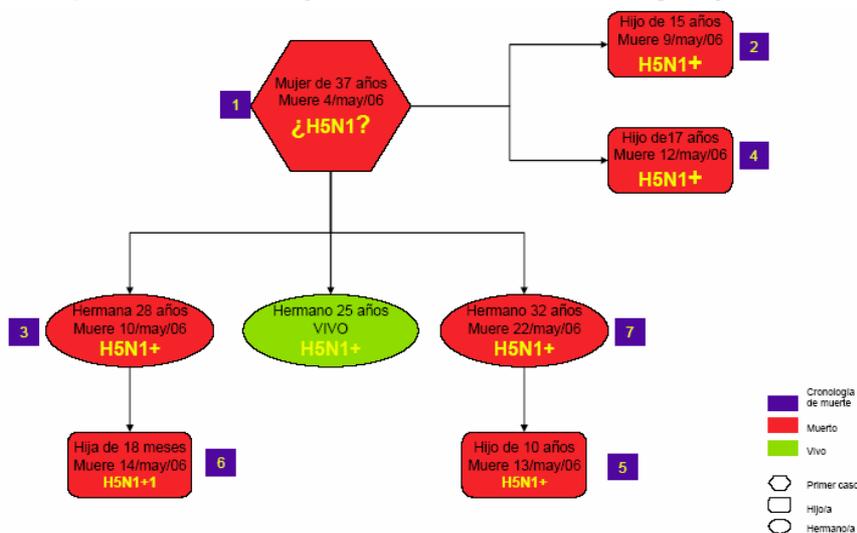
Human cases of H5N1 infection, by date of symptoms onset. November 29th 2006.



Since February 2006, two outbreaks in humans of particular relevance stand out. The first of these occurred on March 14th, when the WHO informed on the first human cases in Azerbaijan. Of the 8 cases reported in this country, 6 occurred in a small village, affecting young women between 15 and 21 years of age. The relevant aspect of these cases is that they were the first to be related to a contact with wild birds, as the exposure of these women was the result of the handling and unfeathering of swans that were found dead. Up to that time, contact had always been associated with domestic poultry.

The second case occurred in early May 2006. The Indonesian health authorities reported 7 cases (6 laboratory-confirmed) in the same family. This is the largest cluster of cases reported and all had a history of close contact with other cases, such as caring for each other during the course of the illness. In this cluster no transmission of the virus to other people outside of the family was found. The health-care staff and others who had close contact with the patients did not present influenza symptoms.

Cases reported in the family cluster in Indonesia during May 2006.



A large part of the research performed during this period focussed on the factors responsible for the pathogenic capacity and transmissibility of the H5N1 virus. The main findings derived from these studies are described below.

Since the H5N1 virus was identified, one of the main aims being pursued is to identify the molecular basis for the virulence of the H5N1 virus in humans. The virulent H5N1 strains for mammals, including humans, have alterations in the sequence of several of the viral proteins such as the haemagglutinin, the PB2 polymerase and the nonstructural protein NS1.²⁴ The possibility of a genetic predisposition towards the infection has been raised, based on the fact that infection often occurred in genetically related individuals, although this possibility will need to be explored in greater depth.²⁵

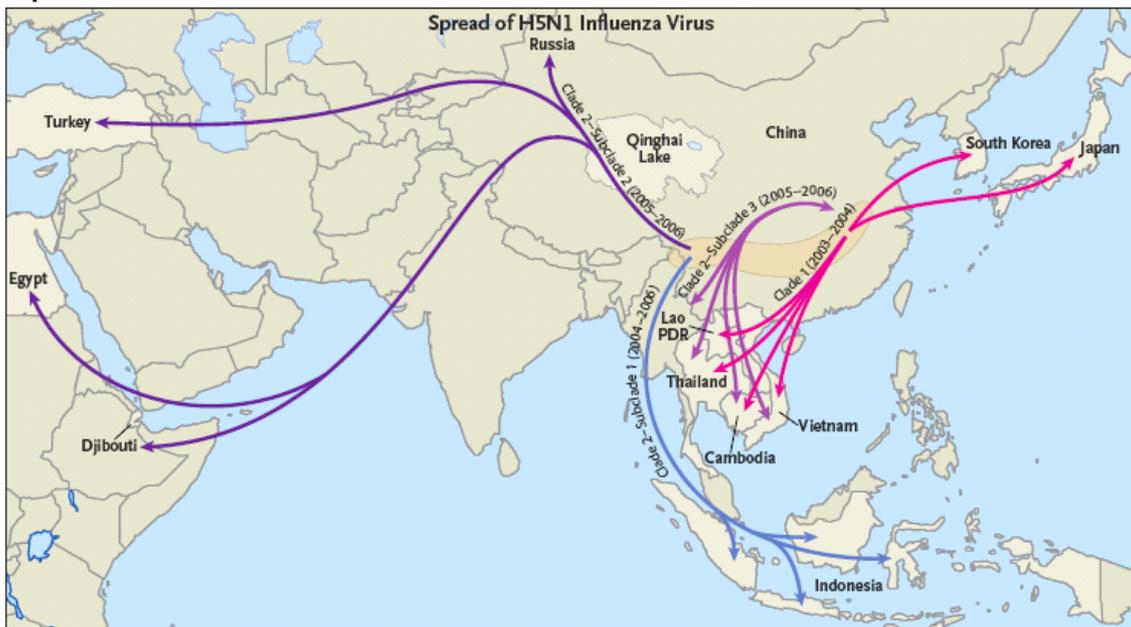
From a genetic analysis of the H5N1 viruses, it can be concluded that the H5N1 virus has been in its place of origin, in the south of China, for at least 10 years, circulating prior to 1997, and has been repeatedly introduced into neighbouring or more distant countries, establishing different colonies of the virus. The H5N1 virus that arose in southern China was the origin of the dominant genotype in Southeast Asia, the Z genotype.²⁶ This later continues to be the dominant genotype in Asia, however, viruses isolated from a number of provinces in southern China present a greater diversity, containing Z, V, W and G genotypes.

In addition, a biogenetic analysis of the genes that code the haemagglutinin of the H5N1 viruses reveal two different lines of genes, concluding that this virus has evolved into two different genetic groups called 1 and 2.²²⁻²⁷

Group 1 has circulated in Thailand, Cambodia and Vietnam in 2004 and 2005 and has been responsible for the infections in humans in these countries. The Group 2 viruses, which are genetically and antigenically different, initially circulated in China and Indonesia in 2003-2004 and the first half of 2005, without causing human cases, however, in mid 2005 the epidemiology of this virus changed, increasing its circulation and beginning to spread westwards, initially in migratory birds, then in domestic poultry and being later detected in the human cases occurring in Turkey, Azerbaijan, Iraq, Egypt and Djibouti. As from the second half of 2005, this virus has also been responsible for human cases in Indonesia and China.²⁵

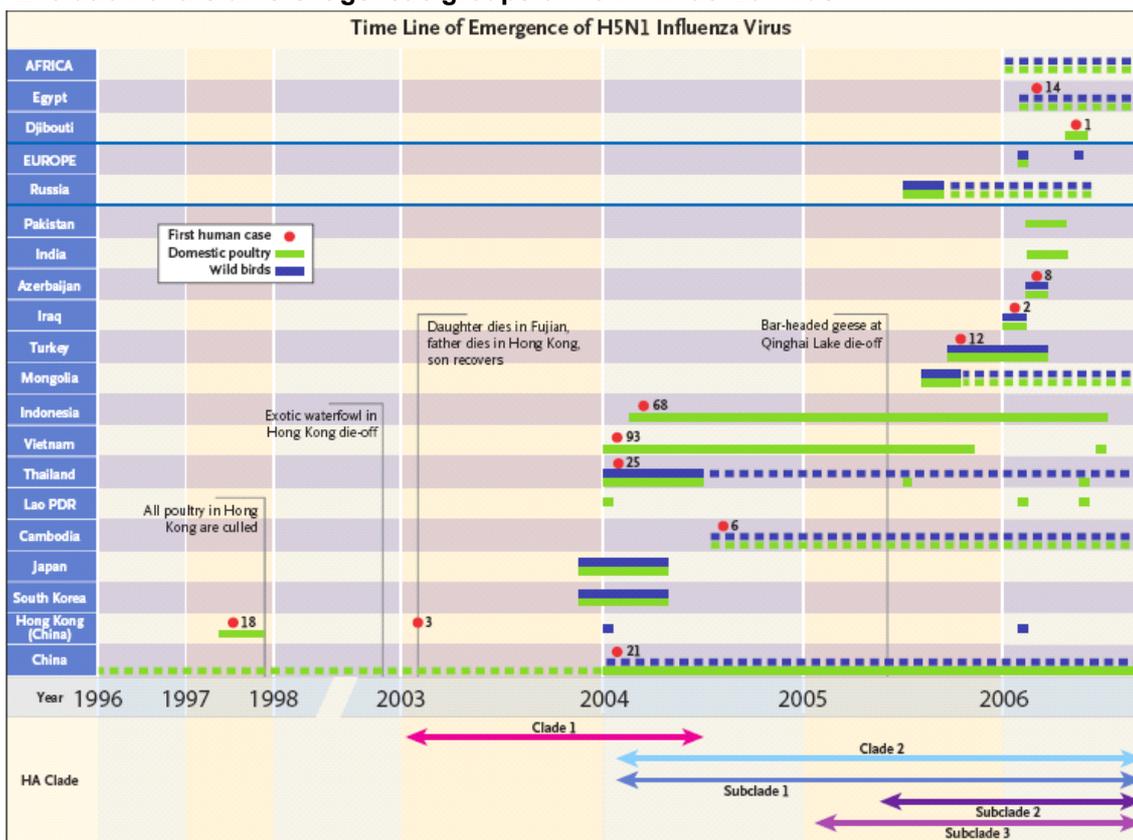
The genetic Group 2 has been the principal cause of human infections since the end of 2005 and has been differentiated into 6 subgroups, three of which also differ with respect to their geographical distribution. One of these has continued to circulate in Indonesia, a second subgroup has caused outbreaks in Europe, the Middle East and Africa and the third subgroup is circulating in China and, although less widespread, in Vietnam.²⁸

Spread of H5N1 influenza virus



Source: N Engl J Med 355 (21): 2174-77

Evolution of the different genetic groups of H5N1 influenza virus



Source: N Engl J Med 355 (21): 2174-77

Derived from the surveillance of H5N1 in birds in China, the results of a paper²⁹ recently published indicate that since the end of 2005, a variant of the H5N1 virus, called Fujian-like,

has emerged and has become predominant. This new sublineage has gradually replaced the various sublineages that were predominant in China, has caused human infections in this

country and has already been transmitted to Hong Kong, Laos, Malaysia and Thailand. The emergence of this variant has a significant impact on control measures, as this strain appears to be resistant to the current vaccines being used in birds in these countries.

The factors required for a viral strain to make the jump from one species to another are not well established, although it is known that an important factor determining host specificity is the receptor to which the viral haemagglutinin binds in order to initiate the infection.³⁰ In 2006, several studies that could help to explain why the H5N1 virus does not readily infect humans and is not transmitted from person to person, have been published.

The various receptors in the human respiratory tract play an important role in the transmission capacity of influenza viruses. That is, there are two types of receptors in the human respiratory tract: the molecules of sialic acid bound to galactose by alpha 2-3 links, which are found principally in the lower respiratory tract (in the nonciliated cells of the bronchoalveolar interface) and the molecules of sialic acid bound to galactose by alpha 2-6 links, which are found principally in the nasal mucosa, trachea and bronchi. The human influenza viruses have a preference for the alpha 2-6 receptors, while the avian viruses, such as the H5N1, prefer the alpha 2-3 receptors, being this the reason why they replicate efficiently in the cells of the lower respiratory tract.³¹

The region where the alpha 2-3 receptors (bronchoalveolar) are found is possibly contributing to the inefficient person-to-person transmission of the virus detected so far. The acquisition of this virus with the ability to recognize the alpha 2-6 receptor would enable the virus to replicate in the upper region of the respiratory tract, where it could be transmitted more readily by coughing or sneezing.³¹

One of the mutations found in the virus isolated in Turkey involves a replacement of the amino acid serine by asparagine in position 223 of the binding protein to the surface receptors of the host cells.³² This mutation has been observed twice previously in H5N1 (in viruses

isolated in a small outbreak detected in Hong Kong in 2003, and in the outbreak in 2005 in Vietnam). This mutation is known to be possibly involved in the increase in the affinity of the H5N1 virus for the alpha 2-6 receptors, and the effect thereof would be an enhancement of the ability of the virus to bind to the human receptors and the decline of its affinity for avian receptors.

Another of the changes that was detected in the specimens from Turkey was the replacement of the glutamic acid by lysine in position 627 of the polymerase, which is associated with an increase in the replication of the virus. This mutation was seen in birds last year and in a person who died in the Netherlands during the H7N7 outbreak that took place in 2003. This mutation has also been seen in some of the people affected by the current H5N1 outbreak in Vietnam and Thailand. The mutation in the polymerase was one of the changes that occurred in the virus that gave rise to the 1918 pandemic.³²

However, the effect of these changes in the transmissibility of the virus from birds to humans, or from one person to another, is not established and, furthermore, to date, in the study of the viruses isolated from humans, it has been found that these mutations are transitory so far and have not become established in the circulating viruses.³³

The results of recent research, based on the production of an experimental genetic recombination model of the H3N2 human virus and the H5N1 avian virus point to a lack of transmissibility of the resulting recombination from these viruses.³⁴

A.2. Characteristics of Human Infection with the H5N1 Virus

This section undertakes a review of the principal clinical characteristics and the factors associated with the transmission of the H5N1 virus to humans. Before doing so, a brief overview will be provided of the outbreaks of avian influenza prior to the current H5N1 outbreak, in which human infection also occurred, as it is important to take into account the fact that although this is the largest outbreak, it is not the first time that humans have been affected by avian influenza viruses.

A.2.1. Human infection with the avian influenza virus prior to the current H5N1 outbreak.

The most severe and most widespread infections by avian influenza viruses have been caused by highly pathogenic influenza viruses. However, the low pathogenic viruses can, on very rare occasions, cause illness in humans, although these have always produced infections with very mild symptoms.

It must also be kept in mind that, although birds have been the principal source of infection for humans, not all of the infections by animal influenza virus that have affected humans were due to transmission from birds. For example, at the end of the seventies, a number of workers who had contact with infections in seals developed conjunctivitis.³⁵ Nevertheless, these cases were very sporadic and the symptoms were mild.

As shown on the table, since 1959 and up to the current H5N1 outbreak, cases of human infection with an avian influenza virus have been documented on 10 occasions,¹ and on these occasions, of the multiple strains of avian influenza A virus, only the following have been involved: H5N1, H7N2, H7N3, H7N7, and H9N2. In general, these infections have been manifested with mild symptoms of illness.

The first of these was detected in the U.S.A in 1959 and was caused by the A/H7N7 virus. The virus was isolated from the blood of a man who developed hepatitis. During the period between 1978-79, a few cases were reported of self-limited conjunctivitis among workers involved in an outbreak of low pathogenic H7N7 influenza in the north-eastern region of the U.S.A. Also, in 1996, a 43-year-old woman in England, who kept domestic ducks that had mingled with wild ducks developed conjunctivitis from which low pathogenic H7N7 was isolated.³⁶

Between December 1998 and March 1999, a low pathogenic H9N2 virus was isolated from seven people between 1 and 70 years of age in China and Hong Kong (fever and respiratory symptoms were detected in the two Hong Kong patients only). In 2002, during a low pathogenic H7N2 outbreak in the U.S.A., positive antibodies against this virus were detected in one person, and in 2003, the low pathogenic H7N2 virus was also isolated from a patient with a severe basic disease.

In February 2003, 2 patients affected with the avian influenza virus H5N1 subtype and 1 death were identified in Hong Kong in a family that had travelled to southern China.

In Europe, an outbreak of avian influenza caused by the subtype H7N7 occurred in the Netherlands in February 2003. The virus was confirmed in 89 cases. Except for a veterinarian who died, the rest of the cases displayed mild symptoms. The reports on this outbreak revealed that at least one thousand people were infected with this virus during the epidemic, and that antibodies were detected in more than half of the people who cohabitated with the workers in contact with infected poultry.³⁷⁻³⁸

During the H7N3 outbreak in Canada in 2004, this highly pathogenic virus was detected in two people, who showed symptoms of conjunctivitis, common cold and headache.

Human cases of infection with avian influenza viruses since 1959 without including the human cases from the current H5N1 outbreak

Year	Sub-type	Country affected	Cases	Deaths
1959	H7N7 (HP)	U.S.A.	1	0
1978-79	H7N7 (LP)	U.S.A.	Several	0
1996	H7N7 (LP)	England	1	0
1997	H5N1 (HP)	Hong Kong	18	6
1999	H9N2 (LP)	China, Hong Kong	7	0
2002-2003	H7N2 (LP)	U.S.A.	2	0
2003	H5N1 (HP)	Hong Kong	2	1
2003	H7N7 (HP)	Netherlands	89	1
2003	H9N2 (LP)	Hong Kong	1	0
2004	H7N3 (HP)	Canada	2	0

HP: High pathogenicity; LP: Low pathogenicity

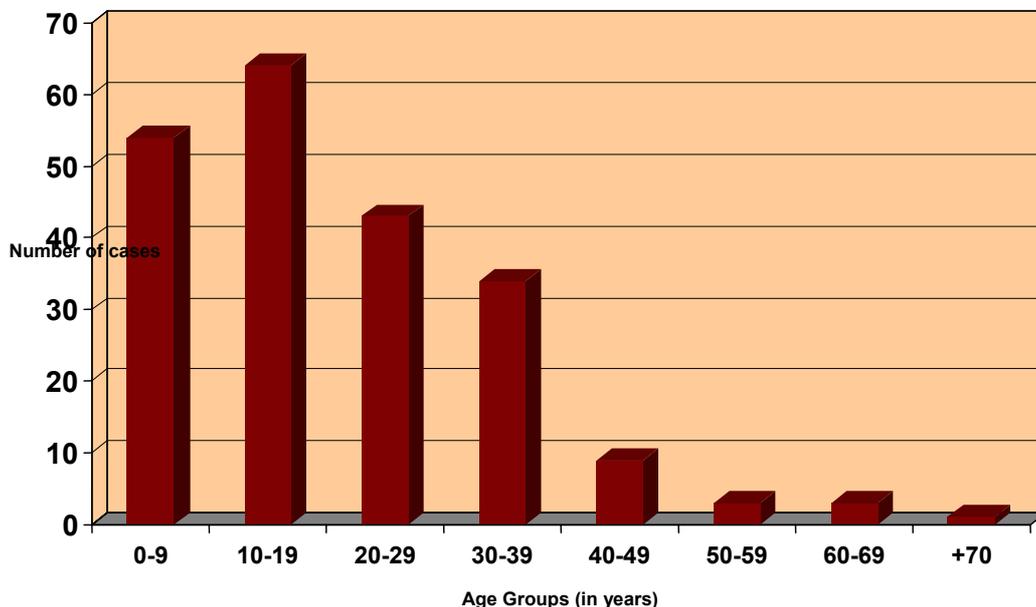
Recently, in May 2006, a worker with occupational exposure developed conjunctivitis in the low pathogenic H7N3 outbreak in the United Kingdom.³⁹

A.2.2. Clinical characteristics of the H5N1 influenza

As in the majority of emerging diseases, the characteristics of the disease caused by the influenza A/H5N1 virus in humans are not yet known in depth. Clinical data from the cases confirmed to date are beginning to provide a picture of the clinical characteristics of the disease,⁴⁰⁻⁴¹ but it must be kept in mind that the current picture could progressively vary, given the propensity of this virus to change rapidly and in an unforeseeable manner.

According to the last update by WHO,⁴¹ the median age of the confirmed cases is 20, ranging from 3 months to 75 years of age. Half of the cases are found in people under 20 years of age. There are no significant differences with respect to the sex of those infected.

Age distribution of human cases of H5N1. November 29th 2006.



The incubation period for the H5N1 avian influenza may be longer than the one described for seasonal influenza, which is from two to three days. Current data point to an incubation period ranging from 2 to 8

days and which may possibly last up to 17 days.⁴⁰ However, the possibility of multiple exposures to the virus makes it difficult to define this period with precision. In this regard, WHO currently recommends the use

of a seven-day incubation period for the investigations to be carried out on the cases of the disease and for the monitoring of the contacts.⁴²

In the cases infected with the A/H5N1 virus described so far, the disease follows an unusually aggressive clinical course, with rapid deterioration and high mortality. The initial symptoms include high fever, generally with a temperature over 38°C, and influenza symptoms. Diarrhoea, vomiting, abdominal pain, chest pain and nose bleeding have also been described as early symptoms in some patients. Watery diarrhoea without blood appears to be more common in the H5N1 avian influenza than in the seasonal influenza.⁴⁰ The spectrum of clinical symptoms may, however, be broader, and not all confirmed patients have presented respiratory symptoms. In two patients in the southern region of Vietnam, the clinical diagnosis was acute encephalitis and neither of the patients had respiratory symptoms when symptoms onset. In another case, in Thailand, the patient presented fever and diarrhoea, without respiratory symptoms⁴³ The three patients had a recent history of direct exposure to infected poultry.

A characteristic observed in many patients is the development of lower respiratory tract manifestations in early stages of the disease. According to available data so far, the respiratory difficulty appears around five days after the first symptoms. Frequently, respiratory distress, hoarseness and crepitant rale are also presented. The production of sputum is variable and at times bloody. Almost all of the patients develop pneumonia.⁴⁰ During the Hong Kong outbreak, all of the patients with serious illness developed primary viral pneumonia, which did not respond to antibiotics. Limited data on the patients affected by the current outbreak indicate the presence of a primary viral pneumonia in H5N1, generally without microbiological evidence of bacterial overinfection in the presentation of the disease. In Turkey, clinicians have also reported the ap-

pearance of pneumonia as a constant characteristic in severe cases; these patients, as in the previous cases, did not respond to antibiotic treatment.

The clinical deterioration is rapid. In Thailand, the time between the establishment of the disease and the development of acute respiratory distress was around six days, with a range of 4 to 13 days. In the severe cases in Turkey, clinicians observed respiratory failure between three and five days after the onset of the symptoms.⁴²

Another common characteristic is multiorgan dysfunction. Laboratory-determined alterations also tend to appear, including leucopenia (principally lymphopenia), mild or moderate thrombocytopenia, high transaminases and, in some cases, disseminated intravascular coagulation. The number of days since the establishment of the symptoms up to the time of death ranges around 10 days.⁴¹

The fatality rate in confirmed cases is around 50% and is higher in the younger age groups (73% in the 10 to 19-year-old group in the latest report by WHO).⁴¹

One of the points not yet clarified to date is that of the existence or not of mild or asymptomatic cases that have not been detected or notified.⁴⁴ The serological studies made to date have not been able to identify mild or asymptomatic cases. However, these serological studies have been very limited and the methods used are only capable of detecting serological responses in severely ill hospitalized patients.

A report published recently by WHO²⁵ includes the results of several seroprevalence studies: the seroprevalence studies carried out in Hong Kong in 1997 found that in workers involved in raising domestic birds the prevalence of antibodies was 10%, greater than that of the workers employed in the slaughter of the birds, where the figure was 3%. The prevalence in the general population was 0%. Recent serological studies, using pairs of sera, per-

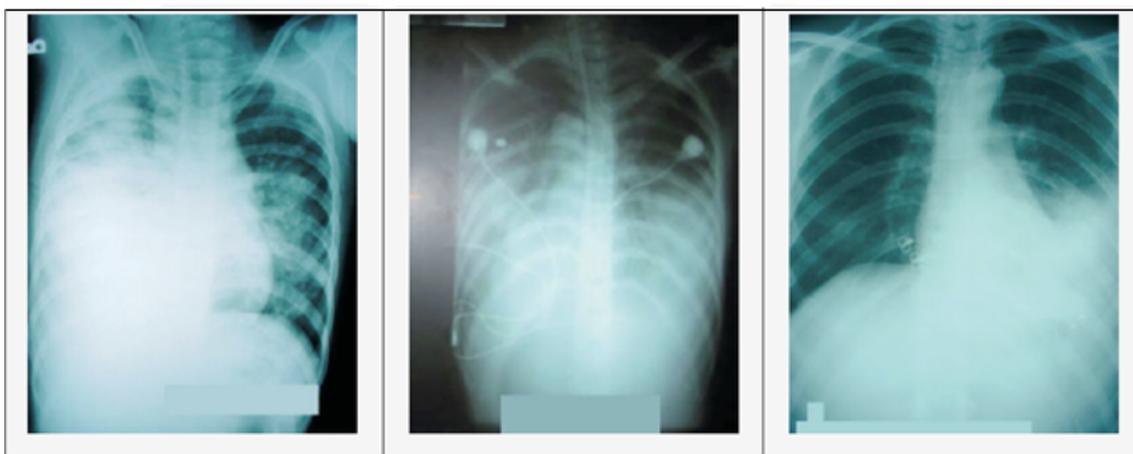
formed on 2,109 workers employed in the slaughter of poultry in the Republic of Korea, detected H5 antibodies in 9 people. These infections were associated with mild or moderate symptoms and were acquired prior to the use of personal protection equipment by the workers. Furthermore, healthcare workers examined in Thailand have shown negative results, while in Vietnam, some of the members of the families of people affected gave positive results, although the rest of the contacts of the cases studied have been consistently negative.

Limited evidence suggests that some antiviral drugs, particularly oseltamivir, can reduce the duration of the viral replication and

improve the possibilities of survival, if they are administered within a period of 48 hours following the onset of the symptoms. However, the clinical data on the effectiveness of oseltamivir are very limited, as the majority of patients are diagnosed and treated late in the course of the disease.⁴²

Oseltamivir and other antiviral drugs were developed for the treatment and prophylaxis of seasonal influenza, which is a less serious disease and in which a less prolonged viral replication occurs. For this reason, the recommendations as to the optimum dosage and duration of the treatment of H5N1 avian influenza need to be reviewed on an ongoing basis.

Chest X-rays of three patients with avian influenza A (H5N1)



Source: *N Engl J Med* 2005;352:686-691

A.2.3. Transmission of the H5N1 avian virus to humans. Factors associated with the risk of human infection

At the present time, H5N1 continues to be a disease that affects birds fundamentally. The species barrier is significant: the virus does not cross this barrier easily in order to infect humans. This is proven by the fact that, despite the infection of tens of millions of poultry over large geographical areas since mid 2003, only around 250 cases in humans have been confirmed.

All of the evidence to date indicates that direct contact with diseased or dead birds is the principal source of human infection with the H5N1 virus, by means of the inhalation

of respiratory droplets or of contaminated dust. The behaviours identified as particularly risky include the slaughtering, defeathering and the butchering of infected birds.⁴²

Indirect contact, exposure to an environment that may have been contaminated by the faeces of infected birds, is a second mechanism of infection for humans, but much less frequent than direct contact. Thus, in a small number of cases, the source of the infection has been associated with exposure to chicken faeces when children were playing in an area frequented by free-ranging poultry. Another possible source of exposure may be the fact of swimming in water into which the carcasses

of infected poultry may have been discarded or that has been contaminated by faeces from ducks or migratory birds.⁴²

In some cases investigations have been unable to identify a plausible source of exposure, suggesting that some environmental factor, as yet to be discovered and involving contamination with the virus, may be associated with a small number of cases.⁴⁰ A number of explanations have been proposed, which include a possible role of peri-domestic birds, such as pigeons, or the use of untreated bird faeces as fertilizers.

The majority of cases have occurred in rural or peri-urban households where a small number of domestic poultry are kept. The outbreaks in these backyard flocks are very difficult to control, and human contact with the birds is very close. These domestic birds are generally free to roam and feed in the same areas as migratory birds, as well as sharing their sources of water. Such situations create abundant opportunities for human exposure to the virus, particularly when birds enter households, when they are brought in during periods of bad weather or when they share areas where children play or sleep.

The Azerbaijan experience showed that there are exceptional situations in which contact with wild birds can involve a risk of infection for humans, if these birds are handled without appropriate precautions.⁴⁴

Another of the characteristics that have been observed in the current H5N1 outbreak is that this virus is capable of infecting certain species of mammals in which influenza viruses had never been detected. Last February, Germany reported the finding of a cat infected with H5N1 on the island of Ruegen⁴⁵ and in Thailand cases involving these animals had been reported in February 2004.⁴⁶ The H5N1 virus has also affected other species such as civets (in July 2005, three civets in captivity were found dead in Vietnam) and ferrets, and the virus has also been detected in Germany in

a marten found dead following contact with infected wild birds.

The evidence available indicates that the infections detected in these animals are exceptional to date and occur in association with H5N1 outbreaks in domestic or wild birds. At the present time there is no evidence that the aforementioned animals play a role in the transmission of H5N1 viruses. Up to now, no cases in humans have been detected in relation to exposure to any of these animals.

A very small number of cases have been detected in theoretical risk groups, such as poultry traders, workers in live poultry markets or involved in slaughtering operations, veterinarians or healthcare personnel who have cared for patients without the proper protective equipment.⁴⁷ Neither is it clear why the cases in humans are concentrated in previously healthy children and young adults. A number of studies and research efforts are in progress in order to better define the circumstances of the exposure, behaviour and possible genetic or immunological factors that could increase the likelihood of human infection.

The fact that domestic ducks can excrete large quantities of highly pathogenic virus without showing signs of the disease must also be taken into account when investigating the exposure history in cases of infection with H5N1. It is also important to keep in mind that a history of consumption of poultry in an affected country is not considered a risk factor if the food has been properly cooked and the person has not been involved in the preparation of the food.

Since 1997, few cases of occasional transmission of the H5N1 virus to very close contacts have been reported.¹⁷ These infections have been found, as a general rule, in very close relatives who provided care to the patient, without the disease having been transmitted in any case in an efficient or sustained manner in the community. The largest family cluster in which a person-to-person transmission occurred was the case

detected in Indonesia in early May 2006, with the infection of 8 members of a single family, 7 of whom died.⁴⁸

In some countries of Southeast Asia, such as China, Indonesia and Vietnam, large-scale vaccination programmes in birds are being implemented as a medium-term strategy aimed at reducing the disease and the need for massive culling. The impact of these strategies on the risk of infection and of disease in humans is not clear. If the immunization of poultry is effective and is well monitored, it could reduce the H5N1

load in the poultry population and, as a result, also lessen the risk of infection in humans.⁴⁹ However, it could also bring along a silent circulation of the virus, thus augmenting the risk for humans in those countries and the risk of co-infection with other influenza viruses. One of the consequences of these programmes could be that of hampering the surveillance of influenza cases in humans and of clusters of these cases, because of the absence of history of exposure to sick birds when investigating cases of pneumonia.⁴⁷

A.3. Assessment of the Risk to Human Health of the H5N1 Virus

The influenza A/H5N1 virus is a cause for concern for human health because of two reasons. In the first place, it has crossed the species barrier to infect humans on at least three occasions in recent years, in 1997 and in 2003 in Hong Kong, and in the current outbreaks that started in December 2003, and it is the avian influenza virus which has caused the greatest number of human cases of severe disease and death.

Secondly, and much more significant for human health, there is a risk that the H5N1 virus will acquire the ability to transmit itself efficiently from person to person and thereby unleash an influenza pandemic. Of the three conditions to be met by an influenza virus in order to cause a pandemic: infect humans, cause illness in them and be capable of efficiently passing from one person to another, the H5N1 virus has already met the first two.

At the present time, the H5N1 virus is endemic in many parts of Asia, having established a permanent ecological niche in birds in this geographical area. The presentation of these outbreaks in rural areas, where the majority of the population has direct contact with the birds affected, which are the basis of their economy, makes it difficult to control these outbreaks.

The appearance of widespread H5N1 outbreaks in a number of countries on the African continent during the past year is an additional reason for being on alert. In these countries, the animal surveillance systems are not fully developed and their production systems, the same as in Asia, are based on small family flocks where no biosecurity measures are applied, making it very difficult for strict control measures to be put into place in order to contain these outbreaks. The population has little information on the risk and the measures to be taken to avoid it. All of this leads to a high risk of human

exposure to infected poultry and means that there is a high probability of a significant number of cases in humans in these areas.

Due to the extension over which the H5N1 outbreaks have spread, there remains a risk that this virus could undergo changes that would involve a human-to-human transmission with the consequent risk of the onset of a pandemic. This situation will continue for as long as the virus remains in the environment and, according to experts, it is unlikely that it will disappear in a short space of time.

The influenza A/H5N1 virus has undergone a number of changes since the first human infections were documented in 1997. Its pathogenicity and its resistance are increasing. It is also known that the different species of domestic and migratory birds respond to the virus in different ways. These differences are important for the identification of the sentinel and the reservoir species and for the assessment of the risk, particularly with respect to the westwards spread of this virus. Moreover, the excretion patterns vary according to the species, and this can affect the manner and the risk of transmission.

For the time being, these changes are affecting fundamentally the patterns of transmission and spread of the virus between domestic poultry and wild birds and do not appear to have a significant impact on the disease in humans, or on the transmission mechanisms in humans.³³ There is no evidence, at the present time, that the virus has increased its ability to pass from one person to another, and in all of the tests performed, it has been found that all of the genes of the H5N1 viruses circulating are of an avian origin, and thus there is no evidence that a recombination of genetic material has occurred.

It is not possible to predict when an influenza virus, such as the H5N1, could acquire the characteristics necessary in order to be transmitted among humans, or if this could even occur because, among other

reasons, it is not known exactly what specific mutations are those that would lead to an increase in the transmissibility of the virus from person to person. For this reason, it is fundamental that the virological study of the mutations in the influenza viruses is done in conjunction with the epidemiological assessment of the patterns of transmission in the population.

The risk of cases appearing in humans due to this virus is still considered to be very low and restricted to certain at-risk groups, which are those that have close contact with infected birds, particularly domestic poultry.

In Europe, although the virus has been detected in many countries, at the present time, it poses a very low risk to human health and, with respect to people who have absolutely no contact with domestic or wild birds, the risk should be considered practically zero at this time.⁴⁷

Since the virus can be carried by migratory birds, the people most at risk are those with small domestic flocks, particularly if the poultry is raised outdoors, as it is more difficult to apply adequate biosecurity measures in these conditions, and there tends to be closer contact between humans and animals.

The pandemic risk situation has not changed and, in accordance with the phases established by the World Health Organization, we are still in a period of pandemic alert, phase 3, which is defined by the appearance of human infection with a new influenza virus subtype but without person-to-person transmission, or at the most, rare cases of transmission to a close contact.

Finally, the European Union, in order to minimize the risk of outbreaks of avian influenza in domestic poultry or wild birds and to avoid human exposure to possible

sources, has established a number of measures for controlling and fighting avian influenza, according to the guidelines established by the OIE.⁵⁰

An active surveillance of the disease in birds has been initiated, which in Spain is coordinated by the Ministry of Agricultural, Fisheries and Food,^{51, 52} and prohibitions have been introduced in relation to imports of live birds and high risk poultry products, originating from all of the countries or regions where outbreaks of the disease have been detected or confirmed within their borders.

Given that the Asian strain of the virus began to spread to the West from Asia, the EU has strengthened the preventive, surveillance and control measures. There was an agreement to apply the strictest biosecurity measures, including the requirement of keeping domestic poultry in confinement in high-risk areas, the prohibition of the concentration of poultry in markets, expositions and cultural events and the drawing up of surveillance plans with respect to wild and domestic birds.

The new Council Directive 2005/94/CE updates the most appropriate prevention and surveillance measures in order to minimize health risks, economic costs and the negative repercussions on society in the event of an outbreak of the disease. A key aspect of the Directive is the new stress on the surveillance and control of the low pathogenic viruses as a means for preventing a significant outbreak of avian influenza. It also allows the Member States to carry out preventive vaccinations and emergency vaccinations against avian influenza, under strictly controlled conditions.

B. COORDINATION AND ORGANIZATIONAL STRUCTURE OF THE NATIONAL PLAN

The composition and the functions of each of the groups that make up the organizational and coordinating structure of the Plan are described in section 5.1 of the National Pandemic Influenza Preparedness and Response Plan of May 2005.

The principal activities carried out by these groups since the publication of the Plan are described below.

B.1. Inter-ministerial Avian Influenza Monitoring and Information Commission

Headed by the Ministry for the Cabinet Office and the Secretariat of State for Communication, this Commission was set up in February 2006 with the participation of representatives from the various governmental departments involved, (Health and Consumer Affairs, Agriculture, Fisheries and Food, Economy and Finance, Home Office, Public Administrations, Industry, Tourism and Trade, Environment and the Ministry for the Cabinet Office). The Commission coordinates the Government's communication policy in relation to avian influenza.

B.2. National Executive Committee for the Prevention, Control and Monitoring of the Epidemiological Evolution of the Influenza Virus.

Chaired by the Minister for Health and Consumer Affairs, this Committee meets regularly in order to monitor the situation, to publicize the risk assessment for the Spanish population and to approve protocols for the actions to be taken.

Since the approval of the National Plan, the protocols listed in the specific paragraphs of the Subcommittees have been submitted to this Committee, together with those drawn up by the Directorate General for Public Health (DGSP) of the Ministry of Health and Consumer Affairs (MSC).

The composition of this Committee has been expanded in recent meetings, to include representatives from three Autonomous Communities (AACC) and one from the Ministry of Environment.

B.3. Public Health Commission

The main objective of this Commission in the organizational structure of the Plan has been to drive the start-up and implementation of the Autonomous Communities' Plans and to ensure that the control measures established for each phase in the National Plan are adopted in a coordinated manner in all of the Communities. As a result of this effort, at the present time, all of the Autonomous Communities have developed up a pandemic influenza preparedness and response plan that includes a health services emergency response plan.

Since the approval of the National Plan in May 2005, this Commission has discussed the issue of avian influenza and pandemic preparedness in all of its meetings, which, as a general rule, are held on a monthly basis, and has played a fundamental role in the coordination and harmonization of the measures that have been progressively adopted as a part of the preparedness effort to cope with a pandemic. A particular mention should be made of the Commission's decision to purchase antiviral drugs for 20% of the population.

B.4. Technical Coordinating Group

This Group has been responsible for the organization and preparation of the documents presented at the meetings of the Subcommittees established in the National Plan. It coordinates the participation of Sci-

entific Societies in the drafting of protocols as well as the meetings of the Scientific Committee.

The Group prepares daily and weekly reports updating the avian influenza situation worldwide and keeps an Intranet tool created by the Ministry of Health permanently updated. It participates in the international meetings for the coordination of national plans in the European Region and has organized the coordination meetings between the regions and Autonomous Communities bordering with Portugal.

B.5. Scientific Committee

This Committee was set up in June 2005. Since then, it has been providing support to the development of the Plan both in the preparation of technical protocols, as well as in the field of communication, as it has been considered that the message and the recommendations issued both to the professionals concerned as well as to the public in general by the Public Administration and by the relevant Scientific Societies should be homogeneous and agreed by consensus.

In addition to the Societies mentioned in the National Plan of May 2005, the Spanish Society for Emergency Medicine and the Spanish Association for Vaccinology have also been included as members of this Committee.

B.6. National Plan Subcommittees

B.6.1 Surveillance Subcommittee

The preparation of the surveillance aspects is considered fundamental, as the situation of pandemic and the phases of pandemic alert will involve a significant increase in the requirements and the operation of the surveillance systems. In the course of a pandemic, the influenza surveillance will need to provide information that was not collected previously and, above all, the time-

frames and the precision that are going to be requested from the surveillance systems in a pandemic are going to change significantly with respect to the annual inter-pandemic seasons. In this regard, it will be necessary to take into account that, in a pandemic situation, there will be excessive demands on the surveillance systems, which may possibly have to organize themselves on the basis of special criteria, considering that they also could be affected by reduced staffing levels due to illness among the personnel entrusted with this surveillance.

The surveillance of the influenza in the various phases of a pandemic will involve different needs and will have different characteristics depending on the pattern of presentation of the disease, and the disease surveillance systems must necessarily be endowed with flexibility in order to be able to adapt to a range of possible scenarios.

Although the objectives of influenza surveillance in a pandemic situation will change over time, there is a certain consensus in that, in the course of the various pandemic phases, the surveillance systems must obtain the information necessary to be able to:

1. Early detect human cases caused by the new influenza strain.
2. Propose effective control measures that will limit its transmission.
3. Identify clusters of cases and initial outbreaks and monitor the pattern of dissemination and impact.
4. Detect any possible change in the pandemic virus.
5. Provide information for the development of a vaccine.
6. Estimate the possible epidemic curve.
7. Serve as a support for decisions in relation to the distribution of vac-

cines, treatments with antiviral drugs and other Public Health measures aimed at the reduction of the transmission.

During 2006, the Subcommittee has worked with representatives from the Autonomous Communities specialized in epidemiological and virological surveillance, the National Centre for Epidemiology and the National Centre for Microbiology, and the following protocols have been agreed:

- The procedure to be followed in the event of the detection of human infection with the influenza virus A/H5 in Phase 3 of pandemic alert
- The protocol of action for workers and people exposed to birds or animals infected with highly pathogenic avian influenza viruses, including the H5N1
- Protocol of contacts in phases 4 and 5 of pandemic alert
- Surveillance of influenza in the course of a pandemic. (WHO Phases 4, 5 and 6)

Issues regarding surveillance included in the above protocols were previously discussed with the ECDC and the WHO Regional Office for Europe.

B.6.2 Vaccines and Antivirals Subcommittee

In the face of a pandemic situation and in the preliminary phases of a pandemic alert, the decisions in relation to the pharmacological control measures (antiviral drugs and vaccines) that will help to reduce the impact of the pandemic are important. These measures will be administered to the population in order to reduce the transmission or to slow down the spread of the infection, to lessen the severity of the disease and to minimize the social upheaval that the pandemic could cause.

The function of this Subcommittee is to advise the Committees and Organizations responsible for the decision-making proc-

esses relating to these control measures on all of the technical aspects of the vaccines and antivirals. For this reason, the Subcommittee has focussed on the issues concerning the characteristics, availability, supply and conditions of administration of both the antiviral drugs as well as the future vaccines to counter the pandemic.

As set out in the section on strategic actions, over the past year this Subcommittee, fundamentally in line with the recommendations drawn up by WHO and the ECDC, has prepared protocols that define the criteria, situations and recommendations for the use of antiviral drugs and provide technical criteria to the relevant Organizations with respect to the supply of these drugs. It has also discussed and made recommendations on future vaccines against the pandemic. The protocols prepared by this Committee, based on a consensus, include:

- Protocol for the definition of priority groups for the use of antivirals
- Indications for prophylaxis with oseltamivir following exposure to the influenza virus A/H5N1 in Phase 3 of pandemic alert.

B.6.3 Healthcare Services Emergency Response Subcommittee

If a virus with characteristics capable of unleashing a new influenza pandemic would appear, its international spread would be rapid. An influenza pandemic would spread worldwide through sea and air connections, and if its behaviour was similar to that of previous pandemics, it could travel around the world in a period from six to eight months. However, if we take into account the increase in air travel since the last pandemic in 1968, these periods could be shortened, as demonstrated in the case of the Severe Acute Respiratory Syndrome (SARS).

In these circumstances, the infection could spread rapidly, and the response capacity

overall could be seriously affected in the event that a large part of the world were to experience outbreaks practically at the same time. It must be kept in mind that many of the public health interventions that were successful in the control of SARS would not be as effective against a disease that is much more contagious, has a short incubation period and can be transmitted before the onset of the first symptoms.

The demand for health care would increase in a brief space of time and, therefore, the preparation for the public health and healthcare services response needs to be intensified. Consideration must be given to the fact that healthcare personnel and the workers in other essential services will be among those affected, with the ensuing shortage of human resources during the period of maximum incidence.

In order to cope with the situation described above, the Healthcare Services Emergency Response Subcommittee prepared the general outline for the drawing up of the Autonomous Community Response Plans, whereby, at the present time, all of the Autonomous Communities and Cities have response plans adapted to the organization of their healthcare services and essential services and are working to ensure that their Plans are brought to the attention of all of the parties involved in this response.

All systems must be ready in order to cope with an abrupt surge in the demand for healthcare services as a consequence of a pandemic. To this end, the Autonomous Communities have worked to put into place local plans that will determine the organization required to cope with the increased demand and to have the resources necessary ready in order to attend to patients in the conditions defined previously for each phase of pandemic alert and pandemic. The channels of distribution of medicines and personal protection equipment are also being established in the Autonomous Communities at all levels, on the basis of their organizational structure. This strategy

is being developed in conjunction with all of the sectors concerned.

The Autonomous Community plans can be accessed from the website of the Ministry of Health and Consumer Affairs.

This Subcommittee has also worked on the following guidelines and protocols regarding the response of the healthcare services, discussed in detail in the section on strategic actions:

- Infection control measures
- Protocol setting out the actions to be taken for workers and people exposed to birds or animals infected with highly pathogenic avian influenza viruses, including the H5N1 virus
- Guidelines for the clinical management of patients with avian influenza
- Legal basis for the implementation of special public health measures in the context of an influenza with pandemic potential
- Guidelines for the classification of patients in demand of healthcare ("Triage").

B.6.4 Communications Subcommittee

This Subcommittee has prepared a communication plan for avian influenza, the first version of which was drafted in June 2005 and is updated on an ongoing basis in relation to the evolution of the situation and to the actions carried out in this field.

The plan includes the preparation of communication strategies, attention to journalists, information to the public and information coordination with other institutions, national as well as international, involved in the monitoring of avian influenza.

In addition to the external communication aspect, this plan also focuses on keeping the internal lines of communication acti-

vated, within the Ministry as well as within the Government itself, and with the Autonomous Communities. Therefore, one of the basic pillars of the communication plan is the establishment of channels of coordination of the information among all of the public administrations that could be affected, both on the national as well as the international level. For this reason, the general communication strategy does not fall upon one particular department, but it is rather established on a global and coordinated basis.

The basic objectives of this coordination are:

- To have a maximum level of knowledge of the actions being undertaken by each of the institutions involved.
- To define, in a coordinated manner, the messages to be conveyed to the general public and, above all, to avoid contradictions in such messages between different public administrations, which can be highly detrimental at times of crisis.
- To put into place channels of ongoing communication among the various public administrations involved.
- To establish protocols for the actions to be taken and to maintain an ongoing assessment of the strategies for informing the general public.

On an international scale, representatives of the Communications Subcommittee have participated in the coordinating meetings called on a regular basis by the European Commission, the ECDC and the European Food Safety Authority (EFSA).

B.7. Role of the European Centre for Disease Prevention and Control

The European Centre for Disease Prevention and Control was created by the European Parliament and Council Regulation (EC) no. 851/2004, and its purpose is to

provide consultancy and expert advice and to assist the Commission in coordinating the Network for the Epidemiological Surveillance and Control of Communicable Diseases in the Community and its Early Warning and Rapid Response System. It began to operate in Stockholm in May 2005.

According to the European Pandemic Preparedness Plan, the ECDC assumes all of the tasks associated with epidemiological surveillance within the Plan, participates in the organization and management of the assistance in the event of an influenza outbreak and offers consultancy on options and guidelines in order to provide an adequate response in each phase and on each level of the Plan.

To this end, since its inception, the ECDC has been working actively in the coordination and standardization of the activities being undertaken in relation to preparedness for an influenza pandemic. It has developed many protocols and guidelines on a range of issues relating to human health, to ensure that the surveillance and measures of protection are as homogeneous as possible throughout Europe. The Centre is working on a surveillance system for the human cases of A/H5N1 that will be compatible with the system developed by the World Health Organization and is carrying out an ongoing monitoring of the risk.

The ECDC has worked in close cooperation with the Member States, with the WHO Regional Office for Europe and with the Directorate General for Health and Consumer Affairs (DG SANCO). At the present time it is finalizing an assessment of the implementation of the Response Plans in EU countries, for which purpose it has already visited or will be visiting all of the EU countries in the next few months in order to assess the preparedness plans and to assist countries in detecting their weak points and those areas that need to be strengthened, as well as to take note of the strengths in the various

plans in order to bring them to the attention of the rest of the countries.

This Centre works closely with the WHO Regional Office for Europe, participating in support and assistance missions in some of the avian influenza outbreaks that have occurred.

B.8. Phases of the pandemic and levels of alert in the EU

In November 2005, the European Commission published the Document on the Planning of Pandemic Influenza Preparedness and Response in the European Community.

In this European Plan, the choice of the phases and levels is in line with the rec-

ommendations by WHO and its definition of the pandemic phases. Nevertheless, after consulting the Member States, WHO and the ECDC, the decision was made to define four levels of alert in the European Union within phase 6 of the WHO designation (pandemic period), in view of the specific circumstances of the EU, which is characterized by the absence of internal borders and the free movement of people and goods.

Based on this proposal by the EU, the levels within Phase 6 have been redefined in the National Plan.

	Main Public Health Objectives
Inter-pandemic Period	
<p>Phase 1 No new subtypes¹ of the influenza virus in humans have been detected. In animals, a subtype of the influenza virus that has previously caused infection in humans may be detected. However, the risk² of infection or disease for humans is considered low.</p>	Strengthen pandemic influenza preparedness at global, regional, national and sub-national levels.
<p>Phase 2 New subtypes of the influenza virus have not been detected in humans. However, a subtype of the influenza virus circulating in animals represents a considerable risk² of disease in humans.</p>	Reduce to a minimum the risk of transmission to humans; detect and report such transmission rapidly, if it occurs.
Period of Pandemic Alert	
<p>Phase 3 Human infection(s) with a new influenza virus subtype, but without person-to-person transmission, or at the most, rare cases of transmission to a close contact.</p>	Ensure a rapid characterization of the new subtype of the virus and the detection and early reporting of additional cases.
<p>Phase 4 Small clusters of cases with limited person-to-person transmission. The transmission is highly localized, which suggests that the virus is not well adapted to humans³.</p>	Contain the transmission of the new virus within the localized foci or delay the spread in order to gain time for applying response measures.
<p>Phase 5 Larger clusters of cases, although the person-to-person transmission continues to be localized, suggesting that the virus is increasing its adaptation to humans but has still not become completely communicable (considerable risk of pandemic)³.</p>	Maximize efforts to contain or delay the spread, in order to impede the pandemic and gain time for applying the pandemic response measures.

	Main Public Health Objectives
Pandemic Period	
Phase 6 Pandemic phase. High and sustained transmission among the general population.	Reduce the impact of the pandemic to a minimum.
Level 1 No human case of infection confirmed in any Member State.	
Level 2 One or several confirmed human cases of infection with the pandemic virus in a Member State. Level 2.a One or several confirmed human cases outside of Spain. Level 2.b One or several confirmed human cases in Spain.	
Level 3 Confirmed (transmission) outbreak of infection with the pandemic virus in a Member State. Level 3.a Confirmed outbreak outside of Spain. Level 3.b Confirmed outbreak in Spain.	
Level 4 Widespread transmission in the EU Member States.	
Post-Pandemic Period	
Return to the inter-pandemic period	Return to the inter-pandemic period

¹ A new subtype is defined as a subtype which has not circulated in humans for several decades, whereby the majority of the population lacks protection against it.

² The difference between phase 1 and phase 2 is related to the risk of infection or disease caused by the strain that is circulating among animals. The difference between the two is due to a number of factors and to the relative importance of each on the basis of current scientific knowledge. The following can be included among these factors: the pathogenicity in animals and humans, the existence of cases among domestic animals and cattle or solely in wild animals; whether it is geographically localized or extended and whether the virus is enzootic or epizootic. Information on the genome of the virus and other scientific information must also be taken into account.

³ The distinction between phases 3, 4 and 5 is related to the assessment of the risk. Several factors and the relative significance of each must be taken into account on the basis of current scientific knowledge. Among the factors to be considered are: the transmission rate, the geographic localization and the spread, the severity of the disease, the presence of genes from human strains. Information on the genome of the virus and other scientific information must also be taken into account.

C. ACTION PLAN. STRATEGIC ACTIONS CARRIED OUT

The activities carried out during this period have revolved around four strategic actions, which the World Health Organization describes in its most recent Strategic Plan⁵³, and which aim four major objectives:

STRATEGIC ACTION	OBJECTIVE
1. Reduce human exposure to the H5N1 virus	Reduce the opportunities for human infection and, in so doing, reduce the possibility for a pandemic to emerge.
2. Strengthen the early warning systems	Ensure that the country is capable of detecting cases rapidly, to enable them to be treated, reporting them to the relevant international bodies for the performance of an accurate risk assessment. Likewise, ensure that the specimens are shared with WHO laboratories.
3. Intensify rapid containment operations	Ensure a rapid investigation of cases and clusters of cases and the management and taking of measures quickly in order to prevent the transmission of the virus. Prevent the H5N1 virus from further increasing its person-to-person transmissibility.
4. Build the capacity to cope with a pandemic	Ensure that the pandemic preparedness and response plans have been formulated and tested on the national and Autonomous Communities levels.

1. REDUCE HUMAN EXPOSURE TO THE H5N1 VIRUS

1.1. Objective.

Reduce opportunities for human infection and, if these do occur, reduce opportunities for the virus to evolve to a form with person-to-person transmissibility.

1.2. Activities carried out

a) Monitoring the risk assessment worldwide and in Europe. Communication to professionals.

- b) Communication of the risk to the general public along with the measures to be adopted in order to avoid this risk.
- c) Coordination with the Ministry of Agriculture, Fisheries and Food (MAPA) for the drawing up of measures of prevention and to protect humans in contact with birds.
- d) Drafting of a protocol with the measures needed to reduce exposure to the infection in hospitals and health-care centres.

1.3. Description of the results of the activities performed

a. Monitoring of the risk assessment worldwide and in Europe. Communication to professionals.

The Directorate General of Public Health (DGSP) in the Ministry of Health and Consumer Affairs issues a daily report which is widely distributed to the various groups of professionals involved in the monitoring of avian influenza and in pandemic preparedness. This report describes the situation and reflects the latest information on the evolution of the avian influenza. In addition, it issues a further report on a weekly basis which is also sent to the members of the Health Commission and of the Scientific Committee.

With the aim of facilitating communication and as a support to the coordination of the different groups involved in the implementation of the National Plan, in October 2005, the Ministry of Health and Consumer Affairs created a Working Group Tool accessed via an Intranet. A Working Group was established under a "WEB Crossing" environment in order to share information on avian influenza and preparedness plans. "WEB Crossing" is a collaboration platform totally based on the Internet, which makes available to users common working areas to be shared with others, in which they can exchange documents and work on a common project.

At the present time, this Working Group has 149 members who have access to the shared information which is updated daily. The protocols and documents relating to the National Plan have been incorporated into this tool, together with the Preparedness and Response Plans of all of the Autonomous Communities and the Plans of other countries, as well as the most relevant articles published in scientific magazines. The daily update on the evolution of the avian influenza is also included.

Furthermore, professionals from the Directorate General of Public Health (Ministry of Health and Consumer Affairs) have participated in many international meetings held in order to monitor the avian influenza situation, to make an ongoing risk assessment and to drive the formulation of national preparedness plans. Particularly important in this regard were the three joint coordination meetings organized by the WHO Regional Office for Europe, the ECDC and the EU on influenza pandemic preparedness. Attendance to these meetings included the officials responsible for influenza pandemic planning, both on the national level as well as on the level of the international organizations involved in the preparedness effort in Europe.

b. Communication of the risk to the general public along with the measures to be adopted to avoid this risk.

The Spanish Government has created a specific website on avian influenza (www.gripeaviar.es), coordinated by the Ministry for the Cabinet Office and with the information provided by the Ministries of Health and Consumer Affairs and of Agriculture, Fisheries and Food. On this website, available in all of the country's official languages, answers are given to the most frequently asked questions concerning this disease, and all of the press releases and official Government communiqués on this issue are inserted. The websites of all of the Ministries of the Spanish Government, as well as those of

their dependent organizations, include a link to this page on their home pages.

In turn, www.gripeaviar.es is complemented by the websites set up by the Ministries of Health and of Agriculture with more detailed information for their respective scopes of action. The website of the Ministry of Health and Consumer Affairs www.msc.es describes more specifically what avian influenza is and how it is transmitted to people and what measures should be adopted in order to prevent this transmission.

In the section on direct communication to the general public, an advertisement was also designed, which was published in all of the major newspapers on Sunday 23rd October 2005, coinciding with the appearance of the first cases of influenza in birds in Europe and the significant news interest reflected in the media. The advertisement contained the key messages on avian influenza and recommendations for the general public. Interested citizens can also obtain information from the Ministry of Health and Consumer Affairs by telephone and e-mail (901 400 100 and oiac@msc.es).

The Ministry of Agriculture, Fisheries and Food has developed communication strategies in conjunction with the Ministry of Health, with respect to the implications of avian influenza in the field of food safety. Specific brochures have been prepared and disseminated to people who work on poultry farms, and communication actions have been developed with at risk sectors, such as hunters, through their federations and the specialized press.

Posters and information cards with basic health advice have been prepared for people who travel to countries where avian influenza is endemic in birds. These materials have been distributed in seaports and airports and through travellers' consultation centres and are also available on the Ministry's website.

One of the major objectives in the Ministry of Health's Communication Plan is the standardization of messages in conjunction with

all of the Autonomous Communities. Consequently, as a part of this Plan, a Group has been formed for the coordination of information with the press offices of the Departments of Health of the Autonomous Communities. At a meeting held in March 2006, the officials responsible for communication in the Ministry of Health and Consumer Affairs reached an agreement with the officials responsible for communication in the Departments of Health of the Autonomous Communities and Cities on the information criteria for dealing with this issue and the aspects relating to communication policy and to the need to coordinate messages and strategies. A telematic channel of communication has been operating since March, through which the Ministry's Press Office sends to the Departments the daily situation reports prepared at the Ministry on avian influenza, together with documents of interest and information on the international meetings it attends.

Since the alert arose at the end of 2003, the Ministry of Health and Consumer Affairs has taken up the responsibility of drafting and disseminating press releases and communiqués on an ongoing basis, as well as organizing press conferences and informative sessions in relation to avian influenza. It has also arranged for interviews in the media and has organized visits by journalists to the various areas concerned with avian influenza monitoring and control, to enable them to obtain images and statements by the officials heading the various units responsible for surveillance at the border posts.

As for the international level, representatives of the Communications Subcommittee have participated in the coordination meetings called regularly by the European Commission, the ECDC and the EFSA. Work has been carried out in all of these forums on the assessment of the situation, from the information perspective, and also on the coordination of messages to the general public and the search for a consensus with respect to the communication strategies to be adopted in each case.

c. Coordination with the Ministry of Agriculture, Fisheries and Food for the establishment of measures of prevention and for protecting people in contact with birds.

The Surveillance Subcommittee, which includes representatives from the Ministry of Agriculture, Fisheries and Food, drew up a protocol, revised in June 2006, on the actions to be undertaken with respect to workers or other people exposed to poultry infected with highly pathogenic influenza viruses (Annex III to the National Plan). This protocol sets out the factors that determine the risk of exposure and the key points for the protection of people exposed to such risk. The protective measures include the recommendation of the use of individual protection equipment (IPE) by personnel directly involved in the control of outbreaks of highly pathogenic influenza in birds. Other recommendations are the application of prophylaxis and treatments indicated according to specific situations, and the surveillance that should be established with respect to people who are potentially exposed to these viruses.

With the arrival in Europe of migratory waterfowl infected with the H5N1 virus, the Directorate General of Public Health in the Ministry of Health and Consumer Affairs established a protocol to ensure the protection of SEPRONA personnel.

d. Drawing up of a protocol with the measures for reducing exposure to infection in hospitals and health-care centres

The Healthcare Services Emergency Response Subcommittee, together with representatives from Scientific Societies concerned with the issue, has drawn up and agreed on an infection control protocol, aimed at healthcare professionals, which contains the individual protection and barrier measures to be implemented in order to control the spread of the infection within a healthcare environment. The recommendations reflected in this protocol are designed to reduce trans-

mission to healthcare workers and to other patients in a situation of pandemic alert (phases 3, 4 and 5). Among the protection measures proposed, this protocol includes recommendations for the use of respiratory protectors and personal protection equipment.

Once the pandemic has started (phase 6) and the infection is widespread among the population, even though preventing its transmission will continue to be a priority, some of these control measures will probably become unfeasible as a consequence of the high number of cases. The decision as to which measures will be recommended to be maintained in this situation will depend on the risk assessment made at the time, taking into account the epidemiological characteristics of the pandemic virus known at that time (mechanisms of transmission, incubation period, mortality rate, etc...).

2. STRENGTHEN THE EARLY WARNING SYSTEM

2.1. Objective.

Ensure that the country is capable of detecting cases rapidly and of treating them appropriately, as well as reporting them to the relevant international organizations and sharing specimens with WHO laboratories.

2.2. Activities carried out

a. Strengthen the early warning system

- a.1. Compliance with the International Health Regulations (IHR) (2005)
- a.2. Development of a surveillance protocol for Phase 3 of pandemic alert
- a.3. Surveillance of imported cases:
 - a.3.1. Information to persons travelling to or returning from risk areas.

- a.3.2. Protocols for actions to be taken in the event of suspect cases in aircraft or ships

- a.4. Extension of the Laboratory Network for Influenza Diagnosis and technology transfer.

b. Strengthening the coordination between the surveillance of animal and human influenza

2.3. Description of the results of the activities performed

a. Strengthening the early warning system

- a.1. Compliance with the International Health Regulations (IHR) approved in 2005.

The application of the new International Health Regulations is going to involve an effort from all countries and should mean the strengthening of the surveillance and response capability. This, in addition to improving the response to a possible pandemic, will also strengthen our defence capacities with respect to other diseases and emergency situations.

The 59th World Health Assembly, held in May 2006, adopted a resolution for immediate compliance, on a voluntary basis, with the provisions of the International Health Regulations (2005) considered relevant in relation to the risk of avian influenza and its pandemic potential.

Point 4 of this Resolution urges States to designate or immediately establish a National IHR Focal Point, in accordance with article 4 of the Regulations, and to mandate the mentioned Focal Point to provide support for the risk assessment in collaboration with WHO. According to this article, the functions of the National IHR Focal Points include sending to the WHO Contact Points, on behalf of the State Party concerned, urgent communications concerning the implementation of these Regulations and disseminating information to the relevant sectors of the administration of

the State Party concerned. In the aforementioned resolution WHA59.2, the States Party are also asked to implement, with respect to the human cases of avian influenza, the mechanisms and procedures contained in the Regulations for those diseases that could constitute a public health emergency of international concern.

For the purpose of implementing the provisions approved at the World Health Assembly, in accordance with the new IHR (2005), a Ministerial Order has been drawn up and published (*ORDEN SCO/3870/2006, of 15 December*), designating the National IHR Focal Point and completing the provisions of the National Epidemiological Surveillance Network for the application of the International Health Regulations with respect to the compulsory and urgent notification of human cases of avian influenza.

According to this Order, the Directorate General of Public Health in the Ministry of Health and Consumer Affairs is the authority responsible for acting as the National IHR Focal Point and as the liaison with the European Commission's Early Warning and Response System created by Commission Decision 2000/57/EC, of 22 December 1999.

Furthermore, the Order establishes that the Public Health authorities of the Autonomous Communities and Cities are to send the information gathered with respect to the existence of a possible, probable or confirmed case of avian influenza in humans to the Directorate General of Public Health, Ministry of Health and Consumer Affairs, on an urgent basis.

a.2 Development of a surveillance protocol for Phase 3 of pandemic alert.

In the Period of Pandemic Alert, the main Public Health objective is to ensure the rapid characterization of the new subtype of the virus and the detection and early reporting of cases. The intensification of the surveillance in order to detect the possible appearance of cases infected with the A/H5 virus is essential, together with the rapid notification of

these cases in order to be able to implement appropriate control measures.

For this purpose, a protocol has been drawn up that sets out the key aspects of surveillance, having been revised and updated in June 2006 (Annex I to the National Plan). The objective of this protocol is to ensure the detection, diagnosis and proper notification of cases of human infection with the A/H5 influenza virus that may appear in Spain during Phase 3 of the Period of Pandemic Alert.

In order to standardize the case definitions, this new proposal has taken into account the development of the new case definition and the notification questionnaires proposed by the ECDC and approved by the European Union.

This document specifies the notification flows in response to the appearance of a suspicion or a case of avian influenza, both with respect to the communication between the Autonomous Community level and the national level, as well as the subsequent notification to the relevant international organizations (ECDC and WHO). This flow at the national level has been updated by the aforementioned Ministerial Order.

The conditions for specimens' sampling and sending and the standards for the transport of such samples to the relevant laboratories are also stipulated in detail.

The revision of this protocol also includes the definition of contacts, which encompasses, among others, the people who live in close proximity to the cases, the workers exposed to infected poultry, healthcare professionals and travellers arriving from countries affected and who have been in contact with infected birds. The protocol also sets out the recommendations to be followed in the event of such contacts.

As the epidemiological situation progresses and the characteristics of the infection with the A/H5 virus become known, this protocol and its definitions will be revised and adapted to the new circumstances.

Moreover, in order for this protocol to be effective, it is indispensable for the public health personnel and the workers in the country's healthcare system to be familiar with the surveillance operations for phase 3.

a.3. Surveillance of imported cases

Travel to a country with outbreaks in poultry or sporadic human cases does not mean that a traveller is at risk of infection with this virus if the traveller keeps in mind a number of measures focussed on avoiding exposure to poultry, such as not visiting live markets, farms or other environments where an exposure to diseased birds could occur.²⁵

a.3.1 Information to persons travelling to or returning from risk areas.

Posters and information cards aimed at travellers have been designed for the purpose of minimizing the risk of exposure in the areas affected, as well as to disseminate the indications of how people should act in the presence of suspect symptoms (Annex V to the National Plan).

a.3.2 Protocols for actions to be taken in the event of suspect cases in aircraft or ships

A protocol (Annex VII to the National Plan) has been developed in which a description is provided of how the passengers and crew are to be submitted to a health control when suspect cases are detected on board. The Directorate General of Public Health has worked with Aeropuertos Españoles y Navegación Aérea (AENA) on developing the measures established in these protocols.

a.4 Extension of the Laboratory Network for Influenza Diagnosis and technology transfer.

One of the essential aspects for the preparedness of the surveillance systems in order to cope with an influenza pandemic is the development of systems that have specialized laboratories with advanced technology, in order to immediately detect the appearance of a new virus and to characterize it in the shortest possible time.

In the phases of pandemic alert, the diagnosis and characterization of the influenza viruses must be addressed as quickly and as effectively as possible, but without losing the sensitivity and specificity of the results in the process. For this reason, laboratories must prepare themselves by introducing new objectives and by constantly optimizing the technology being used, as the implementation of methodological changes is a process that requires time.

The Network of Spanish Influenza Laboratories (ReLEG) is comprised at the present time by the reference laboratories of 15 Autonomous Communities (Castilla La Mancha and Murcia still do not have their own laboratory). The Centro Nacional de Microbiología operates as the Reference Laboratory at the national level and as the coordinator of ReLEG. The Network of Spanish Influenza Laboratories is represented in the European Union's Community Network Reference Laboratory (CNRL).

Three of these laboratories are at the same time WHO National Influenza Centres, through which Spain contributes to the WHO "Global Influenza Program". These laboratories are located in the following institutions: the National Centre of Microbiology (CNM), ISCIII, Madrid; the Hospital Clinic in Barcelona and the Faculty of Medicine of Valladolid.

The CNM has been making an analysis of the situation of the ReLEG laboratories. The development of the ReLEG has been very rapid in the last few years, for which reason some of the laboratories that have joined the Network more recently are finding that they have to adapt to a new methodology in a brief space of time, to be able to undertake additional responsibilities. Therefore, in order to assess the current status of the staffing and equipment and capacities of the laboratories comprising the Network, 3 surveys have been made during the last year and a half on the situation of the most important aspects, such as equipment, space, staff, biosafety and technical capacity. The priority points to be

resolved in the immediate future have also been identified. The questionnaires used were drawn up by the CNM and covered: i. Level or technical capacity of the laboratories and the necessary improvements to be made in the short term; ii Staffing and equipping of the laboratories and other needs, considered essential. The results of the surveys have been analyzed and discussed at meetings attended at all times by representatives from all of the laboratories, for the purpose of unifying the scientific criteria which are to govern the microbiological surveillance, prioritizing the needs identified and determining the levels of capacity required at all times during the development of the ReLEG and the pandemic phases.

Following the survey made in June 2005, it was found that the CNM alone was able to perform the sub-typing of the Haemagglutinin and Neuraminidase of the most probable pandemic viruses, and it was decided that the priority course of action should be to enhance the capacity of the laboratories in the network to identify H5 and increase the speed at which they operate, by means of working diagrams designed to drive efficiency in the detection of A/ H5 viruses.

With this goal of strengthening diagnostic capacity with respect to the H5N1 virus in our country, the CNM, funded by the Directorate General of Public Health, Ministry of Health and Consumer Affairs, organized a training course at the end of June 2005 in order to transfer to the Spanish Network of Influenza Surveillance Laboratories the technology for identifying A (H5N1) by means of an RT-nested-PCR method, developed in the CNM influenza laboratory.

At the present time, of the laboratories comprising the ReLEG, eleven already have the capacity to determine A/H5 by PCR in real time, and at least three (the influenza laboratory of the National Centre of Microbiology, the Barcelona and the Basque Country laboratories) have their own PCR, which means that they have extensive experience in his technique.

Given the geographical distribution of the laboratories, in the majority of the Autonomous Communities, it will be possible to immediately begin a PCR in real time as soon as the first suspect cases appear, and, at the same time, to send specimens to the national reference laboratory at the CNM, for diagnostic confirmation. In this way, there is an assurance that, in less than 48 hours, it will be possible to obtain a confirmed diagnosis. If the diagnosis is positive or there is reasonable doubt as to the result, the specimens would then be sent to WHO laboratories.

b. Strengthening the coordination between the surveillance of animal and human influenza

In phase 3 of pandemic alert, which is the current phase, one of the key points of surveillance is the coordination between animal and human influenza surveillance, since, essentially, the risk of infection for humans is associated with exposure to diseased or dead birds. The early detection of outbreaks in birds is going to make it possible to intensify surveillance in human cases, and the joint research will facilitate the identification of the sources of exposure and help to gain knowledge in greater depth of the relationship between the outbreaks of influenza in birds and the disease in humans.

In this regard, during the past year, there has been close collaboration with the Sub-directorate General for Animal Health, Ministry of Agriculture, Fisheries and Food (MAPA) and, as reflected in its protocols, an agreement was reached to ensure urgent notification to the Directorate General of Public Health in the Ministry of Health and Consumer Affairs (MSC) of the detection of cases of highly pathogenic avian influenza.

Similarly, representatives of the MSC have participated in several meetings coordinated by the MAPA, while representatives of this latter Ministry participate on the Surveillance Subcommittee.

The coordination of the human and the animal surveillance makes it possible to intensify the surveillance of possible human cases in areas where the disease is active in animals, in addition to ensuring that the measures for disease control in animals are compatible with the reduction of the risk of human exposure.

3. INTENSIFY RAPID CONTAINMENT ACTIVITIES

3.1. Objective.

To ensure the rapid investigation of cases and clusters of cases and the management thereof and the taking of measures quickly in order to prevent the transmission of the virus.

3.2. Activities carried out

- a) Drawing up of guidelines for the clinical management of patients with avian influenza.
- b) Drawing up of a protocol for the management of contacts for Phases 4 and 5 of pandemic alert
- c) Establishment of the legal basis for the implementation of special public health measures in the context of influenza with pandemic potential.
- d) Drawing up of recommendations for the use of antiviral drugs
 - d.1. Procedure for the preparation of oseltamivir phosphate solution
 - d.2. Description of the antivirals and definition of priority groups for their use
 - d.3. Indications for the use of prophylaxis with oseltamivir following exposure to the influenza A/H5N1 virus in Phase 3 of pandemic alert.
 - d.4. Standard forms for the request and sending of antivirals
- e) Development of communication protocols that will assist in carrying out the

containment operations and to build trust and minimize stress in the population in the case of the appearance of cases of avian influenza in Spain.

3.3. Description of the results of the activities performed

a. Drawing up of Guidelines for the clinical management of patients with avian influenza.

Clinical Management Guidelines have been drawn up in order to describe the actions to be carried out in the hospital environment with respect to avian influenza patients (Annex VIII to the National Plan).

These Guidelines were drawn up by representatives of the Sociedad Española de Enfermedades Infecciosas y Microbiología Clínica (SEIMC – Spanish Infectious Disease and Clinical Microbiology Society) and the Sociedad Española de Neumología y Cirugía Torácica (SEPAR – Spanish Respiratory Medicine and Thoracic Surgery Society) and were later reviewed by the Scientific Committee and the Healthcare Services Emergency Response Subcommittee.

These guidelines describe the actions to be carried out in the hospital environment with respect to avian influenza patients, setting out the aspects of diagnosis and treatment of these patients. These recommendations are applicable to those cases that fit the definition of a possible, probable or confirmed case of human infection with the influenza A/H5 virus, according to Annex I to the National Pandemic Influenza Preparedness and Response Plan.

The actions proposed can vary depending on the epidemiological and clinical evidence that progressively appears. The recommendations for treatment with antivirals will need to be revised and adapted in line with the scientific knowledge that is eventually generated.

b. Drawing up of a protocol for the management of contacts for Phases 4 and 5 of pandemic alert

In the period of pandemic alert, the priority is to contain the transmission of the new virus in localized foci and to delay the spread, in order to gain time to apply the response measures. To reduce this transmission, when an avian virus acquires the ability to pass from person to person, the action measures with respect to contacts are going to be fundamental.

The Surveillance Subcommittee has drawn up a protocol in which a definition of contacts is established for application in phases 4 and 5 of pandemic alert, and where the procedures to be followed in the management of these contacts are set out in detail (Annex IX to the National Plan).

As in the rest of the protocols developed in the framework of the response to an influenza pandemic, these guidelines have been drawn up on the basis of the current knowledge on the issue, and as the epidemiological situation advances and the characteristics of the possible influenza viruses with pandemic potential become known, it will be necessary to progressively review and update them. Nevertheless, it has been considered important to establish an initial protocol as early as this stage, in order to begin taking into consideration and to be able to foresee the kind of measures that may possibly have to be set in motion, such as quarantine and the administration of antivirals.

c. Establishment of the legal basis for the implementation of special public health measures in the context of influenza with pandemic potential.

Public health measures that may need to be applied for the purpose of containing the transmission of an influenza virus with pandemic potential include the isolation of cases suspected of being infected with avian influ-

enza and the quarantine of the persons in contact with a suspect case.

A document has been drawn up in which an analysis is made of the legislation available in order to ensure the application of these measures in the context of the appearance of influenza cases with pandemic potential (Annex XI to the National Plan). The health authorities will always seek to have such measures be accepted voluntarily by the persons affected, after informing them of what the measures consist of, their expected duration and their purpose and, only in the event that this cannot be achieved, it will be necessary to activate Act 3/86 on Special Public Health Measures.

The Special Public Health Measures Act, on account of its nature as an organic provision, has been given a sufficient legal rank in order to enable its direct application by the Health Authorities with powers and responsibilities in the area of Public Health, provided that the circumstances stipulated in that legal provision have actually arisen. That is, the certitude and foreseeability necessary for the restriction or deprivation of a fundamental right must be guaranteed, as has been consistently required by the case law of the European Court of Human Rights and by the Spain's Constitutional Court. The health measures that may be adopted in accordance with this Act must be proportionate to the ends pursued, be limited to the time strictly necessary in order to overcome the crisis situation and be implemented under the control of the jurisdictional bodies entrusted with the protection of individual fundamental rights.

The administrative court judges, through prior authorization or ratification, will be the authority that will control the proportionality of any intended health measure, insofar as such a measure involves the deprivation or restriction of freedom or of any other fundamental right, thus acting as guarantors of individual fundamental rights.

The procedure for applying a special public health measure is defined on the basis of the

legislation referred to above. Likewise, the document includes a standard resolution for the application of a compulsory quarantine and another for the application of compulsory isolation.

d. Drawing up of recommendations for the use of antiviral drugs

For the purpose of coordinating all of the aspects associated with the use of the stockpiles of antiviral drugs, ranging from their preparation and distribution through to the criteria of their use, and taking into account that in the event of the presentation of the pandemic, pressures on the existing stockpiles may exist, the Vaccines and Antivirals Subcommittee has drawn up a number of protocols and guidelines for the proper use of such drugs, which are set out below.

d.1. Procedure for the preparation of oseltamivir phosphate solution

The Agencia Española de Medicamentos y Productos Sanitarios (AEMPS – Spanish Medicines and Healthcare Products Agency), within the framework of the Vaccines and Antivirals Subcommittee under the National Plan, has drawn up a protocol on the procedure for the preparation of oseltamivir phosphate solution, which describes the equipment necessary for the preparation of the product, the preparation process and labelling. This document has been distributed to the officials responsible on this matter in the Autonomous Communities.

A new working group has been formed, comprised by the Directorate General of Public Health, the AEMPS and the pharmacy officials of the Autonomous Communities, in order to evaluate other possibilities for the preparation of the oseltamivir phosphate.

d.2. Description of the antivirals and definition of priority groups for their use.

A protocol (Annex IV to the National Plan) has been drawn up, describing the different types of antiviral drugs that are available, together with their principal characteristics and

their form of action, also defining the objective of the use of such drugs.

In the phases of pandemic alert (3, 4, and 5) the objective of the use of antivirals will be to prevent the spread of the infection as far as possible. In order to do so, treatment will be administered to all of the confirmed or highly suspect cases of infection, and post-exposure prophylaxis will be administered to the contacts, as established in the relevant specific protocols.

Taking into account the possibility that the availability of antivirals could decline at some stage in the progress of the pandemic, this protocol also establishes a list of groups which will be considered priority groups for the administration of such drugs in pandemic phase 6. These groups have been determined on the basis of the experience obtained from the epidemiological behaviour of previous pandemics and the seasonal influenza epidemics, particularly those which have presented a higher degree of severity. The epidemiological behaviour of the virus strain responsible for the pandemic will not be known until the pandemic actually occurs, for which reason, the groups established will have to be progressively adapted and modified in relation to the clinical and epidemiological characteristics of the presentation of the disease in the course of the pandemic.

d.3. Indications for the use of prophylaxis with oseltamivir following exposure to the influenza A/H5N1 virus in phase 3 of pandemic alert.

A protocol (Annex VI to the National Plan) has been developed, establishing the recommendations for the use of oseltamivir as a post-exposure prophylaxis against infection with the avian influenza A/H5N1 virus, which are applicable at the present time in view of the existing pandemic risk (phase 3 of the period of pandemic alert).

The protocol describes a number of possible situations of exposure that can occur at the present time in relation to wild birds, domestic birds, in people in situations of co-habitation

or social contacts with a probable or confirmed case of H5N1 and/or situations of occupational exposure.

The current knowledge of the transmission of the disease in humans is described with respect to each of these situations and, on this basis, a recommendation on the use of prophylaxis, or not, is indicated. Finally, the protocol includes the dosage and pattern of administration of oseltamivir, when used as prophylaxis, depending on the age and weight of the subject.

As in other protocols, the recommendations made are based on current knowledge of the likelihood of transmission of the avian influenza A/H5N1 virus, whereby such recommendations will need to be updated as new evidence arises with respect to the transmission of the infection.

d.4. Standard forms for the request and sending of antivirals

The Directorate General of Public Health (DGSP) has prepared standardized action protocols and information-gathering forms for requesting antivirals and for the sending of such drugs through the Oficina Central de Farmacia de la Defensa (Defence Central Pharmacy Office). Prior to the arrival of these medicines to the Autonomies Communities, the DGSP distributed antivirals to enable all of the Communities to cope with an emergency situation.

In addition, the DGSP, through the Ministry of Foreign Affairs, has sent antiviral drugs to the Spanish embassies in countries with confirmed human cases of infection with the H5N1 virus, in order to ensure the treatment of expatriate Spanish citizens.

e. Development of communication protocols that will assist in carrying out the containment operations and to build trust and minimize concern in the population in the case of the appearance of cases of avian influenza in Spain.

A single and specific telephone number has already been contracted to take the calls of the public concerning avian influenza. The number will become operational when the situation requires so and will have the following characteristics:

- Cost-free for callers and available 24 hours/day.
- It will be staffed by specialized personnel, who will be given a list of the most likely frequent questions and the appropriate answers and who will receive all of the press communiqués and releases relating to avian influenza as they are issued by the Government.
- It will be available in all of the official languages of the State (and with an evaluation of the possibility of attending to calls in the languages corresponding to the most numerous immigrant communities in our country).

As is the case with the website, this telephone number will appear in all of the materials published on avian influenza (press releases, brochures, advertisements, website...).

Brochures and materials have been published with information for the general public, dealing with basic issues concerning avian influenza and its transmission and prevention.

4. PREPARING FOR A PANDEMIC

4.1. Objective:

Ensure that the pandemic preparedness plans on the national and the Autonomous Community levels are drawn up and tested.

4.2. Activities carried out

- a) Drawing up and dissemination of Autonomous Community Pandemic Influenza Preparedness and Response Plans.

- b) Stockpiling of antivirals
- c) Drawing up of a protocol for the definition of priority groups for the use of antivirals (see point 3.3 paragraph d.2)
- d) Ongoing revision and establishment of recommendations on the strategy for the acquisition of vaccines.
- e) Preparation of Healthcare Services. Drawing up of Guidelines for the classification of patients requiring healthcare (“Triage”).
- f) Review of the indicators and surveillance systems necessary for pandemic phase 6.
- g) Participation in the European Common Ground exercise on an influenza pandemic.

4.3. Description of the results of the activities performed

a. Drawing up and dissemination of Autonomous Community Pandemic Influenza Preparedness and Response Plans.

All of the Autonomous Communities and Cities have drawn up a Pandemic Influenza Preparedness and Response Plan, taking the National Plan as their point of reference. These plans are shared by all of the professionals involved in the different groups and subcommittees of the National Preparedness Plan, through the Working Group Tool created by the Ministry of Health.

In March 2006, a conference was held in the Ministry of Health, with all of the Autonomous Communities, in order to address key aspects of their respective Plans. Basically, the conference reviewed the components of epidemiological and virological surveillance, the information flows established and the use of the various systems in each pandemic phase. A number of proposals for the organization of the response to the emergency by the health-

care services were put forward and discussed. This conference brought to light the effort made by all of the Autonomous Communities and Cities in order to have their Pandemic Influenza Preparedness and Response Plans prepared and in place, in line with similar criteria and within the general framework of the National Plan.

b. Stockpiling of antivirals

The availability of antiviral drugs cannot be assured when the pandemic begins, with a high international demand, since the production of such drugs is limited at the present time. For this reason, all of the international organizations have recommended countries to plan for the expected demand for these drugs and to stockpile them.

The neuraminidase inhibitors (oseltamivir and zanamivir) act by blocking the replication of the virus and inhibiting the release of the virions of the infected cell and thus prevent infection of additional cells, interrupting the spread of the infection in the respiratory tract.

These neuraminidase inhibitors, if administered within 48 hours following the onset of the symptoms, reduce the duration of the illness by approximately 2 days as well as the rate of complications and hospitalization both in healthy adults as well as in people included in risk groups.

The Technical Coordinating Group made estimates of the impact that a possible influenza pandemic could have on the health of the Spanish population, by applying the program designed by the U.S. Centres for Disease Prevention and Control (CDC), which makes it possible to arrive to an estimate of the potential impact of the pandemic in terms of mortality, hospitalization and visits to health-care services.

On the basis of this estimate, and following WHO recommendations, in December 2004, a proposal was submitted to the Public Health Commission for stockpiling antiviral drugs, making it possible for actions to be taken at the very start of the pandemic, and even dur-

ing the phases prior to the pandemic phase, in order to gain time until an effective vaccine is available.

In January 2005, the Public Health Commission reached a decision to acquire an initial stockpile of antiviral drugs for two million treatment courses, with the objective of increasing that stockpile at a later date.

The process was initiated in the first quarter of 2005 for the purchase of the two million treatment courses with oseltamivir, in its active principle form of oseltamivir phosphate. The presentation will be in powder form, which will facilitate the storage of the product and reduce costs by 50% in comparison to the likely expense involved in the purchase of the commercial preparation Tamiflu®. This stockpile was acquired by each of the Autonomous Communities in proportion to their respective populations, while 130,000 treatment courses were acquired by the Ministry of Health and Consumer Affairs for the purpose of covering those population groups dependent on the central administration and, on a priority basis, those persons included in the groups considered essential for ensuring a good response to the emergency.

The first 2 million treatment courses have already been supplied by Roche, with the portion corresponding to the Ministry having been delivered in December 2005 and the rest, to the Autonomous Communities, in August 2006.

In October 2005, the Public Health Commission approved the acquisition of an additional stockpile of antivirals, thereby covering a total of between 15%- 25% of the population.

According to pandemic impact estimates, a stockpile of antivirals that would cover around 20% of the total population of Spain would make it possible to administer an early curative treatment to all of the persons likely to become ill with the influenza during pandemic phase 6 and to administer post-exposure prophylaxis to the established priority groups (Annex IV to the National Plan).

This additional purchase of antivirals, as well as the initial stockpile, will be acquired proportionally by the Autonomous Communities. Of this second request for antiviral drugs, the Ministry of Health and Consumer Affairs has acquired a total of 294,092 treatment courses of oseltamivir/Tamiflu® and 51,000 treatment courses of Relenza®.

The stockpile of antivirals acquired by the Ministry of Health and Consumer Affairs has been stored in facilities belonging to the Ministry of Defence and, through an agreement signed by the two Ministries, the Defence Central Pharmacy Office will be the official body in charge of the preparation of the product and its distribution, whenever this becomes necessary.

Each Autonomous Community must make provision for its own mechanism for the proper storage, preparation and distribution of the antivirals kept in its own stockpile, in order to ensure the efficient use of these drugs.

With the acquisition of this additional stockpile of antivirals by the Ministry and the Autonomous Communities, by January 2007, Spain will have a total of around 10 million treatment courses of Tamiflu® /Oseltamivir phosphate and Relenza®.

c. Drawing up of a protocol for the definition of priority groups for the use of antivirals (point 3.3 paragraph d.2).

d. Ongoing revision and establishment of recommendations on the strategy for the acquisition of vaccines.

An effective vaccine against the pandemic strain cannot be obtained until WHO declares the pandemic and supplies the virus strain responsible for it. At that time, the pharmaceutical companies will be able to initiate the production of a pandemic vaccine.

The European Agency for the Evaluation of Medicinal Products (EMA), in conjunction with WHO, is working to develop a safe, ef-

fective and high-quality vaccine against the pandemic strain, in the shortest possible timeframe. It is expected that an adequate vaccine, administered with an appropriate pattern and dosage, will be able of reducing the impact of the pandemic, basically by reducing the complications of the illness, the number of hospitalizations and the mortality rate among those groups at greatest risk of presenting the more severe forms of the disease. However, it is highly likely that it will not be possible to obtain an adequate vaccine after 4-6 months of the identification of the strain responsible for the pandemic.

- Development and production of pandemic vaccines

In order to gain time once the pandemic strain is known, WHO has proposed the production of “prototype pandemic vaccines” (mock-up vaccines) from selected candidate strains. For this purpose, EMEA has published guidelines with the relevant recommendations to apply for approval for the marketing of a pandemic vaccine. The procedure involves the provision of a core dossier, and approval will be given on the basis of studies made with a prototype vaccine produced from a possible pandemic strain. The submission of a core dossier requires very limited data insofar as effectiveness, immunological response and safety, whereby its approval involves post-approval commitments in order to ensure the proper immunogenicity, effectiveness and safety of the final pandemic vaccine.

The vaccine-producing companies are currently carrying out a range of studies, with the collaboration of a number of countries and international institutions, in order to determine the most appropriate methodology and the different factors that can come into play in a good immunitary response in the production of future pandemic vaccines.

Work is also being performed for the development and production of vaccines containing potentially pandemic avian influenza viruses (i.e.: avian influenza A/H5N1 virus

strain) outside of the context of the submission of a core dossier, that is, vaccines that could be available prior to the onset of the pandemic. If the pandemic strain does not differ significantly from the A/H5N1 strain, against which the vaccine was developed, these vaccines could offer some degree of protection against the pandemic. If this was to occur, the vaccine would have a considerable effect in mitigating the impact of the pandemic. However, if the pandemic strain is very different, these vaccines would provide little or no protection.

Recent publications consider that the implementation of a vaccination strategy with vaccines of this kind, together with other control measures and the use of antivirals, could reduce the accumulated attack rate even in the case where such vaccines would only achieve a 30% reduction in susceptibility and be administered to a small proportion of the population (20%).

In this context, EMEA is drawing up guidelines for the approval of “avian influenza vaccines derived from strains with a pandemic potential for use outside of the core dossier context”. The recommendations of these guidelines will be valid for the vaccines that contain strains derived from influenza viruses with a high pandemic potential of an animal or a human origin but not H1/H3.

Recently, following consultation with experts on vaccines, WHO issued a report.²⁵ expressing its concern with respect to the many unanswered questions in relation to the use of the so-called “pre-pandemic” vaccines and indicating that it is premature to make decisions about the reservation of these vaccines at the present time.

- Recommendations by the Vaccines and Antivirals Subcommittee

This Subcommittee has been continuously analyzing and evaluating all of the technical aspects referred to in the previous section and has considered that at the present time “pandemic vaccines will be a tool that may play an important role during the pandemic,

although they will not be available in the first months following its onset, a period in which a vaccine against potentially pandemic avian influenza could have some impact, even though such impact is not well known”.

The Subcommittee, in view of the incertitude surrounding the pandemic influenza and the avian influenza vaccines presently being developed (quantity of antigen necessary, number of doses, possibility of a crossed reaction with respect to other strains, effectiveness and duration of the protection afforded, safety...), has monitored and will continue to monitor advances in the development of these vaccines and of the EMEA approval process in order to provide technical criteria for supporting the decision-making process on the implementation of future vaccination strategies. At the present time, it does not recommend any purchase action until, at least, these vaccines are approved by EMEA

The Public Health Commission, with the technical support of the Vaccines and Antivirals Subcommittee, has monitored and will continue to monitor a number of proposals by the pharmaceutical industry, in order to ensure an adequate vaccine supply in the event of a pandemic. These proposals refer to the reservation of the production and supply of pandemic vaccines (“Advance Purchase Agreements”, APA), or “bulk” pandemic vaccine supply and storage agreements (stockpiling of bulks) or agreements for the supply of vaccines containing influenza virus strains with a high pandemic potential (which the industry calls “pre-pandemic vaccines”).

e. Preparation of the healthcare level. Drawing up of Guidelines for the classification of patients requiring care (“Triage”).

The Healthcare Services Emergency Response Subcommittee is reviewing the involvement of the Healthcare level in the context of pandemic preparedness and is working to ensure that plans are prepared and updated on the local level. Indicators relating to the response of the healthcare system have

been determined and are being used to assess the development of the plans. These indicators will be modified with a view to intensifying the preparation of the levels of healthcare.

The Subcommittee analyzed how, in a situation of overcrowding in healthcare services and a shortage of human resources, the various levels of healthcare could be organized in order to facilitate the process of clinical assessment in the face of the demand for healthcare and the classification of patients prior to diagnostic evaluation and full treatment, that is, the management of patients demanding care, also known as “triage”.

The “triage” system must be defined previously for situations of alert or pandemic. When these situations arise, the Autonomous Communities will have to activate the strategies necessary for the classification and management of patients in a way that will mitigate the collapse of the healthcare services and lengthy waiting periods.

Many Autonomous Community Plans have developed “triage” models to different degrees, for providing an efficient response to the organization of their healthcare services. On the basis of these models, this Emergency Response Subcommittee has drawn up guidelines for the classification of patients (Annex XII to the National Plan) which compile the various options contained in the Autonomous Community Plans and in the Plans of other countries, to serve as models that can be adapted to the peculiarities of each Community.

In order to maintain the operational level of health services, it is considered essential to have in place clear lines of coordination that will promote efficient performance of the various organizations involved (Primary Care Teams, Critical and Emergency Care Teams and Critical and Emergency Care Services of the Autonomous Community Health Services; Emergency Teams, etc.) and of the different healthcare professionals.

The classification of patients will be made by following a structured and systematic medical protocol of questions. The questions will be aimed at a number of findings that will define the relevant degrees of healthcare priority, depending on the symptoms/signs of alarm, the severity, the impact on the patient's general condition and the existence of chronic illnesses. From the information obtained through the questioning, the protocol should be able to recommend the most appropriate response, what resources need to be allocated or whether a more in-depth assessment by a physician is necessary.

Each Community will establish the channels that will guarantee clear, readily accessible information for the general public, to ensure that the citizenry knows where to seek assistance on presenting the symptoms that activate the process. The Autonomous Community plans will define protocols with algorithms in which all of the activities to be carried out in primary care, hospitalization and in hospital emergency units will be included

f. Revision of the indicators and surveillance systems necessary for pandemic Phase 6.

The Surveillance Subcommittee has developed a protocol specifying the surveillance objectives in pandemic phases 4, 5 and 6, as well as the systems that will have to be ready in order to achieve these objectives (Annex X to the National Plan)

The systems available for the surveillance of the influenza, its degree of development and the indicators that can be obtained therefrom are set out in this protocol. For each of the phases, the protocol specifies what surveillance objectives must be taken into account, what systems are going to be necessary in order to achieve these objectives and what indicators should be used.

The surveillance activities during a pandemic should basically be integrated into the surveillance systems already in place, once the ad-

justment and modifications necessary have been made.

When the pandemic is in progress, the main objectives of the surveillance must be aimed at identifying and characterizing the population groups affected by the disease, in order to be able to define the appropriate control measures, such as, establishing priority groups to be vaccinated or defining or adjusting the use of antivirals. As the pandemic progresses, it will also be necessary to estimate the impact it is causing and to make an assessment of the control activities.

It must be kept in mind that no surveillance system alone will be able to provide the information necessary for an overall view of the problem and that each system will have a greater specific weight in the course of the different stages of the pandemic.

Among the surveillance systems that should take priority in situations of pandemic alert (phases 4 and 5) and even in the initial levels of phase 6, the early detection and investigation of outbreaks of acute respiratory infections stands out. The appearance of these clusters of severe respiratory disease cases, closely linked in time and space, is considered to be the most evident epidemiological indicator of the transition from a situation of the absence of human-to-human transmission of a new influenza virus to a sustained human-to-human transmission. As is reflected in this protocol, this is one of the activities in which our surveillance must be stepped up, as this is one of the least developed aspects of our influenza surveillance system, and a system that would make it possible to detect these clusters of cases, enabling an adequate investigation of them, both in the community as well as in the hospital environment, is considered fundamental in the preparation for and response to an influenza pandemic.

The sentinel surveillance systems are also described in this protocol. In contrast to the universal systems, the sentinel systems are not appropriate for the surveillance of diseases or processes with a very low incidence,

but are adequate and worthwhile for describing the characteristics and spread of a disease with high incidence and therefore can be extremely useful in the pandemic phase in which the disease is widespread in the population, although it may become necessary to adjust these systems.

Furthermore, the compulsory notifiable disease system, which has been in place in Spain since 1904, can provide useful information during the pandemic phase, as the mere compilation of gross incidence rates of reported influenza by units of time and geographical areas can be very useful for estimating the global impact of the pandemic in its advanced phases.

This protocol also sets out other useful systems for gathering information for the surveillance of the influenza pandemic, such as the mortality study method. In a pandemic, information on the number of people using the healthcare services will also be necessary (daily information on emergency treatment and hospitalizations –total and specific figures for influenza, occupation of services, and presence of complications in hospitalized influenza cases...). The way this information is collected and analyzed could vary from one Community to another, depending on the number of inhabitants and the functionality of their hospitals.

g. Participation in the European Common Ground exercise on an influenza pandemic.

The European Commission organized an exercise of pandemic influenza (Common Ground exercise) in order to test the communications, the preparedness plans and the coordination among the Member States, the Commission and Community agencies, such as the ECDC or EMEA, as well as WHO.

Spain participated in this exercise, held in November 23rd and 24th 2005, through the Ministry of Health and Consumer Affairs, with the participation of the Ministry's General Di-

rectorate of Public Health, the Instituto de Salud Carlos III, the AEMPS and the General Directorates of Public Health of the Autonomous Communities. It is estimated that as many as 50 players took part in this exercise.

The objectives determined for this exercise were:

- To assess the implementation of the national plans of the Member States;
- To improve the compatibility and the inter-operability of the national plans of the Member States;
- To examine the role and the availability of control measures.
- To determine the availability and the advisability of containment measures.
- To examine the role of the European Commission during an influenza pandemic and
- To assess the communications among countries and between countries and the European Commission

The exercises demonstrated the clear disposition of the European countries and organizations to improve their preparedness for the new healthcare emergencies.

The most important points derived from the assessment of the exercise were that the existing communication systems on the European level must be improved in order to achieve greater operational capacity. The roles of each system must be reviewed, and the users of those systems must be better trained. Similarly, there is a need to achieve greater interaction among the various European institutions and agencies and to do so in the light of the recent changes marked by the new International Health Regulations.

The exercises have provided a good opportunity to explore and improve national and international preparedness capacities, and the need to carry out similar exercises in the future has been identified in order to continue improving the level of preparedness.

D. ACTIVITIES TO BE DEVELOPED

Among the strategic actions recommended by WHO in order to attain the objectives that will enable us to cope with a situation of pan-

demical alert and a pandemic, further to the activities carried out and described in the preceding section, the following activities have been identified on which, from this moment on, the work of the Committees and Groups included in the organizational structure of the Plan is going to focus:

STRATEGIC ACTION	ACTIVITIES
<p>Reduce human exposure to the H5N1 virus</p>	<p>Continue monitoring the activity of the outbreaks of avian influenza and the assessment of the risk in Europe and the world.</p>
	<p>Ongoing revision of the recommendations to be adopted in order to avoid the risk. Continue the communication of the risk and of the measures to be adopted to the general public and to healthcare professionals.</p>
<p>Strengthen the early warning systems</p>	<p>Integrate avian influenza surveillance into an early alert system on a national level, developed on the basis of the new International Health Regulations.</p>
	<p>Intensify surveillance and the rapid detection of outbreaks of severe acute respiratory disease, in order to be capable of making a quick assessment of situations that could potentially be a sign of the person-to-person transmission of the disease.</p>
	<p>Continue strengthening the capacity of the network of laboratories for performing the virological diagnosis of strains with pandemic potential.</p>
	<p>Remain in contact with the Ministry of Agriculture, Fisheries and Food for the joint assessment of possible risk situations in our country.</p>
<p>Intensify the rapid containment operations</p>	<p>Develop Guidelines for Public Health measures (not pharmacological) to reduce the transmission of the influenza virus among humans.</p>
	<p>Performance of exercises in order to test the protocols, algorithms and guidelines for the management of cases and the control of the infection.</p>

STRATEGIC ACTION	ACTIVITIES
Develop the capacities for managing a pandemic	Draw up the criteria for the development by the public and private companies in charge of essential services of pandemic influenza preparedness plans that will ensure the operation of the essential services in the event of a pandemic.
	Monitoring of the research on and approval of pandemic vaccines and avian influenza H5N1 vaccines.
	Ongoing monitoring and establishment of recommendations on the strategy for the acquisition of vaccines, in order to ensure access to vaccines in the event of a pandemic.
	Draw up a program for the control and monitoring of adverse effects derived from the use of antiviral drugs.
	Draw up a program for the control and monitoring of adverse effects derived from the use of pandemic vaccines.
	Regular review of the priority groups for the administration of vaccines and antivirals.
	Intensify the drawing up of response plans on the local level.
	Test the operation of the response plans at the local level.
	Preparation of communication protocols and of materials to be used in a pandemic situation.

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ABBREVIATIONS

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AENA	Aeropuertos Españoles y Navegación Aérea (Spanish Airports and Air Navigation)
AMPS	Agencia Española de Medicamentos y Productos Sanitarios (Spanish Drug and Healthcare Products Agency)
AACC	Autonomous Communities
CNM	Centro Nacional de Microbiología (ISCI – National Centre of Microbiology)
CSP	Public Health Commission
DGSP	Directorate General of Public Health (Ministry of Health)
ECDC	European Centre for Disease Prevention and Control
EFSA	European Food Safety Agency
EMA	European Agency for the Evaluation of Medicinal Products
FAO	United Nations Food and Agriculture Organization
ISCI	Instituto de Salud Carlos III (Carlos III Health Institute – Ministry of Health)
MAPA	Ministry of Agriculture, Fisheries and Food
MSC	Ministry of Health and Consumer Affairs
OIE	Organization International des Epizooties
WHO	World Health Organization
PCR	Polymerase Chain Reaction Test
ReLEG	Network of Spanish Influenza Laboratories
RT-PCR	Real Time-Polymerase Chain Reaction
EU	European Union