NATIONAL INFLUENZA PREPAREDNESS AND RESPONSE PLAN

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1. INTRODUCTION

Influenza is an infectious disease caused by virus of the Orthomyxoviridae family which include the genera Influenzavirus A and B and Influenzavirus C. From an epidemiological perspective, Influenza virus A is the main cause of winter influenza epidemics which repeat each year, while the influenza virus B generally occurs in more localised epidemic outbreaks. Influenza virus C is related with the appearance of sporadic cases of influenza.

From a clinical perspective, influenza is usually a self-limiting disease that affects the general population and for which the morbidity and mortality are especially important in certain high risk population groups (people over 65 years old and younger than this age with underlying chronic conditions that can decompensate the influenza infection). The influenza infection is transmitted rapidly during seasonal epidemics and affects 10 to 20% of the general population. Mortality from the influenza epidemics range from 0.1-5% of individuals infected, although this depends on the influenza strain causing the epidemic disease.

An influenza pandemic results from the appearance of a new subtype of influenza A virus, different from the strains previously circulating in the population, and for which the population has no immunity, and therefore, the whole population is susceptible.

The influenza A virus can undergo major antigenic shifts, which can result in the appearance of a new influenza virus different from those that have been circulating in the previous years. In addition to these major changes, the influenza virus can undergo mutations or minor changes (antigenic drift), which is why the influenza vaccine must be updated yearly and adapted to the strains expected to circulate each season.

After the appearance of a new influenza virus, three conditions must prevail for a pandemic to occur: first, that this new virus can be transmitted to humans; secondly, that this virus can replicate in humans and cause disease and, thirdly, that this new virus can be effectively transmitted from one person to another and can cause outbreaks in the community.

Since 1997, the two first requirements were fulfilled on several occasions. In Hong Kong in 1997, 18 people were affected by a new avian virus subtype H5N1, and 6 of them died. In February 2003, 2 patients were identified as being affected and 1 died in Hong-Kong, all members of the same family who had made a trip to southern China, also by avian virus subtype H5N1. In Europe, in February 2003, there was an outbreak of avian influenza caused by subtype H7N7 in the Netherlands: 83 mild cases and 1 veterinary death. Three members of the family of two of the affected workers also suffered minor respiratory disease, suggesting a possible person-to-person transmission although the World Health Organization (WHO) concluded that effective interhuman transmission had not taken place.

Since the end of 2003, an outbreak has been produced by subtype H5N1 in Southeast Asia, with human cases in Vietnam, Thailand and Cambodia, where the two first requirements are also being fulfilled.

A new viral strain can acquire the capacity to produce an effective person-to-person transmission in two different ways. The first consists in a recombination, in other words, genetic exchange between human and animal viruses (this can occur when simultaneous infection occurs in humans or swine by human and avian influenza viruses simultaneously). The second mechanism concerns the adaptation and mutation of the new virus during human infection until this acquires the changes required to be able to produce an effective interhuman transmission.

In 1997, when the first cases of human infection by the H5N1 strain of avian influenza were detected in Hong Kong, research into influenza was greatly increased. The studies carried out showed for the first time that a new strain of the influenza virus of avian origin could directly infect man without requiring prior adaptation in a mammal acting as an intermediate host.

1.1. Pandemics produced in the Twentieth Century

Since the Sixteenth Century, several influenza pandemics have been recorded. Around three pandemics have been detected each century at intervals of 10 to 50 years apart. There are important differences between them but they have the common characteristic of spreading very rapidly. Usually, in less than one year they spread all over the world and cause disease in approximately one quarter of the population. Owing to their sudden appearance and the high resulting morbimortality over a short period of time, the response capacity is limited in many areas.

Throughout the Twentieth century, three important influenza pandemics have taken place, all caused by type A influenza viruses, corresponding with the appearance of subtypes H1N1 (1918-19, Spanish flu), H2N2 (1957-58, Asian flu) and H3N2 (1968-69, Hong Kong flu).

The pandemic of 1918 was estimated to cause more than 40 million deaths in less than one year and illness in 25 to 30% of the population. The first outbreaks were detected in March in Europe and in different regions of the United States (US). The first wave, which took place in Spring and Summer, was highly contagious but not particularly lethal. When the second wave appeared at the end of August, no country was fully prepared. This second wave appeared as explosive outbreaks. Mortality was greatest among young and healthy people. Around 99% of the deaths occurred in the population under 65 years old. Many of the deaths were from pneumonia caused by secondary bacterial infection but there were also some cases of direct primary viral pneumonias caused by bacterial infection.

The pandemic that began in 1957 was caused by a less virulent virus than that of 1918, and the health services were better prepared to tackle it, there were also antibiotics available and influenza vaccines were being produced. The outbreaks started in February in a province of China and spread throughout China during March to reach Hong Kong by mid-April, where it was detected for the first time. In less than six months, cases had been reported worldwide.

The first wave of the 1957 pandemic behaved differently in different parts of the World. In the tropics and Japan, introduction of the virus was rapidly followed by outbreaks throughout the whole region. However, in Europe and the US there was a period of at least 6 weeks after the virus was first introduced until outbreaks appeared. Cases were most common among school children, probably due to their close contact and the high density in schools. Mortality followed similar tendencies to seasonal epidemics, with the elderly and young children being by far the most affected. By December the first wave was in remission.

The second wave occurred one or two months after the first one and caused high rates of infection and an increase in mortality, affecting mainly the elderly population and people with chronic underlying conditions. Global excess mortality was estimated to be around 2 million people.

Vaccines were available in August in the US, by October in the United Kingdom and by November in Japan. However, these were produced in insufficient amounts to be used on a large scale. The vaccine producing countries only had sufficient quantities to cover their high risk population. No country had sufficient amounts to protect the whole population.

The last pandemic occurred in 1968, and was milder than the pandemic of 1957. In July, an epidemic of an acute respiratory disease was described in southeast China. In the same month, the disease spread to Hong Kong where it reached its greatest intensity in two weeks causing more than half a million cases. The virus was rapidly identified and on the 16 August the WHO gave the alert for possible worldwide dissemination. The initial spread was similar to that occurring in 1957. The clinical symptoms were moderate and mortality was low and in most cases disease progression was slow. Some tropical countries did not experience the first outbreaks until the beginning of 1969. The excess mortality rate was around 1 million. It is not certain why this pandemic had such a low mortality, al-

though some explanations suggest that the virus was genetically similar to that of previous pandemics, including that of 1957. As with the previous pandemic, the vaccine arrived late and in insufficient quantities.

Genetic and biochemical analyses of the viruses have shown that the pandemics of 1957 and 1968 were produced by a recombination of human and avian viruses. The virus of 1957 (H2N2) obtained three of its genes from an avian virus and the five remaining ones from the circulating H1N1 strain. The virus from 1968 (H3N2) also took three genes from an avian strain and the five remaining ones from the human H2N2 strain responsible for the previous pandemic. Both epidemics began with an explosion of human cases. On both occasions, the experts had assumed that the recombination had been produced in swine that has an equal number of human and avian receptors in its respiratory tract cells. After recent research about the pandemic virus H1N1 of 1918, the experts have reached the conclusion that this pandemic was produced by a mechanism of adaptive mutation of the avian virus.

1.2. Characteristics of an influenza pandemic

The main characteristics of an influenza pandemic, deduced from studying pandemics of the Twentieth century are summarised below:

- Pandemics behave unpredictably, as unpredictable as the virus that causes them. Important variations have been observed in mortality, severity of the disease and patterns of diffusion are detected. Accumulated infection rates throughout the waves can reach 50% and the attack rates around 25%.
- Cases appear very quickly and increase exponentially over a very short time (weeks). It is essential to take this into account when preparing for a pandemic.
- It can cause serious illness in groups not usually affected by influenza epidemics such as young adults, and this determines the impact of the pandemic. Therefore, epidemiological surveillance is essential to timely characterize the high risk groups affected at each moment and adapt the control measures required accordingly.
- The new virus tends to produce several waves and the age groups and areas not affected in the first one can be the most vulnerable in subsequent waves. The second waves usually have the strongest impact.
- The first wave will present a maximum peak at 3 to 6 months after which the first cases are detected, and the second wave can reach its peak around one year after the start of the pandemic. If the pandemic started outside Europe, from 1 to 4 months can pass before it reaches our country.
- Virological surveillance plays an essential role to quickly confirm the start of a pandemic, to isolate and characterize the virus and to make it available for vaccine production.
- Most pandemics started in parts of Asia, where a large proportion of the population live in close proximity with birds and swine. In these parts of the world, surveillance of the disease in animals and a study of clusters of human cases in humans is essential to detect a pandemic early on.
- Public health actions can delay its spread, but cannot usually detain an influenza pandemic. However, it is important to delay diffusion since the appearance of new cases is delayed to a maximum permitting measures to improve control of the pandemic to be implemented.
- In 1957 and 1968, vaccines against the new strain were produced very quickly but the production capacity for the vaccines was limited and these arrived too late to reduce the impact.

According to the WHO, the combined effort of all countries and epidemiological surveillance systems will enable the appearance of a new pandemic strain to be detected early on and plans of action and contingency plans to be started immediately,

enabling the organization of an adequate international response that can tackle the pandemic without too many losses.

1.3. How the influenza virus affects birds

Avian influenza, better known as avian flu, is an infectious disease caused by the type A influenza virus. This disease, well known in the area of animal health, was first identified in Italy more than 100 years ago. The infection can affect any bird although some species are more vulnerable than others. In these animals, there are many forms of the disease, some of which have a high mortality and are highly contagious between domestic birds and only rarely transmitted to man. There are at least 16 different subtypes of influenza A virus that can affect birds, although to date all the highly pathogenic outbreaks have been caused by subtypes H5 and H7.

Migratory birds, especially wild ducks, are the natural reservoir of the avian influenza virus, and these birds are the most resistant to the infection. Domestic birds are especially susceptible to lethal epidemics. Direct or indirect contact of domestic and migratory birds is considered to be the main causal factor of epidemics. Bird markets selling live birds have also been found to play an important role in disease transmission.

If there are not adequate measures of surveillance and control of these outbreaks, epizooites can be prolonged for years. After circulating even for short periods of time in bird populations, viruses with a low pathogenicity, can mutate into highly pathogenic viruses.

1.4. Outbreaks of H5N1 in 2004/2005. Epidemiological situation. Risk assessment

1.4.1. Epidemiological situation

The WHO considers that the situation that arose in December 2003 in southeast Asia, caused by circulation of the avian influenza virus strain H5N1, could potentially start the next pandemic.

In mid-December, most of the birds on a large bird farm near Seoul in the Korean Republic died suddenly. It was later confirmed that death was caused by a highly pathogenic strain of the avian influenza virus H5N1, which corresponded to the start of an unprecedented situation regarding its geographical extension and economic repercussions for the farming sector. Nine countries were affected by outbreaks of avian influenza H5N1 (Southern Korea, Vietnam, Japan, Thailand, Cambodia, China, Laos, Indonesia and more recently, Malaysia, in August 2004) and in more than half of these this was the first time that this type of outbreak had been detected. In the actions taken to control the epizootic more than 100 million birds were sacrificed in the first three months.

The WHO was first notified about this outbreak at the beginning of January 2004, and were informed of the first three human cases in which the avian influenza strain H5N1 was also detected. These corresponded to two children and one adult admitted to a hospital in Hanoi with severe respiratory disease.

From January to March in 2004, 35 cases were confirmed in Vietnam and Thailand of which 24 died. After several months with no new cases, between August and October 2004, 9 more cases, 8 of which were fatal were notified and from December 2004 to the 14 April 2005 another 44 cases have been notified with 19 deaths in Vietnam and Cambodia.

Nonetheless, the WHO is studying other unpublished cases and conducting serological studies in the exposed population, and the preliminary results (they found that 13% of the exposed population presents antibodies) suggests that the infection is more widespread and less lethal than originally deduced from the evolution of the first cases detected and confirmed. At present, it is not possible to calculate the lethality rate, since many symptomatic cases or cases with mild or moderate symptoms are not detected.

Confirmed cases mainly correspond to children and young adults, with a mean age of

17 years, and a very variable disease severity. In the cases described, the mean time between exposure and the start of the disease is 3 days (with a range of 2 to 4 days). According to the first published cases, the mean time between the start of symptoms and death is 13 days (mean of 13.5 and range of 5 to 31 days).

The clinical picture presented by these patients is characterized by a rapidly developing symptomatology, with high fever, respiratory symptoms with viral pneumonia that progresses to respiratory distress and in some cases death. However, as reported in the New England Journal of Medicine (17 Feb. 2005), one case has been notified of a Vietnamese child with severe diarrhoea followed by coma and death without respiratory symptoms. This case was confirmed as H5N1 when it was included in a study on encephalitis. Samples collected from the patients in the same study are being analysed to detect other possible cases of infection by H5N1.

In most of the human cases studied in the present outbreak, the disease has been spread by inhaled route of transmission, after direct contact with the birds or their excrement. These cases have been diagnosed in individuals exposed in a direct continuous way to birds.

Regarding the possible risk of transmission by food products, the WHO has published that there has been no recorded case of infection by the H5N1 virus associated with eating eggs or birds suitably cooked, when internal temperatures of 70ºC, the temperature at which the H5N1 is destroyed, are reached. Some cases have been described associated with exposure during slaughtering, waste elimination and the handling or preparation of birds for cooking.

Since the first outbreaks, the European Commission, as a precautionary measure have prohibited importation of bird products and susceptible species from affected geographical areas.

In September 2004, the Thailand authorities reported a probable case of inter-human transmission within a family (a mother became ill after looking after her daughter in hospital and had no apparent contact with birds). However, the increased surveillance implemented after these occurrences has not demonstrated that an effective and sustained person-to-person transmission can take place. After this case, some cases have been detected in Vietnam, but these are very limited and a family grouping has not been verified either.

Hence, the evidence seems to suggest that in the current outbreak person-to-person transmission could have taken place but this would be limited transmission within a family unit which have been in very close contact, without a sustained effective transmission in the community. In other previous outbreaks by H5N1 a possible inter-human transmission of this virus had been detected that was not capable of producing diffusion of the disease.

In 2003, in the outbreak of avian influenza by H7N7 virus that occurred in Holland mainly affecting farm workers, some cases of inter-human transmission were described although this was not effective transmission either. Recently, the final report of this outbreak has been published and it has been concluded that a possible inter-human transmission could have taken place in at least 3 cases (which presented conjunctivitis, an important symptom of this outbreak), and they also found that 59% of the close contacts of affected workers presented antibodies against this virus but did not manifest any symptom.

1.4.2. Risk assessment. Analysis of pandemic potential of subtype H5N1

According to published reports of the WHO, since 1968 there has never before been such a high risk of starting a pandemic as that posed by the current outbreak of the virus H5N1. The ecology of the virus has changed since the first time it was detected and the probability that a pandemic strain emerges has increased.

The characteristics of the H5N1 virus that define this situation are summarized below:

- The H5N1 virus is, currently, endemic in some parts of Asia and has established a permanent ecological niche in birds. The presentation of these out-

breaks in rural areas where most of the population live with these affected birds, which form the basis of their economy, makes it difficult to control these outbreaks. The risk of a new pandemic by this virus emerging persists while this remains in the environment and it is unlikely that the threat of H5N1 will disappear in the near future.

- Recent publications suggest that the pathogenicity of the H5N1 virus is increasing in birds and experimentally in mice models. The studies carried out have also described a greater viral resistance in the environment compared with the H5N1 strain that started the outbreak.
- The H5N1 virus is extending its range to include mammals. Recently, it has caused disease and death in a number of species including experimentally infected domestic cats and naturally infected tigers. These species are not considered to be susceptible to infection by influenza virus A. The most likely cause of infection for the outbreak in tigers which started in October 2004 in a zoo in Thailand was feeding them infected dead chickens.
- Domestic ducks could be acting as a silent reservoir of the virus H5N1. This virus has been detected in asymptomatic domestic ducks. In laboratory studies on ducks, these animals are found to eliminate large amounts of the virus over long periods, even when they appear to be healthy. The role of these domestic ducks could explain why in some cases of infection by H5N1, exposure to diseased ducks has not been found.
- Another recent finding was detection of the H5N1 influenza virus in dead migratory birds. Migratory birds are a natural reservoir of all influenza viruses, but historically these do not present symptoms of this disease. Although further evidence is required, these data suggest that the role of these birds in the evolution and maintenance of the H5N1 virus could be changing.

Another aspect of this epidemic, which has been debated over the past few months is the possibility that swine could become infected by H5N1. A Chinese research team presented a study in which they detected the presence of H5N1 virus in swine from different farms in China in 2003. The Chinese authorities have confirmed this finding but notified that in the follow up during 2004, all tests in swine were negative for this virus. Pigs have receptors in the respiratory tract that make them susceptible both to infection by the human influenza virus and to the avian influenza virus. If swine are simultaneously infected by both viruses, the possibilities of recombination occurring between the genes of both types of virus (avian and human) are increased with the subsequent risk of appearance of a potentially pandemic strain.

2. THE NEED TO UPDATE THE PLAN FOR PREPAREDNESS AND RESPONSE TO AN INFLUENZA PANDEMIC

In Spain in 2003, a "Plan of action against a possible influenza pandemic" was prepared by a working group established by the Public Health Department of the Ministry of Health.

The WHO, considering the current epidemiological situation existing in southeast Asia and taking into consideration the progress in knowledge and evolution of the influenza virus, presented in April 2005 a new plan to support Member Countries in the preparation and response to the threat of the next influenza pandemic. The new plan redefined the phases previously established in 1999 in their *"Global plan for Preparedness for the Influenza Pandemic: The role of the WHO and guidelines for national and regional planning"*1. The new phases are defined in relation to the risk of appearance of a pandemic after emergence of a new subtype of the influenza virus. The Plan described the measures to be taken by the WHO and the national authorities during each phase, with the aim of improving the international coordination and transparency in the recommended measures.

The WHO proposes that each country develops or updates their national plans for preparedness for an influenza pandemic and provides guidelines for each of the phases proposed.

The phases are defined with the objective of managing the risks for public health caused by infection by the influenza virus in animals, and changes in each phase are directly linked to changes in the public health activities and the response that should be contemplated. It is proposed to increase surveillance of initial events at the start of a "pandemic alert" and to detect circulation of the virus early on, and quickly implement control measures in a coordinated way both nationally and internationally, in order to control or delay diffusion of a new strain of human influenza. Even if it were not possible to completely detain the spread, diffusion of the virus could be delayed in order to gain more time to develop vaccines against the new strain and to proceed early on to update preparatory measures to prepare the pandemic. The success of this approach would depend on several factors and surveillance of the infection with new subtypes of the influenza virus in humans would be essential.

Because of the new plan published by the WHO, and the epidemiological situation and the events that have taken place since 2004, the Ministry of Health will update their existing Plan and present this new proposal.

2.1. New pandemic phases

	Main Public Health Objectives
Interpandemic period	
Phase 1 New subtypes[1] of the influenza virus are detected in people. In animals some subtypes of the influenza virus previously producing infection in humans are detected. However, there is considered to be a low risk[2] of infection or disease for humans.	To consolidate the preparation for an influenza pandemic at a world, international, national and subnational level.
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 risk[2] of the disease for humans.	Minimize the risk of transmission to humans, detect and notify this transmission rapidly if it occurs.
Period of pandemic alert	
Phase 3 Human infection (s) with a new subtype of influenza virus, but without person-to-person transmission, or at maximum, rare cases of transmission when in close contact.	Ensure the rapid typing of the new subtype of virus and the detection and early notification of additional cases.
Phase 4 Small groups of cases with limited person-to-person transmission. The transmission is much localized suggesting that the virus is not well adapted to humans[3].	Limit transmission of the new virus within localized foci or delay the spread in order to gain time to apply effective response measures.
Phase 5 Larger clusters of cases, although person-to-person transmission is still localized suggesting that the virus is continually becoming more adapted to humans but is still not completely transmissible (high risk of pandemic)[3].	Maximize the effort to limit or delay spread of the virus to prevent the pandemic and to gain time to apply effective response measures to the pandemic.
Pandemic period **Phase 6** Pandemic phase. High and sustained transmission among the general population.	Reduce the impact of the pandemic to a minimum.
Post-Pandemic period	
Return to the interpandemic period	Return to the interpandemic period

[1] *Definition of a new subtype: a subtype that has not been circulating in humans for several years so that most of the population does not have protection against it.*

[2] *The difference between phase 1 and phase 2 is related with the risk of infection or disease caused by the strain that is circulating among animals. The difference between both of these is due to several factors and to the relative importance of each of them in relation to current scientific knowledge. These factors can include: pathogenicity in animals and humans, the existence of cases between domestic animals and cattle or only in wild animals. Whether it is geographically localized or widespread and if the virus is enzootic or epizootic. Information about the viral genome and other scientific data must also be taken into account.*

[3] *The distinction between phases 3, 4 and 5 is related with risk assessment. Several factors must be taken into account and the relative importance of each of these in relation to current scientific knowledge must be considered. These factors include: the transmission rate, the geographical location and diffusion, the severity of the disease, the presence of genes from human strains. Information about the viral genome and other scientific data must also be taken into account.*

2.2. Criteria to announce a change in phase

The change in phase will be announced by the Director-General of the WHO. The change will be made according to current legislation for the notification and control of diseases (International Health Regulations) and by consulting international organizations if necessary.

Since the origin of the new strains and their progression sequence in the following pandemic can be difficult to predict, the WHO can decide to advance or to recede in the scale of phases following a non-sequential order. Announcement of a new phase would imply the implementation of actions recommended for the new phase.

The Ministry of Health can subdivide phases depending on the national situation.

The WHO suggests that Phases 2-5 can be subdivided depending on whether the country is affected (or has an important commercial relationship or via trips to an affected country) or not. They also suggest that Phase 6, the Pandemic Phase, can also be subdivided depending on whether a country is affected (or has an important commercial relationship or via trips to an affected country) or is not, or whether the first wave of infection is in remission or whether the second wave has begun to appear.

3. THE ROLE OF THE EUROPEAN UNION IN THE PREPAREDNESS AND RESPONSE TO AN INFLUENZA PANDEMIC

In March 2004, the European Commission drafted the working document "*Community Planning for the Preparedness and Response to Influenza Pandemics"* in which important questions, both nationally and for the European Union, were posed related with legislation on animal health and the actions to prevent and control influenza in animals, especially avian flu.

The document dealt with the planning required for the European Community to be able to respond effectively to a potential or real influenza pandemic, and was prepared taking into consideration the «Influenza pandemic preparedness plan. The Role of the World Health Organization and Guidelines for National and Regional Planning» (WHO, Geneva, 1999)

The objective of the preparedness plan is to minimize the risk of pandemics, to ensure the preparedness for them and to achieve a coordinated Community response:

- Identifying key components of the response;
- Determining the activities of the Commission, the European Drug Agency and the Member States that could help response measures and assist in their coordination.

The most important surveillance task of the Member States is to detect and characterize the pandemic strains early on from clinical or other types of samples and to determine the risks to establish the potential of these strains to cause widespread outbreaks in humans.

Definitions of influenza cases that should be used in notifications are established in the Commission Decision 2003/534/CE for which Policy Decision n° 2119/98/CE of the European Parliament and Committee and Policy Decision 2000/96/CE in relation to the transmissible diseases was modified and Policy Decision 2002/253/CE11 in relation to the definitions of cases for transmissible diseases.

As part of the attempt to establish a broad base of action in the Community, the Commission has given financial support to the EISS, European Influenza Surveillance Scheme, since 1999, according to the specifications of policy decision nº 647/96/CE of the European Parliament and Committee.

The working document was prepared for use in a debate on the coordination of preparatory measures against influenza and about recommendations that can be formulated.

In June 2004, the European Union Committee extended the mandate of the Health Security Committee (HSC)- to develop community planning for the preparedness and response to influenza pandemics and to assess the suitability of possible negotiation with the pharmaceutical industry about the production and distribution of vaccines and antivirals. As a result, this Committee has extended its responsibilities to take on aspects related with the Influenza Pandemic Plan. This mandate will be updated when the European Centre for the Prevention and Control of Diseases is in operation (26 May, 2005).

4. OBJECTIVES OF THE PLAN

This National Plan will be elaborated according to recent recommendations of the WHO and the EU to harmonize the preparation and response measures and to prepare response plans for all operative levels for the Autonomous Communities (AC).

General objectives:

- To reduce the impact of the pandemic on the population's health and to maintain the function of services essential to society.
- To take measures to reduce diffusion of the new virus, after identifying a new subtype of the influenza virus with confirmed efficacy in person-to-person transmission, to implement protective measures for the population.
- To guarantee that the response and measures adopted correspond to the recommendations of the WHO in each phase.

Specific objectives:

- To define a system that can give a flexible response to an influenza pandemic of unpredictable characteristics.
- To rapidly identify a new potentially pandemic strain of the influenza virus.
- To rapidly assess the emerging epidemiological situation in a new pandemic, to adjust the control measures accordingly and to reduce as far as possible the spread of the pandemic.
- To constantly review epidemiological and clinical data to indicate the guidelines to follow for case detection, isolation and management.
- To administer treatment and health care to the largest possible proportion of the population according to the latest scientific knowledge.
- To develop and validate diagnostic tests for the new virus and to provide the reference services required nationally.
- To reduce the impact on the health and social services as a consequence of the pandemic (cancellation of routine tasks, reorganization of priorities of the services, etc.).
- To guarantee and to maintain the essential services and to reduce the impact on the daily life of the population.
- To provide professionals, the population and the media with suitable validated and updated information during the pandemic.
- To quantify the global magnitude and the load of the pandemic in our country and to determine its impact.
- To effectively collaborate with international institutions and with Autonomous Communities to coordinate measures to take.
- To effectively coordinate the actions taken by the Ministry of Health with those of other public institutions responsible for controlling the impact of the pandemic.

5. KEY ELEMENTS OF THE RESPONSE

5.1. Organizacional structure and coordination.

5.1.1. National Influenza Pandemic Planning Committee for the Prevention, Control and surveillance of the epidemiological development of the influenza virus.

Following the recommendations of the WHO, in Spain the National Influenza Pandemic Planning Committee has been set up (NIPPC) with the aim of developing and coordinating the actions related with the Plan of Action. (ROYAL DECREE 1131/2003, 5 September, BOE nº. 214 Saturday 6 September 2003)

According to the Royal Decree, the composition and functions of the Committee are as follows:

Composition of the Committee:

- The Committee is presided over by the Ministry of Health or a representative.
- Spokespersons of the Committee are: The Secretary of State for Health.
  a) The Secretary of State for Public Health.
  b) The Director General for Public Health.
  c) The Secretary of State for Cohesion of the National Health Service and the Autonomous Communities.
  d) The Directorate General for Pharmacy and Health Products.
  e) The Director of the Spanish Drug Agency (SDA).
  f) The Director of Health Institute Carlos III (HICIII).
  g) The Directors of the National Influenza Centres of the WHO and the Animal Health Research Centre (AHRC) and the National Institute for Farming and Food Technology and Research (INIA).
  h) One representative, of a similar rank to Director General of the following ministries: of Foreign Affairs, of the Interior, Urbanisation and Construction, Employment and Social Services, Agriculture, Food and Fisheries, Public Administrations, Economy, Science and Education, and, representing the Ministry of Defence, the Inspector General of Health for Defence.

The Director General of Public Health will act as Secretary of the Executive Committee.

- When considered necessary or useful, leading positions in other Government entities can attend the meetings and any experts considered as capable of making a valuable contribution to the Committee's work.

Functions and responsibilities of the Committee:

The Committee is responsible for monitoring, coordinating and where relevant, proposing actions to be taken by the State Departments.

The Committee has the following specific functions:

a) To design the organizational structure and levels of responsibility in decision-making and control to tackle a possible influenza pandemic.
b) To monitor and assess planning activities, including response plans.
c) To adopt criteria for action, for the different phases of the pandemic, following the WHO's recommendations at all times.
d) To coordinate information that must be made available to international and national organizations.

e) To coordinate the actions of the State Administration with other Public Entities with competences in the area and cooperation with them.

f) Any other action related with the influenza pandemic that requires coordination of the actions of the State Administration and, where relevant, with other public entities.

In collaboration with the task force to guarantee equal access within the Spanish State to health resources if availability is limited.

5.1.2. Public Health Board

The Planning Committee coordinates Plans for Preparedness and Response prepared in the Autonomous Communities by the Public Health Boards (PHB). The objective of this coordination is to harmonize response plans between the autonomous communities and with recommendations of the EU and the WHO.

To do this, the PHB will hold the meetings it considers necessary which will also be attended by the authors of the Autonomous Community plans.

This Board has the following functions:

- To guarantee that the control measures established for each phase in the National Plan are adopted and coordinated throughout the ACs.
- To ensure that the activities proposed in the Autonomous Plans are adapted to the organizational structures of each Autonomous Community.
- To guarantee equal access to health resources in the Spanish State in the case of limited availability.

5.1.3. Working Group of the Executive Committee

The Working Group of the Executive Committee (WGEC), set up in response to a decision of the Executive Committee, will help to implement measures to reduce the impact of the pandemic on the population's health.

This Group has the following functions:

- To plan, initiate and coordinate the response of institutions involved in the National Pandemic Preparedness and Response Plan
- To support the health service at all levels to prepare the Plans.
- In the pandemic alert and pandemic phases to guarantee continuous updating of the Plan in accordance with epidemiological evidence provided by the WHO in these phases.
- To propose control strategies for the pandemic to the Planning Committee
- To guarantee equal access to health resources in the case of limited availability in the Spanish State.

It is composed of the following members:

- President: Director General for Public Health of the MH
- Vice-president: an expert appointed by the President of the Planning Committee.
- Spokespersons:
  - 1 Representative of Carlos III health institute
  - 1 Representative of the State Department of Pharmacy and Sanitary Products.
  - 1 representative of the Animal Production Department of the Ministry of Farming Food and Fisheries.
  - 1 representative of the State Department of Civil Protection of the Ministry of the Interior.
  - 1 representative of the Ministry of Defence
  - The President of the Planning Committee and

- 1 representative of the technical coordination group.

This group will meet regularly every six months and whenever considered necessary can be urgently summoned.

5.1.4. Technical Coordination Group

The role of the technical coordination group TCG is to assess and to support the previous committees to achieve their objectives and coordinate activities of the subcommittees.

Its functions are:

- To be in contact with experts of the WHO and other international agencies.
- To provide the information necessary to maintain the National Preparedness and Response Plan continually updated
- To coordinate virological, clinical and epidemiological data to support strategic decisions for use of antivirals and vaccines.
- In the pandemic alert phases to have a mobile team of specialists in field epidemiology to assess the risk of spread and to support measures to contain the infection.
- To coordinate with the different specialists to prepare national guidelines for public health recommendations.
- To coordinate activities of the health sector with other technical sectors involved.
- To collaborate with the communications subcommittee to identify the most appropriate way to inform the population transparently.
- In the pandemic alert phases, to daily update world information and to communicate relevant information to the Task Force.
- They will be responsible for notifying cases to the WHO.

This Committee is comprised of: the Director General for Public Health of the MH, representatives of the General Sub Department for Promotion of Health and Epidemiology (GSPHE), and the General Subdepartment for Overseas Health (GSOH). It can be constituted of expert groups that can give advice in different areas when required.

5.1.5. Scientific committee

The function of the scientific committee is to support, advise and inform about scientific issues in response to queries from the Planning Committee, in relation to the National Plan and the policy decisions required in the event of an influenza pandemic.

It is composed of the following members:

- President: Secretary of State for Health of the MH
- Vice-president: Director General for Public Health of the MH.
- Secretary: A representative of the GSPHE
- Spokespersons: 14 spokespersons appointed from the members of the scientific committee with a recognized professional experience and belonging to any of the following scientific associations or professional colleges:
  - Spanish Family and Community Medicine Society
  - Spanish Infectious Diseases and Clinical Microbiology Society
  - Spanish Epidemiology Society
  - Spanish Public Health and Health Administration Society
  - Spanish Society for Preventive Medicine, Public Health and Hygiene.
  - Spanish Pneumology and Chest Surgery Society
  - Spanish Paediatrics Society
  - Spanish Geriatrics Society

- Spanish Virology Society
- Governing Body of the Official College of Medicine
- Governing Body of the Official College of Veterinary Science
- Governing Body of Nursing in Spain
- 1 representative of the University
- Carlos III Health Institute

5.1.6. Subcommittees or special working groups

For the technical development of each of the key issues of the National preparedness and response plan in the advance of an influenza pandemic, the following subcommittees or working groups will be established:

1. Surveillance subcommittee
2. Vaccines and Antiviral Agents Subcommittee
3. Emergency Response Subcommittee
4. Communications Subcommittee

The following sections specify the detailed objectives and structure of each of the subcommittees.

Key elements of the National Plan

In the Influenza Pandemic Preparedness Plan, published in April 2005 the WHO recommends to the health authorities that they develop preparedness and response plans in which they should define:

- An organizational and coordination structure
- Epidemiological and virological surveillance
- Prevention and control measures (vaccines, antiviral agents and non pharmaceutical interventions)
- The response of the health service, and
- Communications strategy.

5.2. Epidemiological and virological surveillance.

Owing to continuous antigenic changes of the influenza virus a rigorous and continuous surveillance system of the disease is required, including both virological and epidemiological aspects. Virological surveillance should include isolation of the virus and implementation of antigenic and genetic studies, while epidemiological surveillance consists of establishing the diffusion and clinical impact of the possible new antigenic strains detected. Although the detection of major variants (antigenic shift or change) is the maximum objective of virological surveillance, minor antigenic changes should also be monitored (antigenic shift) that occur in each yearly epidemic and are the reason for modifying each year the composition of the antiinfluenza vaccine.

The information derived from surveillance of the influenza is essential to rapidly identify the onset of an influenza pandemic and to take policy decisions at each moment.

The objectives of influenza surveillance should be modified according to the epidemiological context of the disease and the possibility of intervention. The main objective of surveillance in the pandemic phase is to keep the systems active and to ensure that a rapid alert system is activated.

After the pandemic has started the main surveillance objectives are to provide information about the characteristics of infection in the population, to monitor the progress of the disease and the impact on the health services and other essential services.

During an influenza pandemic it is important that surveillance systems are flexible since the definition of a case can be altered and the notification system must be modified to suit the new situation.

On the other hand, it is essential in the inter-pandemic phase to have a rapid alert system to be able to detect unusual clusters or cases of influenza that could be caused

by a new strain of the influenza virus. This surveillance is essential in the first stages since early detection will permit public health measures to be applied from the start, when these measures can delay the onset and reduce the impact of the pandemic.

The start of a new pandemic does not necessarily coincide with the usual annual influenza epidemic and can appear at any time during the year.

There are three WHO Reference Centres in Spain responsible for the annual identification of strains to be included in the antiinfluenza vaccine (National Microbiology Centre, Majadahonda; Influenza Centre Valladolid; and the Microbiology Laboratory of the - Hospital Clinico /Barcelona University). The Majadahonda laboratory also functions as a national reference laboratory.

Most of the Autonomous Communities have a virology laboratory where the influenza virus can be isolated.

During the influenza season there is a series of epidemiological surveillance Groups (medical surveillance groups) that constitute the Influenza Surveillance Network in Spain in which 14 AC participate. When the pandemic alert phase 5 is announced, these Networks will be activated.

This network participates as part of the European Influenza Surveillance Scheme by providing virological and epidemiological data obtained in the national network.

Detailed description of the structure and function of influenza surveillance in Spain.

Influenza surveillance in the advance of an influenza pandemic should include a parallel influenza surveillance in animals to that carried out in the human population that should operate together in a coordinated manner.

5.2.1. Surveillance subcommittee.

The function of this subcommittee is to guarantee that surveillance can respond to the objectives of this Plan in each of the phases of the Pandemic.

This Subcommittee is comprised of:

- The Director General of Public Health of the MH (GSPHE and GSOH)
- State Department for Cohesion with the Autonomous Communities of the MH
- National Epidemiology Centre (NEC) of the HICIII
- National Microbiology Centre (NMC) of the HICIII
- State Department for Animal Production of the MAFF
- Animal Health Research Centre (AHRC)
- Heads of epidemiological and virological surveillance in all the Autonomous Communities

To develop the different facets of surveillance this Subcommittee will create the working groups it considers necessary.

5.3. Vaccines and antivirals.

Since vaccination programmes against influenza were first introduced in the 1950's, they have been shown to constitute a key element to prevent and control this infection, although it must be taken into consideration that the annual vaccine will not provide protection against a new influenza strain. One of the challenges, in response to a pandemic threat is, therefore, to develop a safe immunogenic vaccine that produces protection against a new strain in as short a time as possible.

After the onset of the pandemic, three successive situations will take place regarding vaccination as a public health measure that conditions the implementation of other control measures. The three situations are as follows: vaccines are not available globally, limited supplies of vaccines are available and, finally, the scenario of a widely available vaccine.

In the advance of a pandemic, a series of issues about the availability, administration and application of the new vaccine must be considered:

- Since the pandemic strain can appear at any time and the fact that pharmaceutical laboratories require a minimum of 4 to 6 months to produce a new vaccine, it must be assumed that the vaccine will not be available during the first few weeks of a pandemic.
- The whole population will be susceptible to a novel strain so risk groups requiring vaccination would encompass more of the population than before, ideally vaccinating the whole Spanish population.
- Generally, the immune response to a vaccine in seronegative persons is quite low and the emergence of a novel strain would require administration of a second dose to ensure maximum protection.
- The capacity of the pharmaceutical industry to produce a vaccine is currently limited to its annual production capacity in interpandemic periods.

Consequently, in response to the challenge of an influenza pandemic there would probably be insufficient amounts of vaccine available and, so, antivirals, which can be used from the onset, should be available in the country at the onset of the pandemic.

Recent data from the World Influenza Surveillance Scheme of the WHO suggest that H5N1 viral strains are susceptible to neuraminadase inhibitors. All strains isolated from humans and those isolated from birds have shown an *in vitro* susceptibility to these medicinal products.

Antiviral inhibitors of neuraminidase (oseltamivir and zanamivir) are used to treat the disease. If they are administered in the first 48 hours after the onset of symptoms, they can reduce disease progression by around two days, reducing the rate of complications and hospitalization in both healthy adults and members of the risk group.

On the other hand, prophylaxis can also be used for the influenza pandemic. In studies carried out in the inter-pandemic period, both medicinal products showed an efficacy between 65% and 85% at preventing the disease. These are also effective when used as a prophylactic measure in nursing homes for the elderly.

The response to a pandemic threat requires a reliable supply of antivirals and vaccines and task forces to administer both of these and also clearly defined distribution channels before the onset of the pandemic.

5.3.1. Vaccines and antiviral subcommittee

Its role is to advise the Committees and Institutions responsible for making policy decisions about control measures about all the technical aspects related with vaccines and antivirals.

The objectives of this Subcommittee relative to vaccines are to:

- Define and prioritize target groups in each phase and revise them according to the epidemiological situation during the pandemic.
- To define storage conditions.
- To assess the extent of vaccine protection.
- To set up a programme to control and monitor vaccine safety.
- To set up a programme to monitor the efficacy of the vaccine in the population.

The main objective for using antivirals in an influenza pandemic response plan is to minimize disease severity and the number of deaths and, secondly, to minimize the degree of social disruption the pandemic can cause.

The initial identification of risk groups is based on previous years in which the rate

of influenza disease was high and the experience of previous pandemics. The "level of individual risk" cannot be precisely defined until the pandemic virus has been detected and has caused disease in the population. It is, therefore important to consider that the definition of "high risk groups" must be redefined after the onset of the pandemic based on epidemiological data available at each moment.

The objectives of this Subcommittee regarding antivirals are:

- To define and review authorized indications for each antiviral and possible suppliers
- To review the evidence about the efficacy of each antiviral.
- To establish the conditions for their supply, storage and their shelf-life.
- To define and prioritize population groups to which antivirals should be administered
- To develop a programme to control and monitor adverse effects.
- To identify laboratories capable of detecting resistant strains and developing surveillance programmes for these.

This Subcommittee is composed of the following institutions:

- MH: Department of Pharmacy and Sanitary Products
- MH: Spanish Drugs Agency
- MH: Department of the MH for Cohesion between Autonomous Communities
- MH: Department of Public Health
- MH: Carlos III Health Institute
- AHRC: Animal Health Research Centre
- Ministry of Foreign Affairs
- Ministry of Finance
- Ministry of the Interior
- Valladolid Influenza Centre

5.4. Response Programmes to health services.

During an influenza pandemic there is a very rapid increase in the demand on health care over a short period, and health leaders require defined Programmes to specify the actions to be taken by the health services and its centres in each pandemic phase.

The AC have a Regional Plan for Preparedness and Response and a Planning/Advisory Committee, with representatives of the Regional Health Department, the emergency services responsible for setting up the chain of responsibility in the Autonomous Community and representatives of public and private entities that play a role in the different phases of the pandemic.

The emergency response programmes for the health services should:

1. Draw up a plan to establish the actions required for the control, surveillance and monitoring of the patient, to guarantee health care, rapid access to public health measures (antivirals and vaccine) and communication within each level in each of the phases.
2. To ensure that the regional response programme is known by all those involved and regularly revised and tested.
3. To assess the availability of hospital beds in each region or district and to study ways to increase the existing capacity.
4. To prepare protocols so that after onset of the pandemic the greatest number of patients not requiring continuous care can be discharged.
5. To refer patients with compatible respiratory conditions similar to influenza to special waiting units either in the hospital or established especially for this purpose.
6. To set up a centre to monitor the influenza pandemic (physically or by telephone) to manage the flow of patients.

7. To strengthen surveillance of control measures of the infection in the Hospital and to study probable cases of hospital transmission to review the efficacy and/or compliance with recommended control measures.

Diversion of patients is done to reduce the risk of transmission of infection, identifying persons that can have the pandemic disease and separating them from the other patients, and also to assess the type of care they need. Wherever possible, a specific area should be allocated to patients with fever or respiratory disease. Since not all patients diverted to this Area will have influenza, measures will be taken to control the infection, such as the use of face masks for patients with cough and special hand washing units will be set up. Transmission of the infection should be prevented to other patients staying in the hospital or visiting the out-patients clinic belonging to groups at risk of presenting complications if they contract the disease.

The Pandemic Surveillance Centre (physical monitoring or by telephone) can manage the movement of patients, referring them to primary care centres or to other hospitals or health centres when they do not require hospital admission.

Ambulatory monitoring services should be set up for patients not requiring hospital admission who can stay at home.

During the peak of the pandemic, centres to divert patients sufficiently staffed with health care professionals will be set up to respond to the large number of persons requiring health care.

5.4.1. Subcommittee for emergency response of health care

The objective of this Subcommittee is that each Autonomous Community should have an influenza pandemic response programme and that heath care programmes are developed according to common criteria of the WHO and the European Union.

This Subcommittee should guarantee that all Health Care Programmes include the following:

- The organization of health care to satisfy a rapid increase in the demand due to an influenza pandemic.
- Strategies to increase the management capacity of resources and staff to tackle the pandemic. Coordination of all the sectors involved.
- Distribution channels for antivirals and vaccines on a local level.
- Protocols for the treatment and management of patients and control of the infection.
- Estimation of the needs for medicinal products and the provision of other materials.
- Mechanisms to train health care professionals in aspects related with an influenza pandemic.
- Coordination of aspects related with communication to health care professionals.

This Subcommittee is coordinated by the State Department for Public Health and Cohesion with Autonomous Communities of the MH composed of the leaders of Health Service Emergency Response Programmes. Representatives of the Expert Coordination Group will also participate.

5.5. Communications.

A pandemic is an international event and for this reason communication agreements exist with international organizations such as WHO and the European Union, in both directions. The WHO is responsible for announcing a change in the phase of the pandemic and of the period at a global level.

With the objective of developing a global telecommunications strategy to ensure adequate diffusion, access, suitability and

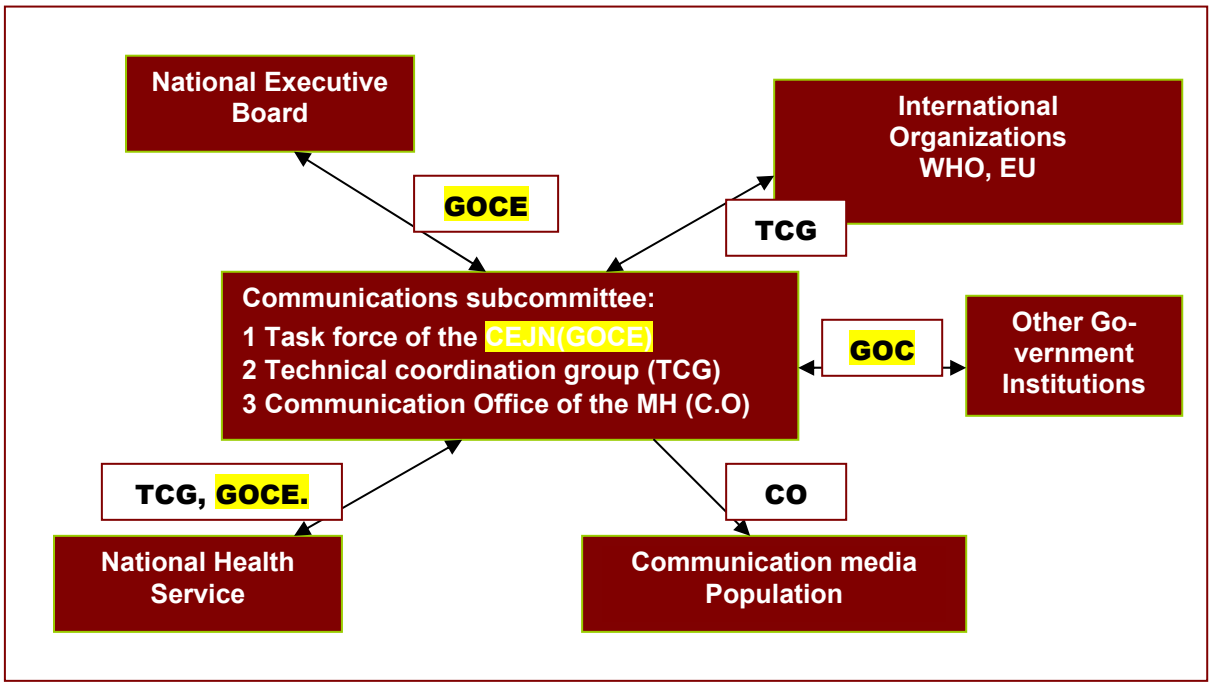
speed of the information, a series of activities must be developed including:

- A steady improvement in already existing communication systems, including electronic mail (e-mail and Internet), telephone information lines (900 lines), regular informative leaflets about the prepandemic situation and clear and simple leaflets about the influenza pandemic, its characteristics and methods of action (vaccination and antiinfluenza medication).
- Preparation of different educational material including clearly explained up-to-date information, preferably in the form of: information leaflets for the general public, both written and audiovisual press releases to be sent to the media,
- Setting up a telephone hotline for rapid replies.
- Development of a national videoconference system that permits non-physical contacts between the institutions during a pandemic.
- To set up a Webpage with two modes of access, by the general public and also by health care professionals showing the response plans, manuals, protocols and all the information considered convenient in each phase.

To facilitate and to assist the different health and social, local and community institutions in managing an increased health care demand, by preparing a set of manuals and information leaflets emphasizing the most important aspects in each phase.

One of the main objectives of all the informative activities is to create a favourable opinion and wide knowledge about the social and sanitary repercussions of an influenza pandemic and to avoid duplicity of effort that can reduce available human resources at the time of action. To reach a consensus about most decisions will favour their acceptance and subsequent implementation when required.

Flow chart of information:



The information will be compiled by the communications subcommittee and shared with the institutions specified in the box.

5.5.1. Communications' subcommittee

The objective of this subcommittee is to coordinate the information requirements to optimize the efficacy of the response and, therefore, to communicate updated and relevant information to all levels: the media, the general public and professionals involved in the response plan using the means of diffusion considered to be most effective for each phase and group.

This subcommittee is composed of representatives of the Task Force, Coordination Group and Communications Office of the MH.

5.6. Other measures to prevent the disease from spreading within the population.

The basic measures to prevent transmission of the infection and to minimize the degree of social disruption that the pandemic could cause include:

- Antivirals and vaccines dealt with in section 5.3.
- Non-medical interventions: based on recommendations of the WHO. Protocols and manuals have been developed that should be regularly updated about the following measures:

  a.) Manuals about respiratory hygiene and hand-washing.

  b.) Advice to travellers who arrive or are travelling to affected regions.

  c.) Measures to detect cases and actions to be taken in airports and ports.

  d.) Voluntary home isolation.

  e.) Voluntary isolation of the contacts of cases.

  f.) Local restrictions in persons' mobility.

  g.) Restriction of large meetings, public events, international meetings on national territory etc.

  h.) Closure of schools (study the impact of this measure in the maintenance of some sectors).

  Most of these measures would require a revision of public health legislation.

5.7. Legal aspects

The legal services of the Ministry of Health should study the legal aspects relative to compulsory vaccination and isolation and the restriction of movement according to the Constitutional Act 3/1996 of 14 April of Special Public Health Measures in Public Health, articles 2 and 3.

The administration of antivirals to staff involved in implementing this plan in its different phases and contacts with patients could become compulsory.

When vaccination is compulsory, the legal department will study how the State can compensate for adverse reactions if these arise.

6. OBJECTIVES AND ACTIONS IN THE DIFFERENT PANDEMIC PHASES

6.1. Interpandemic period, Phase 1.

In this phase, new subtypes of the influenza virus have not been detected in people. In animals, subtypes of the virus that have previously caused infection in humans can exist. However, there is considered to be a low risk of infection or disease for people.

During this phase the actions are centred around strengthening the preparation for an influenza pandemic at world, regional, national, and autonomous community levels. Attention will be centred around surveillance of seasonal influenza and the WHO will be responsible for coordinating research of initial occurrences.

Objectives:

- To develop and maintain preparedness and response plans harmonized with international plans.
- To improve and control seasonal influenza.
- To heighten surveillance of human and animal influenza to facilitate detection of a new subtype of influenza virus if this should appear in Spain.
- To maintain coordination between surveillance networks and international organizations.
- To improve national, regional and intergovernmental coordination to diminish the risk of infections in humans with a new influenza virus.
- To define the strategies and processes to coordinate rapid mobilisation of resources during the warning phases and mechanisms for rapid decision making.

Phase 1

	Actions	Actions to be taken by
Planning and coordination	To set up a National Planning Committee for Influenza	Ministry of Health
	To set up a national task force	Public Health Department
	To develop a Preparedness and Response Plan and update it regularly	NIPPC
	To create a planning committee in each Autonomous Community to prepare a Regional Response Plan	PHB
	To inform about the importance of persons involved in policy decision making to have access to preparedness plans.	NIPPC, PHD and PHB
	To identify the key persons to be mobilised when a new strain appears.	NIPPC
	To set up a scientific committee	Secretary of State for the MH
	To develop special Subcommittees	NIPPC, PHD
Antivirals and vaccines	To maintain contacts with producers of vaccines and antivirals to guarantee access to these in the event of a pandemic.	PHD
	To develop use strategies for antivirals	VAS
	To revise vaccination strategies for seasonal influenza and to increase the protection in established risk groups.	PHD .AC
	To define action strategies aimed at the workers of bird breeding farms.	PHD + MAAF

Phase 1		
	Actions	**Actions to be taken by**
Surveillance	To strengthen surveillance to detect the emergence of novel variants and new influenza virus strains both in humans and in animals.	NEC-AC-MAAF
	To develop a surveillance system to detect outbreaks of severe acute respiratory disease.	NEC-AC
	To describe morbidity and mortality patterns and the incidence of disease caused by seasonal influenza.	NEC
	To prepare an early warning system.	NEC
	To coordinate with the European Influenza Surveillance Scheme (EISS)	NEC
	To characterize and share isolations of the influenza virus and information about circulating strains with the relevant international organizations (WHO, FAO, IEO)	WHO reference laboratories
	To strengthen virological surveillance so that the each AC has at least one laboratory that can isolate the influenza virus, identifying type and H1 and H3 subtype.	AC
	To organize courses teaching the different diagnostic techniques to incorporate new methods of molecular typing and subtyping (RT-PCR multiplex) in the laboratory networks.	CNM
	To enhance surveillance in workers with exposure to a probable high risk situation.	MAAF, PHD
Response to appearance	To assess the capacity of health and emergency systems to determine the needs in a pandemic challenge	ERS
	To ensure the identification of persons in the health care system responsible for the response to the pandemic and the circuits required to implement this response in a pandemic challenge.	ERS
	To prepare protocols, mathematical models and manuals to manage cases, control the infection, divert patients, organize the health care staff etc.	ERS
	To ensure access to biosafety laboratories.	AC. NMC
	To increase the knowledge and preparation of health care workers for an influenza pandemic challenge.	AC
Communications	To review existing infrastructure and communication systems.	Communications subcommittee
	To set up a web page with relevant information about influenza.	PHD
	To inform the media about national plans and preparatory actions relative to seasonal and pandemic influenza.	VSC
	To set up formal communication channels with the WHO and other institutions to exchange information about influenza.	PHD

6.2. **Interpandemic period. Phase 2.**

In phase 2, novel virus subtypes of the influenza virus have not been detected in persons. However, a subtype of the influenza virus circulating in animals represents a considerable risk for humans of contracting the disease.

During this phase, actions are centred around reducing the risk of transmission to humans to a minimum, the rapid detection and notification of cases of a novel strain in humans and strengthening the coordination with leaders in animal health, to reduce the risk of infection in humans.

Objectives:

- Activate coordination with the national authorities on animal health.
- Revise the development of preparedness and response plans to detect insufficiencies.
- Activate and strengthen surveillance of animal and human influenza to be able to identify the novel virus subtype if it appears in Spain.
- Maintain coordination with surveillance systems and international organizations.
- Improve national, intersectorial, and intergovernmental coordination to reduce the risk of infection in humans with the new influenza virus.
- Develop strategies and processes to coordinate the rapid mobilization of resources during the warning phases and for rapid policy decision making.

Phase 2

	Actions	Actions to be taken by who
Planning and coordination	To inform persons responsible for the response about the possible appearance of a new pandemic	PHD, NIPPC
	Revise the National Preparedness and Response Plan	NIPPC
	Revise and update the Autonomous Preparedness and Response Plans	NIPPC, PHB
	To maintain regular contact with the key persons to be mobilized on appearance of a novel strain.	NIPPC
	To prepare national manuals for public health care interventions.	TCG
	To inform persons responsible for the response about the possibility of a new pandemic appearing	PHD, NIPPC
	To revise the National Preparedness and Response Plan	NIPPC
	To revise and update Autonomous Community Preparedness Response Plans	NIPPC and PHB
Antivirals and vaccines	To maintain contact with vaccine and antiviral producers	PHD
	To revise antiviral use strategies	PHD
	To strengthen strategies to increase vaccine protection against seasonal influenza	PHD- AC
	To revise action strategies for workers in bird breeding farms.	PHD+ MAAF
Surveillance	To strengthen surveillance to detect the emergence of new variants and novel influenza virus strains both in humans and in animals.	NEC- -NMC- AC- MAAF
	To detect outbreaks of severe acute respiratory disease.	NEC-AC
	To annually describe patterns of morbidity, mortality and incidence of influenza disease.	NEC
	To maintain the early warning system active.	NEC
	To continue to participate in the European Influenza Surveillance Scheme (EISS)	NEC

Phase 2		
	Actions	**Actions to be taken by who**
	To strengthen virological surveillance in each Autonomous Community so that each one has at least one laboratory than can isolate the influenza virus, identifying type and H1 and H3 subtype.	AC
	Urgently inform the WHO and the IEO of any suspicious isolation of infection in animals.	NMC
	To increase surveillance in workers exposed to possible high risk situations.	MAAF
	To perform serological studies in workers of bird breeding farms affected by animal influenza outbreaks.	MAAF and PHD
	To develop a protocol for action in cases of suspected infection by a new influenza virus.	
Response to Appearance	To assess the capacity of health and emergency programmes to detect and control outbreaks of the disease in hospitals.	ERS
	To warn health care professionals so that in the case of severe respiratory infection they can implement the action protocol for suspected influenza by a novel virus.	ERS
	To update and test the protocols, mathematical models and manuals for the management of cases and infection control.	ERS
Communications	To regularly test the operation of the existing communication systems.	VSC
	To maintain the web page on influenza updated.	PHD
	To keep the communication media informed of actions taken associated with pandemic or seasonal influenza.	VSC

6.3. Pandemic alert period. Phase 3

In this phase, infection has been detected in humans with a novel influenza virus subtype, but without person-to-person transmission, or at the most rare cases of transmission to a close contact.

The actions are based on a rapid characterization of the novel virus subtype and early detection and notification of additional cases. Probably, the first cases occurred outside Spain and the presence of cases was low and mainly associated to persons who had travelled to affected areas.

Only one case in Spain required a complete investigation and the adoption of strict control measures for him and his contacts.

When detection of outbreaks increases outside Spain, the control measures must be tightened.

Objectives:

- To ensure the existence of mechanisms to recognise and control the risks of transmission to humans in our country.
- To coordinate the implementation of processes that contain or delay transmission of infection to the population from a small focus.
- To rapidly detect the first cases in Spain and to take measures to control and contain them.

- To guarantee that epidemiological surveillance can detect, study and adequately control the outbreaks and to study the risk of diffusion.
- To assess the use of antivirals in these and subsequent phases.
- To prevent nosocomial infection and infections in laboratories.
- To keep health care professionals adequately informed
- To maintain a close contact between persons responsible for Autonomous Community plans, and other sectors and government departments, as well as with international organizations such as the WHO and the EU.

Phase 3

	Actions	Actions to be taken by
Planning and coordination	To activate the National Preparedness and Response Plan	NIPPC
	To activate the National Planning Committee and all the Groups that depend on it.	NIPPC
	To increase coordination with autonomous leaders, the WHO and the EU to standardize the measures to be taken in a pandemic alert.	PHD-PHB y TCG
	To develop models and apply the results to improve pandemic plans.	PHD and TCG
	To study current legislation about applying public health measures.	MH- Legal Dept.
Antivirals and vaccines	To revise the use, supply and storage of antivirals for use when required.	PHD-SDA
	To establish supply agreements with antiviral producing laboratories	PHD-PHB
	To revise the definition of priority groups and administration strategies for antivirals and vaccines in the case of limited supply. To assess the requirements for their adequate administration.	VAS + TCG
	To study ways to obtain and to store vaccines against new strains available on the market.	PHD- SDA
	To determine and study initiatives of the European Commission to obtain pandemic vaccines and antivirals.	PHD-SDA
	To develop Manuals for Use of the Antivirals.	CGA
	To develop a programme to control and monitor adverse effects of antivirals.	SDA
	To develop a programme to control and monitor vaccine safety	SDA
	Protocol for the local preparation of antivirals for their immediate use	SDA

Phase 3		
	Actions	**Actions to be taken by**
Surveillance	To ensure that surveillance activities can detect the first imported cases of influenza by a novel virus subtype, strengthening surveillance in persons coming from high risk regions.	AC- SC
	To ensure that there is an action protocol at all levels with case definition and manuals and mathematical models for the management of samples and the notification circuit.	PHD- SC-
	Study of contacts in the first imported cases.	AC-TCG
	To ensure that notification channels with international organisations are defined and coordinated.	AC-NEC-TCG
	To prepare a Protocol to study outbreaks of severe acute respiratory disease in travellers	TCG- AC
	To develop surveillance programmes for antiviral resistant strains	SC
	To strengthen the capacity for diagnosis and coordination with WHO regional laboratories.	NMC-HICIII SC
	To ensure that national influenza reference libraries have the resources to diagnose a novel subtype of virus.	AC- NMC
	To enhance the coordination of actions of human and animal surveillance.	NEC-MAPA
	To design a study to assess the efficacy of the vaccine during the pandemic	SC
Response to the Emergency	To activate the Autonomous Community Plans for Preparedness and Response and reinforce coordination of emergency services and representatives of public and private institutions who play a role in implementing these plans.	AC; ERS
	To verify that the mechanisms to amplify the current capacity for hospital beds and isolation rooms are prepared in each area and region.	AC ERS
	To ensure that all the health centres have suitable infection control protocols, individual protection measures and adequate management of cases and controls.	AC ERS
	To maintain the health care professionals continually informed about the situation and the activities in which they are involved.	AC-SC
	To ensure that the protocols for antiviral use and provision of materials are available at all levels.	AC- ERS
	To develop strategies for the urgent distribution and administration of vaccines and antivirals.	AC ERS
	To ensure that the supply of sanitary materials and equipment is available at all levels.	AC ERS
Response of Overseas Health System to the Emergency	Continuous information to International Vaccination Centres	PHD(Overseas Health)
	Action protocol in airports to control travellers coming from high risk areas.	PHD- Overseas Health
	Information and recommendations to travellers in high risk areas (individual cards, posters, health advice etc.)	PHD- Overseas Health
	Preparation of questionnaires to compile information from people coming from high risk areas.	PHD- Overseas Health

Phase 3		
	Actions	**Actions to be taken by**
	Recommendations to manage possible international entry	PHD- Overseas Health
	Guidelines to protect persons exposed in airports and ports.	PHD- Overseas Health
	Health recommendations for adoptions from international high risk areas.	PHD- Overseas Health
	Recommendations for Spanish embassies and consulates to send to Spanish citizens living in affected regions.	PHD- Overseas Health
	Prohibition of imports following the EU guidelines. Actions in the PIF.	PHD- Overseas Health, MAAF
Comunicaciones	To revise and update the information sent to the media, the general public, health care workers and politicians.	SC
	Constant revision and updating of the Web page.	

6.4. Pandemic alert period. Phase 4

In this phase small clusters of cases are identified with limited person-to-person transmission. Transmission is very localized suggesting that the virus is not well adapted to humans.

Actions are aimed at containing transmission of the new virus within localized foci or delaying its spread to gain time to apply the response measures.

Objectives:

- To ensure that the surveillance system is capable of detecting and characterizing outbreaks and to assess the risk of transmission,
- To coordinate the implementation of measures that delay spread of the infection in the population,
- To limit the morbimortality associated with cases in humans,
- To prevent nosocomial transmission, and
- To prepare the population for the possible arrival of a pandemic

Phase 4		
	Actions	**Actions to be taken by**
Planning and coordination	Activate the National Preparedness and Response Plan	NIPPC
	Assess the current state of preparation and to take measures to amend the weaknesses detected.	NIPPC –PHB
	Strengthen coordination with the health authorities of neighbouring countries to coordinate the emergency response	PHD- and TCG
	Ensure that autonomous plans are coordinated and ready for implementation	PHB
Antivirals and vac-	Revise the use, provision and storage of antivirals for use when required	PHD-SD

Phase 4		
	Actions	**Actions to be taken by**
cines	Assess the needs for antivirals for the following phases.	CS and TCG
	Participate in and study the initiatives of the European Commission to acquire pandemic vaccines and antivirals.	PHD-SDA
Surveillance	Ensure that surveillance can enable all existing cases and outbreaks to be identified.	AC- CS
	Ensure that an action protocol is available at all levels with a case definition, manuals and mathematical models of management of samples and the notification channels.	PHD- CS-
	Identification and monitoring of the contacts of all cases.	AC-TCG
	To ensure that notification channels with international organizations are defined and coordinated.	AC-NEC-TCG
	To revise and adjust the definition of cases and their management.	TCG- CS and CGA
	Assess the impact of measures to contain infection to readjust the recommendations and share the results with international organizations.	TCG
	Reinforce the diagnostic capacity and coordination with regional and WHO laboratories.	NMC-HICIII CS
Response to the emergency	Activate Autonomous Plans for Preparedness and Response and strengthen coordination of emergency services and representatives of public and private institutions which play a role in the implementation of these plans.	AC SER
	To maintain the health care professionals well informed about the situation and activities in which they are involved	AC-VSC
	To verify that the supply of health materials and equipment is available at all levels	AC SER
	To apply and revise action protocols developed by Overseas Health	PHD (Overseas)
Communications	To inform the authorities involved in the National Plan of the new situation and future implications.	VSC
	To update the information sent to the media, general public, health care workers and politicians.	VSC
	To constantly revise and update the Web.	PHD

6.5. Pandemic alert period. Phase 5

More clusters of cases are detected in this phase, although person-to-person transmission is still localized, suggesting that the virus is becoming increasingly adapted to humans but has still not become completely transmissible (very high risk of pandemic).

Actions are aimed at maximising efforts to contain or delay the spread, to detain the pandemic and gain time to apply response measures in a pandemic alert. During this phase the risk of a pandemic is imminent owing to the existence of maintained person-to-person transmission in some parts of the world. There is a high risk of cases appearing in Spain.

Objectives:

- To coordinate the implementation of all measures to contain or delay spread of the pandemic on national territory.
- To verify that plans for response to a pandemic can satisfy the populations predicted demand for health care.
- To prevent nosocomial transmission and maintain biosafety.
- To check available reserves of antivirals.
- To revise Agreement to Acquire Antivirals.
- To intensify common international and national actions to be taken and to share the most relevant information with all the sectors involved in the response plans.

Phase 5		
	Actions	**Actions to be taken by**
Planning and coordination	Maintain active all groups dependent on the NIPPC	NIPPC
	Announce the situation of an imminent pandemic	NIPPC
	Inform persons responsible for the AC Plans and all organizations involved in the response of the imminent pandemic.	NIPPC/PHB
	Revise and update the actions and operation of the pandemic plan	NIPPC
	Heighten international and national coordination about the actions to be taken	TCG
	Negotiate with vaccine producers the supply agreements already established	NIPPC
	Revision and implementation of the legal mechanisms to implement the control measures	NIPPC
Antivirals and vaccines	Revise the use strategies for antivirals and vaccines	VAS
	Plan implementation of the programme to control and monitor adverse effects of antivirals	VAS. SDA. AC
	Revise the Guidelines for use of antivirals	VAS
	Plan the implementation of the programme to control and monitor vaccine safety	VAS. SDA. AC
	Revise antiviral requirements	VAS. PHB
Surveillance	Strengthen the surveillance activities to detect imported cases of influenza by the novel virus subtype, increasing surveillance in persons coming from high risk areas and ensuring follow up of cases.	AC- NEC- CS.
	Implementation of surveillance programmes for strains resistant to antivirals.	NMC-AC
	Heightening the diagnostic capacity and coordination between regional and WHO laboratories.	NEC-HICIII
	Revising and updating case definition.	CS
	Revising and updating patient and contact management programmes.	TCG and Clinical Group

Phase 5		
	Actions	**Actions to be taken by**
	Ensure that the laboratories have sufficient resources to detect and identify the new virus strain.	NMC-AC
Response to the emergency	Complete activation of autonomous response plans	SER .PHB
	Ensure that all those involved in implementing the Plan know its contents and the situation of imminent pandemic.	AC-VSC
	Implement the response Plan in all health care centres.	AC
	Ensure that the distribution chain for antivirals and vaccines is prepared at all points.	AC. NIPPC.
	Implement procedures used to manage corpses.	AC
	Assess the impact of measures to contain the infection to adjust the recommendations and share the results with international organizations.	TCG
	Activate and revise all protocols related with merchandise and travellers coming from affected countries.	PHD (Overseas Health)
	Revise the recommendations for Spanish embassies and consulates aimed at Spanish citizens who live in affected areas.	PHD (Overseas Health)
Communications	Increase access to updated information via the Ministry's Web page and other communication channels.	VSC
	To have regular meetings with the communication media to disseminate up-to-date information.	VSC
	Ensure adequate communication of information to health care professionals and other workers involved.	VSC

6.6. Pandemic period. Phase 6

This phase is characterized by the existence of a high and sustained transmission in the general population.

This phase is divided into:

Phase 6.1: Pandemic period announced by the WHO, although Spain is not yet affected.

Phase 6.2: Announcement of the pandemic in Spain

Phase 6.3: End of the first wave in Spain and preparation for the second and subsequent waves

Phase 6.4: Announcement of the end of the pandemic, the start of the postpandemic period

Each subphase is characterized by:

Phase 6.1: Although Spain is not affected the arrival of the pandemic over the next few weeks is imminent.

Phase 6.2: The virus is circulating in Spain and will reach its maximum peak of activity in a few weeks.

The country must cope with the increased pressure on the health care and other services.

Phase 6.3: The number of cases and the demand for health care will diminish but the system must be prepared for the arrival of a new wave of a similar or greater magnitude than the previous one.

Phase 6.4: Return to the seasonal cycle is started with the new circulating virus.

Objectives:

Phase 6.1: The diagnostic capacity and surveillance are enhanced to detect cases in Spain.

Vaccine Supply Agreements are revised with the companies involved.

Antiviral reserves are replenished.

Communication strategies are reinforced.

Phase 6.2: The function of the health care services and other essential services is maintained.

To revise, with updated information, vaccination strategies and plans for vaccine and antiviral distribution and administration.

To adapt the surveillance system to provide useful data to assess the measures implemented.

Surveillance and control of cases.

To give adequate and timely information to all levels.

Phase 6.3: To revise all aspects of the response based on the experience from the first wave.

To continue with surveillance and preparation for the next wave.

Early detection of arrival of the second wave.

Phase 6.4: Analysis and evaluation of the measures taken and revision of the plans.

Phase 6.1	
Actions	Intensify the actions proposed in phase 5.

Phase 6.2		
	Actions	**Actions to be taken by**
Planning and coordination	Announce the situation of a pandemic in Spain	NIPPC
	Activation of all groups dependent on the NIPPC	NIPPC
	Inform persons responsible for the AC Plans of the pandemic situation in Spain and all the organizations involved in the response. To implement the Autonomous Community Plans.	NIPPC/ PHB
	Increase international and national coordination about actions to be taken	TCG
	Negotiate with vaccine producers vaccine supply agreements	NIPPC- PHD
Antivirals and Vaccines	Define and distribute on all levels the vaccination strategies and priority groups.	VAS. SER
	Monitor the adverse effects of antivirals and resistance to them.	VAS. SDA. AC
	Continually update use indications for antivirals and management of cases.	CGA
	Evaluate vaccine protection and monitor vaccine safety	VAS. SDA. AC

Phase 6.2

	Actions	Actions to be taken by
Surveillance	Adapt the surveillance system to provide useful information to help evaluate the measures implemented and the evolution of the pandemic.	AC. NEC. CS.
	Maintain the surveillance programme for strains resistant to antivirals	NMC-AC
	Ensure the laboratories have sufficient resources to detect and identify the pandemic strain.	NMC-AC
	Coordinate with the European surveillance scheme.	CS-NEC-NMC
Response to the emergency	Maintain in operation the health services and other essential services.	NIPPC. AC
	Implement plans for distribution and storage of antiviral medications.	AC
	Ensure that all the persons involved in implementing the Plan know the pandemic evolution	AC-VSC
	Implement the plan for the urgent administration of a vaccine when this is available.	AC
	Ensure that all the material required for the pandemic response will be available and distributed during the pandemic.	AC
Communications	Strengthen updated information on the Ministry's Web page and other communication channels.	VSC
	Regular meetings with the media and the general public to update information.	VSC

Phase 6.3

	Actions	Actions to be taken by
Planning and Coordination	Monitor the implementation of the National Plan for preparedness and Response for all dependent groups of the NIPPC	NIPPC
	Inform those responsible for the AC Plans about the pandemic evolution in Spain and all institutions involved in the response.	NIPPC; PHB
	Permanent coordination and follow up of international and autonomous community evolution about common actions to take.	TCG
	Negotiate with vaccine producers about vaccine delivery	NIPPC- PHD
Antivirals and vaccines	To ensure and assess follow up of vaccination and revision strategies of priority groups.	VAS. ERS
	Continuous updating of indications for use of antivirals and case management	CGA
	Assessment and follow up of vaccine safety	SDA. AC-TCG

Phase 6.3

	Actions	Actions to be taken by
Surveillance	Assess and reorganize the surveillance system and the network of laboratories based on experience acquired	AC. CS.
	Maintain surveillance programmes for strains resistant to antivirals	NMC-CS
	Coordination with the European surveillance scheme	CS-NEC-NMC
Response to Emergency	Maintain in operation the health services and other essential services	NIPPC. AC
	Maintain the plans for distribution and administration of antivirals	AC
	Ensure that all those involved in implementation of the Plan know the evolution of the pandemic.	AC-VSC
	Implement the plan for urgent administration of the vaccine when this is available.	AC
	Assess the need for additional resources and to ensure their distribution at all levels.	AC
	Identify the most effective control and surveillance measures to apply in the different waves.	NIPPC-TCG
	Update manuals, protocols and mathematical models.	CS; TCG; CGA
Communications	Assess the response to communication in previous phases and to reorganize this on the basis of experience acquired.	VSC
	Presentation of the impact of the measures adopted to the media and inform about possible new pandemic waves.	VSC

Phase 6.4

Actions	The NIPPC announces the end of the pandemic During this phase the global impact of the pandemic will be assessed and the actions taken will be evaluated. Reports will be prepared and conclusions will be drawn that will be used to revise the actions to be taken to prepare for subsequent influenza pandemic threats.

7. ABBREVIATIONS

ABBREVIATIONS	
SDA	Spanish Drug Agency
AC	Autonomous Communities
NIPPC	National Influenza Pandemic Planning Committee
AHRC	Animal Health Research Centre
NEC	National Epidemiology Centre (HICIII)
NMC	National Microbiology Centre (HICIII)
PHB	Public Health Board
PHD	Public Health Department (MH)
CGA	Clinical Group Advisor
NTF	National Task Force
TCG	Technical Coordination Group
HICIII	Health Institute Carlos III (MSC)
MAFF	Ministry of Agriculture, Fisheries and Food
MES	Ministry of Education and Science
MH	Ministry of Health
IEO	Internacional Epizooite Organization
WHO	World Health Organization
CO	MH Communication Office
VSC	Vaccine Subcommittee
GSPHE	General Subdepartment for Promotion of Health and Epidemiology
GSOH	General Subdepartment for Overseas Health
ERS	Emergency Response Subcommittee
CS	Communications Subcommittee
VAS	Vaccines and Antiviral Subcommittee
EU	European Union