

# **NATIONAL INFLUENZA PANDEMIC PLAN**



**CENTER FOR DISEASE CONTROL &  
PREVENTION (H.C.D.C.P.)**

**MINISTRY FOR HEALTH  
AND SOCIAL SOLIDARITY**

**October 2005  
2ND EDITION**

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## 1. INTRODUCTION

Type A influenza viruses are the cause of regular epidemics or pandemics leading to high morbidity and mortality rates.

An influenza pandemic may occur at any time and have severe impact on public health as well as the social and economic sectors.

Experts on influenza concur that future influenza pandemics are inevitable; nonetheless, there is no way of predicting when the next influenza pandemic may strike. According to historical data, pandemics occur three to four times per century.

The last recorded influenza pandemic took place in 1968, while in 1998 the World Health Organization issued a global influenza pandemic warning due to a human epidemic in Southeast Asia caused by the highly pathogenic avian influenza strain H5N1.

Since December 2003, a severe and geographically widespread avian influenza epidemic has been taking its toll in birds in Asia. Epidemiologic data from the aforementioned area show that:

a) individuals who became sick are in their vast majority professionally exposed to sick poultry, but there is a small number of people who have fallen ill that did not come into direct contact with poultry,

b) the avian virus has transcended the species barrier, and

c) the avian influenza virus has been detected in samples from wild fowl that showed no sign of the disease (silent carriers). Based on all this and as long as people are still falling ill, there is a significant chance of re-assortment of the genetic material of the human and the avian influenza viruses, leading to a completely new strain which could cause a new influenza pandemic..

According to data from the last two recorded pandemics, it would take about two to three months for a new pandemic virus to spread from its country of origin to another country, and six months to spread worldwide. Taking current conditions into consideration, i.e. the facilitated and rapid travel from one country to another, a new pandemic influenza strain may actually need much less time than that. At the same time, based on the same data from previous pandemics, in countries where the influenza season spans from October till April, such as Greece, the arrival of the pandemic strain within this very timeframe may rapidly lead to multiple epidemics.

Moreover, an influenza pandemic usually strikes in two or more waves, either during the same year or in successive influenza seasons. The second pandemic wave may appear within three to nine months after the first one, and be severe enough to bring about even more morbidity and mortality. Each pandemic wave may last six to eight weeks.

In summary, on one hand, the time between the beginning of the pandemic and the emergence of the pandemic strain in our country may be rather short; on the other hand, the pandemic itself may last a considerable amount of time.

It is, thus, imperative to plan ahead the measures that will need to be taken in order to minimize the impact of the next influenza pandemic in Greece.

## **2. INFLUENZA EPIDEMIOLOGY**

Influenza poses one of the greatest health problems to developed countries.

It is one of the main causes of mortality, claiming more than 1,000 lives per million, especially in the >65 age group, while increasing the number of hospital admissions and work absenteeism. Influenza was first described by Hippocrates in 412 BC, while the first pandemic resembling influenza was recorded in 1580 AD. Since then 31 influenza pandemics have been recorded, three of which occurred during the 20<sup>th</sup> century – in 1918, 1957, and 1968. Even nowadays, seasonal influenza affects large numbers of people on a yearly basis.

### **2.1. Influenza virus characteristics**

There are 3 different antigenic types of the influenza virus: A, B, and C. Besides humans, who are the natural reservoir for the relevant subtypes affecting them, several animal species, such as wild fowl, pigs, ducks, chickens, turkeys, horses, whales, and seals, are the natural reservoir for type A influenza viruses. Wild birds usually do not become ill, contrary to domestic poultry, such as chickens, ducks, and turkeys, which may suffer from severe disease if infected. Moreover, pigs can get infected with influenza virus and may present symptoms similar to humans, such as cough, fever, and runny nose. The disease is rarely transmitted from animal to human. Type B influenza viruses do not affect animals.

Type A and B viruses cause epidemics every winter, while type C is of little epidemiologic importance since it causes mild or asymptomatic disease. The surface proteins of type A influenza viruses are subject to slight but constant antigenic changes, called "antigenic drift", which is the reason why influenza viruses are different from season to season. Type B viruses do not have subtypes nor are they subject to antigenic drift.

Type A viruses are distinguished in subtypes according to two proteins found on their surface: haemagglutinin (H) and neuraminidase (N). A total of 16 different haemagglutinin subtypes have been identified (H1-H16) as well as 9 different neuraminidase subtypes (N1-N9). Among these subtypes, only H1, H2, and H3 from the haemagglutinin group and N1 and N2 from the neuraminidase group have been known to affect humans. In addition, humans have been recently affected, albeit in a limited way, by subtypes H5, H7, and H9 – typically affecting fowl – without any cases of human-to-human transmission (except, maybe, for exceptionally rare circumstances). The rest of the subtypes have been identified in influenza viruses isolated from diseased water fowl, horses, pigs, and other animals.

The globally circulating strains of the influenza virus affecting humans for the last few years during influenza season are strain A(H1N1) and strain A(H3N2).

Influenza may occasionally affect world population through epidemics, called "pandemics", due to significant antigenic changes in type A viruses, called "antigenic shifts", that are not dependent on season. When such antigenic shifts occur, a new virus strain appears, against which there is no immunity in the human population. Consequently, large population groups may be affected, leading to a possible influenza pandemic.

### **2.2. Influenza Pandemics**

Prior to World War I, influenza was not considered a significant risk to public health. This point of view was altered due to the 1918-1920 so called "Spanish flu" pandemic caused by the A(H1N1) strain, which it has been lately found to have originated from fowl, costing the lives of more than 20,000,000 people. The 1957 (Asian influenza) and 1968 (Hong Kong influenza) pandemics were caused by the strains A(H2N2) and A(H3N2) respectively, originating from the genetic material reassortment of the avian influenza virus and the then circulating human influenza virus. In 1976, the older strain A(H1N1), widely spread until 1957, resurfaced causing severe disease in certain population groups (people born approximately after 1957). During the 1997-1998 period, a new type of virus – A(H5N1) – originating from fowl, caused an epidemic in Hong Kong, which fortunately did not evolve into an influenza pandemic.

### 2.3. Transmission

Influenza is an acute viral respiratory infection and it cannot be differentially diagnosed from other acute respiratory infections based on clinical manifestations. Laboratory tests are necessary to confirm the presence of influenza virus. The disease caused by influenza viruses is usually mild, transmitted from one person to another via droplets from respiratory secretions produced during sneezing or coughing. It may also be transmitted through immediate contact, i.e. hands or face, with an infected individual or with surfaces infected with the respiratory secretions of a patient.

### 2.4. Clinical Manifestations

Influenza symptoms include high fever, cough, sore throat, runny nose, headache, myalgia, and often malaise. Most patients recover fully within 1-2 weeks. In comparison to other respiratory infections, such as the common cold, influenza causes more severe complications, including bacterial pneumonia, especially in children, the elderly and other high risk groups.

### 2.5. Complications

Pneumonia is the most common complication of influenza and may be either viral, due to the influenza virus itself, (primary) or bacterial (secondary). Bacterial pneumonia is most commonly caused by *Streptococcus*, *Haemophilus* and *Staphylococcus*. Bacterial pneumonia usually affects people with underlying chronic pulmonary diseases, such as chronic bronchitis, asthma, and cystic fibrosis. Viral pneumonia is less common, but may progress rapidly and lead to acute respiratory failure and death.

Other complications of influenza infection include arrhythmias, myocarditis, pericarditis, encephalitis and transverse myelitis, Reye syndrome, especially reported in children under treatment with salicylates.

### 2.6. Laboratory diagnosis

Laboratory testing for the diagnosis of influenza includes viral culture, serological haemagglutinin inhibition tests, rapid antigen detection, polymerase chain reaction (PCR) or ELISA, and fluorescent immunoassay. The sensitivity and specificity of the aforementioned tests may vary depending on the laboratory performing them, the laboratory examination method used, as well as the type of clinical sample tested. Nasopharyngeal secretions are considered the most reliable material to isolate the virus or rapidly detect it.

Several rapid diagnostic tests, able to detect influenza viruses within 30 minutes are used in primary health care during the last few years. These rapid tests detect antigens or nucleic acid of the influenza virus, and vary according to the types of virus they are able to detect and their ability to distinguish between virus types.

Rapid tests currently available in the market can detect

- a) type A influenza virus only,
- b) type A and B influenza virus, without being able to distinguish between them, or
- c) type A or B influenza virus, with the ability to distinguish between them.

Clinical samples used vary according to the test method. Specificity and mostly sensitivity of those rapid tests vary and are lower than that of viral culture. Based on bibliography sensitivity of most of these tests is about 70%, while specificity reaches up to 90%.

Clinical samples for laboratory testing should be collected within four (4) days from the appearance of symptoms, while proper sampling procedure plays a significant role in test sensitivity.

Despite the availability of rapid tests, it is particularly important to collect clinical samples for cultures, considering this is the only way to identify the influenza virus subtype. This information is necessary in order to

- 1) compare the circulating strains with those contained in the available influenza vaccine,
- 2) issue directions concerning the vaccine composition for the following year, and

3) monitor the strain antiviral susceptibility and the possible emergence of a new strain, which may suggest a pandemic risk.

Two serum samples are needed for serology testing. One sample should be collected within 1 week since the first symptoms of the disease. Recent infection by an influenza virus can be diagnosed when the second serum sample (2-4 wks after the first one) shows fourfold increase of the specific antibody titre.

**Table 1.** Available diagnostic tests for influenza<sup>1</sup>

| Test method  | Influenza virus types detected | Clinical samples needed   | Time to results        |
|--|--------------------------------|---|------------------------|
| <b>Virus culture</b>                                       | A and B                        | NP swab <sup>2</sup> , pharyngeal swab, nasal wash, bronchial wash, nasal secretion, saliva | 5-10 days <sup>3</sup> |
| <b>Fluorescent immunoassay</b>                             | A and B                        | NP swab <sup>2</sup> , nasal wash, bronchial wash, nasal secretion, saliva                  | 2-4 hours              |
| <b>RT-PCR<sup>4</sup></b>                                  | A and B                        | NP swab <sup>2</sup> , pharyngeal swab, nasal wash, bronchial wash, nasal secretion, saliva | 1-2 days               |
| <b>Serological test</b>                                    | A and B                        | Two serum samples, one during acute phase and one during recovery phase <sup>5</sup>        | > 2 weeks              |
| <b>Enzyme immunoassay (EIA)</b>                            | A and B                        | NP swab <sup>2</sup> , pharyngeal swab, nasal wash, bronchial wash                          | 2 hours                |
| <b>Directigen Flu A<sup>6</sup> (Becton-Dickinson)</b>     | A                              | NP swab <sup>2</sup> , pharyngeal swab, nasal wash, nasal secretion                         | < 30 minutes           |
| <b>Directigen Flu A+B<sup>6,7</sup> (Becton-Dickinson)</b> | A and B                        | NP swab <sup>2</sup> , pharyngeal swab, nasal wash, nasal secretion                         | < 30 minutes           |
| <b>FLU OIA<sup>7</sup> (Thermo Electron)</b>               | A and B <sup>8</sup>           | NP swab <sup>2</sup> , pharyngeal swab, nasal secretion, saliva                             | < 30 minutes           |
| <b>FLU OIA A/B<sup>6,7</sup> (Thermo Electron)</b>         | A and B                        | NP swab <sup>2</sup> , pharyngeal swab, nasal secretion, saliva                             | < 30 minutes           |
| <b>XPECT Flu A &amp; B<sup>6,7</sup> (Remel)</b>           | A and B                        | NP swab <sup>2</sup> , pharyngeal swab, nasal secretion                                     | < 30 minutes           |
| <b>NOW Influenza A &amp; B<sup>6,7</sup> (Binax)</b>       | A and B                        | NP swab <sup>2</sup> , nasal secretion  | < 30 minutes           |
| <b>QuickVue Influenza Test (Quidel)</b>                    | A and B                        | NP swab <sup>2</sup> , nasal secretion, nasal wash  | < 30 minutes           |
| <b>QuickVue Influenza A+B Test (Quidel)</b>                | A and B                        | NP swab <sup>2</sup> , nasal secretion, nasal wash  | < 30 minutes           |
| <b>SAS Influenza A Test<sup>6,7</sup></b>                  | A                              | NP swab <sup>2</sup> , nasal secretion  | < 30 minutes           |
| <b>SAS Influenza B Test<sup>6,7</sup></b>                  | B                              | NP swab <sup>2</sup> , nasal secretion  | < 30 minutes           |
| <b>ZstatFlu<sup>7</sup> (ZymeTx)</b>                       | A and B                        | Pharyngeal swab   | < 30 minutes           |
| <b>Actim Influenza A&amp;B</b>                             | A and B                        | Nasal secretion, nasal wash, nasal swab   | < 30 minutes           |

<sup>1</sup> The list may include test kits not yet available in Greece, or may not include tests that are readily available in domestic market.

<sup>2</sup> NP = nasopharyngeal

<sup>3</sup> Rapid culture in vials, wherever available, may produce results in as soon as two days.

<sup>4</sup> RT-PCR = reverse transcriptase polymerase chain reaction

<sup>5</sup> If the antibody titre in the recovery phase sample (2-4 weeks since the first sample) is increased by four or more times in comparison to the acute phase sample (within first week of disease), this would indicate a recent infection.

<sup>6</sup> Rather complex test; special laboratory approval needed.

<sup>7</sup> Distinction between influenza virus types A and B.

<sup>8</sup> No distinction between influenza virus types A and B.

### **3. AVIAN INFLUENZA**

Avian influenza is a highly infectious disease among fowl, affecting all kinds of birds and caused by influenza type A viruses. The natural reservoir of the virus is wild fowl, where it typically causes a mild or asymptomatic infection. However, it can bring about severe disease and death in domestic poultry, especially chickens and turkeys. The virus is transmitted to vulnerable poultry after coming into contact with nasal, pulmonary secretions and feces of ailing or infected fowl. Transmission most commonly occurs through the fecal-oral route. Recent data show that domestic ducks may also get infected without showing any signs of disease; thus, they can play a crucial part in disseminating the virus under certain circumstances.

Subtypes H5 and H7 of the virus cause severe disease in domestic poultry, hence they are characterized as "highly pathogenic". Other subtypes may induce milder disease.

When humans are infected with these strains, Public Health Services monitor the situation closely due to the risk of widespread transmission to the human population.

#### **3.1. Transmission of Avian Influenza to Humans**

The avian influenza virus usually does not affect humans. Since 1997 though, there have been incidents of transmission of this virus to humans, even some epidemics. Contact with infected birds, their feces or inhalation of infected dust particles has been implicated, while typically there is none or very rare human-to-human transmission. (e.g. under certain circumstances of close contact in a health care setting)

Symptoms of the human infection with avian influenza are of a flu-like illness (fever, sore throat, myalgias) with conjunctivitis. Bacterial or viral pneumonia, acute respiratory failure, and other serious or even lethal complications may occur.

Public Health services monitor closely such cases due to the concern of human-to-human transmission and the possible connection with an influenza pandemic.

#### **3.2. Epidemics caused by the avian influenza virus**

Despite the fact that avian influenza does not usually affect humans, several epidemics caused by avian influenza among humans have been confirmed. In particular, the following epidemics have been recorded since 1997:

- In 1997, 18 people were infected and died due to subtype H5N1, in Hong Kong. A total of 1.5 million poultry were slaughtered.
- In 1999, two children were infected by subtype H9N2 in Hong Kong, while several cases of infection due to this subtype were reported in China.
- In 2002, one individual was found positive during a serological test for subtype H7N2 in Virginia.
- In 2003, more than 80 human cases of infection due to subtype H7N7 were recorded among people working in poultry farms and their families, including the death of a veterinarian, in the Netherlands.
- In 2003, two members of a family, one of which died, were infected during a trip from Hong Kong to China.
- In 2003, a child was infected, and subsequently recovered, with subtype H9N2 in Hong Kong.
- In 2003, one individual was infected, and recovered, with subtype H7N2 in New York.
- In 2004, several people working in a poultry factory in Canada, where a subtype H7N3 outbreak was reported, reported mild conjunctivitis.
- In 2004-2005, up until 12/10/2005, a total of 117 people, 60 of which died, were infected with subtype H5N1 in several Asian countries – 5 in Indonesia, 91 in Vietnam, 17 in Thailand, 4 in Cambodia.

### **3.3. Current Situation and Public Health Risks**

In comparison to historical data, the 2004 epidemics caused by the highly pathogenic H5N1 strain differ significantly with regards to the geographic spread and endemic areas of the virus, which seems to be steadily affecting certain areas in Asia.

Some characteristics of recent epidemics suggest that the complex ecology of the virus is undergoing changes which may, under certain circumstances, increase the risk for the appearance of a new (pandemic) strain. It is known that domestic ducks excrete this highly pathogenic form of the virus without showing any sign of disease. Consequently, they may silently transmit the virus to chickens and other kinds of poultry, and possibly even to humans.

The most recent data suggest the presence of the highly pathogenic strain A(H5N1) in dead migratory birds, which were until now considered to be asymptomatic carriers.

Despite the fact that during the second half of 2004 epidemics in birds in Southeast Asia seem to be reduced, the risk for human infection is intensified. The virus does not cause large epizooties in bird farms any more, so consequently poultry workers involved in farming or culling are not the only high risk group. Some cases of infection are reported among people who were not directly exposed to H5N1 virus through ailing or dead poultry. This suggests a risk for a larger part of the population of Southeast Asia, especially children and young adults residing in rural areas.

### **3.4. Avian Influenza in Greece**

According to data collected by the Directorate for Animal Health of the Ministry of Rural Development and Food, there are no recorded epizooties of avian influenza in our country.

#### **3.4.1. Measures for the control of avian influenza in poultry farms**

The Directorate for Animal Health of the Ministry of Rural Development and Food has prepared an action plan against any suspected or confirmed influenza epizooties in poultry farms.

This plan operates via Local Emergency Centers, in collaboration with the peripheral Veterinary Directorates and the peripheral Veterinary public health authorities.

According to this plan the necessary measures in the event of the reporting of a suspicious farm for influenza infection, are the following:

- Inventory of the poultry on the farm.
- The poultry should be quarantined within the farm area.
- No transportation of poultry to and from the farm area.
- No transportation of persons, vehicles, other animals, meat and carcasses, feedstuff, feces, litter, etc. except under specific license from the competent Veterinary Directorate.
- No exportation of eggs from the farm area unless they are meant for processing according to the relevant EU directive, and only after specific license from the competent Veterinary Directorate.
- Obligatory use of disinfectants at the points of entrance and exit of the farm buildings.
- Epizootic investigation.
- Measures may need to cover neighbouring farms due to their geographical position and contact with the suspect farm.

In the event that avian influenza is confirmed in a farm, the following additional measures are recommended:

- On-the-spot culling of all poultry on the farm and hygienic disposal of carcasses and eggs.
- Processing or disposal of feedstuff, straw litter and manure.
- Tracking and disposal of meat from poultry slaughtered during the incubation period of the disease.
- Tracking and disposal of hatching eggs laid during the incubation period of the disease.

- Testing of chicks hatched during the incubation period of the disease.
- Tracking and disposal of eggs from the particular farm from the consumer market laid during the incubation period of the disease, unless they were properly disinfected.
- Following the aforementioned measures, disinfection of buildings, surrounding areas, transport vehicles, tools, etc within the farm.
- No new poultry in the farm before 21 days after disinfection.
- Delimitation of a 3km protection zone, included within a 10km monitoring zone around the farm, and application in those areas of the measures as described in the relevant legislation, for at least 21 and 30 days respectively, after disinfection.
- Expansion of the aforementioned measures on other farms suspect for possible infections due to their position, etc. (adjoining affected farms etc).
- In case the poultry of another farm are suspect for having been infected due to the transportation of persons, animals, vehicles, etc., then that farm is also placed under official monitoring for infection, and the following measures are applied:
  - a.** obligatory inventory of the poultry, and
  - b.** no exportation of poultry from the farm during a 21-day period starting on the last day of possible infection, except by specific permit for transportation to immediate culling, following clinical examination.

## **4. PANDEMIC PHASES**

The phases of a pandemic are used internationally and render progressive planning and action possible during the various stages of pandemic development.

In 1999, the World Health Organization (WHO) announced pandemic phases for the first time, which were recently modified (March 2005) based on the knowledge acquired from the analysis of animal as well as human epidemics.

According to this newer version, there are four rather distinct periods, namely the interpandemic period, the pandemic alert period, the pandemic period, and the postpandemic period. Each period contains phases, differentiated through the possibility of animal-to-human and human-to-human transmission of a new influenza virus strain, leading to world-wide dissemination. There are 6 phases in total, starting from the first case of animal infection due to a new influenza virus strain, leading up to its continued transmission in the general population.

### **4.1. Interpandemic Period**

During this period, new, possibly pandemic, strains of type A influenza may emerge. The timely identification of such strains by the Influenza National Reference Centers on a national as well as global level is crucial. This period contains two phases:

#### **4.1.1. Phase 1**

No new influenza virus subtypes have been detected in humans. An influenza virus subtype may be present in animals, causing epizooties. The risk of human infection is considered low.

Phase 1 is further distinguished with regard to Greece based on the geographical distribution of the new subtype:

*Phase 1 outside Greece:* The subtype may circulate among animals in countries other than Greece.

*Phase 1 in Greece:* The subtype may circulate among animals within Greece.

#### **4.1.2. Phase 2**

No new influenza virus subtypes have been detected in humans. An influenza virus subtype may be present in animals, causing epizooties. The risk of human infection is considered substantial.

Phase 2 is further distinguished with regard to Greece based on the geographical distribution of the new subtype:

*Phase 2 outside Greece:* The subtype may circulate among animals in countries other than Greece.

*Phase 2 in Greece:* The subtype may circulate among animals within Greece.

### **4.2. Pandemic Alert Period**

During this period, human influenza cases caused by a new influenza virus subtype are reported. This period contains three phases:

#### **4.2.1. Phase 3**

Cases of human infection due to a new subtype are reported, but there is no human-to-human transmission, except in rare instances, after close contact.

Phase 3 is further distinguished with regard to our country based on the countries where human infection due to the new strain occurs:

*Phase 3 outside Greece:* Cases of human infection in countries other than Greece.

*Phase 3 in Greece:* Cases of human infection within Greece.

#### **4.2.2. Phase 4**

Small clusters with limited human-to-human transmission are reported, but spread is highly localized, suggesting that the virus is not well adapted to humans.

Phase 4 is further distinguished with regard to Greece based on the countries where human infection due to the new strain occurs:

*Phase 4 outside Greece:* Clusters in countries other than Greece.

*Phase 4 in Greece:* Clusters within Greece.

#### **4.2.3. Phase 5**

Larger clusters of human infection are reported, although human-to-human spread remains localized, suggesting that the virus is becoming increasingly better adapted to humans, but may not yet be fully transmissible.

Phase 5 is further distinguished with regard to Greece based on the countries where human infection due to the new strain occurs:

*Phase 5 outside Greece:* Clusters in countries other than Greece.

*Phase 5 in Greece:* Clusters within Greece.

### **4.3. Pandemic Period**

During this period, the pandemic has begun. This period contains one phase:

#### **4.3.1. Phase 6**

The transmission of the new subtype is increased and sustained throughout the general population.

Phase 6 is further distinguished with regard to Greece based on the countries where outbreaks of the pandemic strain occur, as well as a second wave of pandemic strain infections has appeared:

*Phase 6 outside Greece:* Epidemics due to the new subtype occur in countries other than Greece.

*Phase 6a in Greece:* Clusters due to the new subtype within Greece.

*Phase 6b in Greece:* Limited influenza epidemics due to the new subtype within Greece.

*Phase 6c in Greece:* Widespread influenza epidemics due to the new subtype within Greece.

*Phase 6d in Greece:* Cases of pandemic influenza receding within Greece.

*Phase 6e in Greece:* Second pandemic wave in Greece.

### **4.4. Postpandemic Period**

During this period:

- influenza activity is back to interpandemic levels, and
- the general population has developed immunity to the new strain that caused the pandemic.

This may occur within 2-3 years after the initial outbreak of the pandemic.

WHO announces the end of the pandemic.

**Table 2.** Summary of influenza pandemic phases

| <b>International Phases (WHO, 2005)</b> | <b>International Phase Description</b>  | <b>Greek Phases</b>  | <b>Greek Phase Description</b> |
|---|---|--|--------------------------------|
| <b><i>Interpandemic period</i></b>      |   |  |                                |
| 1                                       | No new subtypes detected in humans. Human infection caused by animal subtype. Low transmission risk.  | Phase 1 outside Greece   | Animals in other countries     |
|   |   | Phase 1 within Greece  | Animals in Greece              |
| 2                                       | No new subtypes detected in humans. Human infection caused by animal subtype. High transmission risk. | Phase 2 outside Greece   | Animals in other countries     |
|   |   | Phase 2 within Greece  | Animals in Greece              |
| <b><i>Pandemic alert period</i></b>     |   |  |                                |
| 3                                       | Human infection with new subtype. No h2h transmission, or rare after close contact.                   | Phase 3 outside Greece   | Cases in other countries       |
|   |   | Phase 3 within Greece  | Cases in Greece                |
| 4                                       | Small clusters with limited h2h transmission.   | Phase 4 outside Greece   | Clusters in other countries    |
|   |   | Phase 4 within Greece  | Clusters in Greece             |
| 5                                       | Larger clusters with limited h2h transmission.  | Phase 5 outside Greece   | Clusters in other countries    |
|   |   | Phase 5 within Greece  | Clusters in Greece             |
| <b><i>Pandemic period</i></b>           |   |  |                                |
| 6                                       | Increased and sustained transmission of new subtype to general population.                            | Phase 6 outside Greece   | Cases in other countries       |
|   |   | Phase 6a within Greece   | Clusters in Greece             |
|   |   | Phase 6b within Greece   | Limited epidemics in Greece    |
|   |   | Phase 6c within Greece   | Widespread epidemics in Greece |
|   |   | Phase 6d within Greece   | Epidemic recession in Greece   |
|   |   | Phase 6e within Greece   | Second wave in Greece          |
| <b><i>Postpandemic period</i></b>       |   |  |                                |
|   |   | <ul style="list-style-type: none"> <li>- Return to alert levels for seasonal influenza monitoring</li> <li>- Evaluation of influenza pandemic impact</li> <li>- Evaluation of planning gaps</li> </ul> |                                |

h2h: human-to-human

## **5. INFLUENZA SURVEILLANCE**

### **5.1. Surveillance Goals**

The goals of epidemiologic surveillance for influenza in Greece are the following:

- Monitoring of influenza activity trends in the entire geographic area of Greece, as well as in each district.
- Detection of seasonal outbreaks, in order to issue directions to the general population.
- Description of high-risk patient groups in order to prepare a vaccination policy or take other preventive measures.
- Identification of prevalent serotypes in order to produce vaccines whose composition meets the demands of the following influenza season.
- Timely identification of a possible new subtype with pandemic potential, as well as the distribution of new influenza strains.

### **5.2. Global Influenza Surveillance**

WHO set up in 1948 an international influenza monitoring and alert network. At the moment, the network consists of 110 Influenza National Reference Centers in 83 countries and 4 WHO Collaborating Reference and Research Centers (in Melbourne (Australia), Tokyo (Japan), London (United Kingdom), and Atlanta (United States)). Every year, these Centers isolate and identify influenza viruses from both humans and animals in order to promptly detect any new viral strains.

The goal of this network is to collect epidemiologic data on worldwide influenza activity and information on the viral strains isolated around the globe.

The network updates and alerts all countries about new influenza strains that may cause a pandemic. The network's microbiology laboratories play a significant role in the epidemiologic intervention for epidemics and in the laboratory confirmation of influenza cases.

Moreover, it analyses the strains isolated in each country every February in the North Hemisphere, and every September in the South Hemisphere. It then submits the recommendation concerning the composition of the influenza vaccine for the following year.

Greece participates in this network through two National Influenza Reference Centers – the Pasteur Institute, Athens (covering southern Greece), and the 2<sup>nd</sup> Microbiology Laboratory of the Medical School in the Aristotelian University of Thessalonica (covering northern Greece).

### **5.3. Influenza Surveillance in Greece**

#### **5.3.1. Influenza surveillance systems**

- **Sentinel Surveillance System – Private Physician Network**

The Sentinel Surveillance System has been responsible for influenza surveillance in Greece since December 1999. At the moment, 180 private physicians (internists, general practitioners and paediatricians) participate in this network voluntarily. These physicians report on a weekly basis the number of cases of influenza-like illness (ILI), according to the agreed clinical definition of the term adopted at a European level. Restructuring and improvement of this system started in June 2004, consisting in a gradual increase of the number of reporting physicians and the creation of a specific reporting form for ILI, accompanied by the total number of patient visits, which is used as the denominator. The ILI form includes also demographic data, such as sex and age of the patients. The data collected are recorded into an electronic database, analyzed and reported on a weekly basis on the website of the Hellenic Center for Disease Control & Prevention ([www.keel.org.gr](http://www.keel.org.gr)).

- **Sentinel Surveillance System – Institute for Social Security Physician Network**

In order to improve influenza surveillance in Greece, the Department for Epidemiological Surveillance and Intervention of the Hellenic Center for Disease Control & Prevention, in collaboration with the Directorate of Medical Services of the Institute for Social Security, set up an additional sentinel surveillance network for influenza in February 2003. This sentinel network

includes 30 physicians (internists and paediatricians) in 24 out-patient clinics of the Institute for Social Security in northern and southern Greece.

A specific form is filled on a weekly basis collecting information on the total daily visits to the internists and paediatricians for all causes, and the total number of patients diagnosed with influenza-like illness according to the aforementioned European definition. Information on each patient diagnosed with ILI, such as their name, age, sex, and vaccination status, are also recorded. These forms are faxed every Monday to the Department for Epidemiological Surveillance and Intervention of the HCDCP. The data collected are going to be cumulatively analyzed with the above data from private physicians and presented at the HCDCP website on a weekly basis.

- **Sentinel Surveillance System – Health Center Physician Network**

In July 2004, a third surveillance network was set up through physicians working in Health Centers in Northern and Southern Greece in collaboration with the Laboratory for Hygiene in the Medical School of the Aristotelian University of Thessalonica. This system includes 72 Health Centers and a total of 78 physicians (general practitioners and paediatricians). The collected data are analyzed on a weekly basis aiming at monitoring influenza-like illness in rural areas.

- **Notifiable Disease Reporting System**

Influenza is a disease subject to mandatory report only when recording a laboratory-confirmed case or reporting a connection to a laboratory-confirmed case.

- **Laboratory Reporting System – serological surveillance**

Fifteen hospital laboratories participate in this system; their laboratories send a form on a weekly basis reporting the detection of antibodies against influenza virus.

- **Laboratory Surveillance through the National Influenza Reference Centers**

As mentioned above there are two National Influenza Reference Laboratories in Greece, namely the Pasteur Institute Athens (covering southern Greece), and the 2<sup>nd</sup> Microbiology Department in the Medical School of the Aristotelian University of Thessalonica (covering northern Greece). Both of these laboratories perform viral cultures and PCR testing on clinical samples; the results are forwarded to the HCDCP on a weekly basis.

- **Expansion of laboratory influenza surveillance**

Starting with this year's influenza season, laboratory surveillance will be expanded to other specialized collaborating laboratories. This expansion will cover laboratories performing rapid influenza virus detection tests aiming at increasing the number of tested clinical samples and the prompt detection of circulating influenza strains.

### **5.3.2. Avian influenza surveillance in poultry**

The surveillance of avian influenza is conducted by the Ministry of Rural Development and Food.

Avian influenza is a disease subject to mandatory reporting, conforming to a relevant EU directive. The disease must be reported as suspected or confirmed case. The report is filed in the peripheral Veterinary public health authorities, which immediately inform the Directorate for Animal Health of the Ministry of Rural Development.

Clinical and blood samples are also systematically collected from poultry on farms, as well as from imported poultry by the Department for Avian Diseases of the Directorate for Animal Health.

The aforementioned tests aim at isolating and identifying the viral strains that may be circulating among poultry, and detecting any antibodies against the influenza virus.

The detection and identification of avian influenza viruses is performed at the National Avian Influenza Reference Centre (Microbiology Laboratory of the Veterinary School, in the Aristotelian University of Thessalonica).

## **6. VACCINES**

Vaccination against influenza virus is the most effective way to reduce mortality and morbidity caused by the disease, especially in high-risk groups, by avoiding complications.

### **6.1. Vaccine Production during the Interpandemic Period**

The seasonal influenza vaccine is trivalent, covering the type A influenza strains that have been circulating in the last few years (currently A(H1N1), A(H3N2), as well as type B).

The yearly influenza vaccine production for the northern hemisphere begins in February, when WHO submits its recommendations concerning the suggested composition of the new vaccine, based on scientific predictions for the strains that will be circulating during the following influenza season.

In order to produce an influenza vaccine early on, viral strains that can be grown in embryonated chicken eggs are chosen. These strains are inoculated and grown in chicken eggs and the allantoic fluid is collected. The viruses are extracted, deactivated and processed in order to produce vaccines that will contain either whole virus particles or parts of the virus. A period of approximately 6 months is needed for the development and production of the seasonal influenza vaccine.

In case one of the viral strains changes, clinical studies are first conducted over a limited number of healthy young adults, as well as elderly persons, in order to evaluate the safety and effectiveness of the vaccine. After the collection of this data the producer can apply for a marketing license.

Greece does not have a vaccine production facility. Every year, Greece procures influenza vaccines from international pharmaceutical industries in order to cover internal demand.

### **6.2. Vaccine Production during the Pandemic Period**

The production of a new vaccine against a pandemic strain of the influenza virus may begin only after the pandemic strain is isolated, considering that it is impossible to predict which virus will induce a pandemic. Taking into account the vaccine production procedure mentioned in paragraph 6.1, a period of 5-6 months is needed for the first doses of a new monovalent vaccine to become available. Consequently, it is rather improbable to have a special vaccine against any pandemic strain ready beforehand during the initial stages of a pandemic.

On the other hand clinical experience until now suggests that one dose of the pandemic vaccine is inadequate to produce sufficient immunity against a pandemic influenza strain. It would probably require two doses of the new vaccine to produce an adequate immune response. Consequently, it should be taken into account that the time needed for the development of proper immunity is longer than usual. There are also indications that vaccines containing only parts of a new virus may not be as effective as those containing the whole virus. Finally, it should be noted that vaccination against influenza is never 100% effective as regards disease prevention.

### **6.3. Pandemic Vaccine Production Capability**

The capability to produce vaccine against a pandemic strain depends on various factors, including a host of technical ones.

Factors limiting the production capacity of a satisfactory number of vaccines may relate to the following:

- availability of embryonated chicken eggs,
- availability of viral cultures of the new strain,
- viral multiplication rate in chicken eggs, and
- time needed to obtain market license.

Preparedness planning during the interpandemic period should include the following conditions in order to facilitate the development of such a vaccine:

- Improvement of the vaccination coverage of high-risk groups for seasonal influenza.

- Development of “prototype” vaccines against a pandemic strain according to scientific predictions based on existing genetic modifications of the virus or data from a new virus.
- Stockpiling of reagents for potency testing.
- Conducting clinical studies to evaluate the safety, immunogenicity, and dose plan of “prototype” pandemic vaccines.
- Standardization of the authorization procedure for a pandemic vaccine.
- Understanding the differences between a vaccine against a pandemic strain and the “usual” seasonal trivalent vaccine. The pandemic vaccine is going to be monovalent and would probably contain excipients to increase immunogenicity.
- Development of appropriate, safe strains to produce genetically modified vaccines.
- Development of “seed stock library” containing several avian influenza virus strains that can be used in various combinations.
- Use of cell cultures to produce new vaccines.
- Revision of the procedures to establish the rights of ownership of a new vaccine.
- Consider advance purchase agreements with vaccine-producing pharmaceutical industries.

#### **6.4. Vaccination Policy**

Despite the fact that there are antiviral medications for influenza treatment and prophylaxis, their use is subject to several limitations. Vaccination remains a priority, once the vaccine becomes available. The vaccine is expected to reduce the impact of the pandemic on the population, especially on high-risk groups, diminishing complications of the disease, hospitalization rates and mortality.

Given the possibility of limited vaccine quantities especially at the beginning, a vaccination policy needs to be developed beforehand with predefined and accepted priority groups to receive the vaccine.

These priority immunization groups are proposed based on several factors, mainly aiming at maintaining the basic infrastructure of the country and limiting the disruption to the society.

The vaccination policy for the pandemic vaccine in Greece will finally be endorsed by the National Influenza Pandemic Committee in collaboration with the National Immunization Committee. The recommendations issued by international organizations, such as the World Health Organization, will be taken into account for defining the priority groups.

##### **6.4.1. Suggested vaccination priority groups**

- Healthcare workers
- Individuals working in services that are necessary for proper social and political administration.
- Individuals pertaining to vulnerable high-risk groups, e.g. immunocompromized patients
- Individuals living in closed communities, e.g. nursing homes.
- Individuals in areas where there is considerable crowding and thus increased transmissibility, e.g. schools.

#### **6.5. Vaccination against Pneumococcus**

The vaccination of high-risk population groups against pneumococcus may significantly diminish the frequency of pneumococcal pneumonia as a complication of influenza. It is estimated that the pneumococcal vaccine has approximately 80% effectiveness and that immunity lasts about 5 years. In Greece, both the 23valent polysaccharide vaccine (for adults with indications) and the 7valent conjugate vaccine (for children under 5 years of age) are available.

Vaccination is advisable for the following groups:

- adults over 65 years old, and
- patients suffering from chronic diseases, such as cardiovascular diseases, pulmonary diseases, diabetes, alcoholism, liver cirrhosis.

The systematic promotion of vaccination against pneumococcus for the high-risk groups during the interpandemic period can play a significant part in the protection of the population from influenza complications in the event of a pandemic.

## **7. INFLUENZA TREATMENT AND USE OF ANTIVIRAL MEDICATIONS DURING A PANDEMIC**

As mentioned above it may take several months to produce a vaccine against a new pandemic influenza strain. During this latent period, antivirals against the influenza virus may play a significant role for the control of spread of the new strain and the maintenance of important services. Antiviral agents for use against influenza can be stockpiled in advance. Just like vaccines though, demand is expected to be quite high; thus, sufficiency is impossible. Avian influenza cases in Hong Kong in 1997 lead to the rapid depletion of global stocks of influenza antiviral medications.

A policy needs to be developed in advance to include indications and priorities as regards the therapeutic and possibly prophylactic use of influenza antiviral medications.

### **7.1. Antiviral Categories**

There are two main categories of influenza antivirals: the first one includes the cyclic amines Amantadine and Rimantadine, which suppress the function of M2 ion channels, while the second one includes viral neuraminidase inhibitors, mainly zanamivir and oseltamivir.

There are significant differences between these two categories with regard to pharmacokinetics, side-effects and development of resistance. These factors, as well as cost, should be taken into account when deciding on prophylaxis or treatment policies.

#### **7.1.1. Cyclic amines**

##### **Amantadine**

Amantadine is available in Greece under the brand name Symmetrel®, produced and marketed by Novartis Pharmaceuticals. Amantadine has been used for the treatment of type A influenza virus infections since 1960.

The use of amantadine involves two major drawbacks, namely significant side-effects and reduced effectiveness in pandemic conditions due to the fact that type A influenza viruses rapidly develop resistance during its use. Moreover, amantadine triggers the synthesis and release of dopamine, which is the reason for its use also against Parkinson's disease.

##### **Rimantadine**

Rimantadine is not available in Greece, although it is marketed in the United States under the brand name Flumadine®, by Forest Laboratories Inc. Rimantadine is 4 times more effective than amantadine against type A influenza viruses.

##### **Clinical use of amantadine and rimantadine**

They are fully but slowly absorbed – maximal plasma concentration is achieved within 3-4 hours. Half-life is 15-20 hrs, and maybe even longer in elderly patients. They are considered effective when administered at the onset of clinical symptoms; they have been found to reduce the duration of fever and respiratory symptoms in comparison to placebo. There is no indication of reduced mortality or complication prevention.

They are indicated mainly for type A influenza prevention. Several studies have shown that a 200mg/24h dose of amantadine taken within 48 hours from the onset of symptoms has a preventive effect in 70-90% of cases during a type A influenza epidemic. Pregnant women are advised to avoid amantadine, while care should also be taken when treating alcoholics and individuals with a psychiatric background or a history of seizure disorder. Children and patients suffering from chronic renal failure should receive smaller doses. It has been reported to interact with antihistamines, anticholinergics and alcohol. Side-effects are uncommon but significant, considering they stem from the central nervous system.

#### **7.1.2. Neuraminidase inhibitors**

Neuraminidase inhibitors belong to a rather new category of influenza antiviral medications. They inhibit an important viral enzyme, neuraminidase, which is found in both type A and B influenza viruses. By inhibiting neuraminidase, the virus cannot replicate or disseminate.

## **Zanamivir**

Zanamivir has been approved and is available in Greece under the brand name Relenza<sup>®</sup>, marketed by Glaxo Wellcome. Indications for use, according to the Greek licensure, include type A and B influenza treatment at the onset of the disease, if there is an epidemic in the community. Its therapeutic use does not seem to interfere with the development of inherent immunity. It is effective if administered within 48 hours from the onset of symptoms, via a special oral inhaler. Two inhalations (5mg x 2) are used twice a day for 5 days.

Only 4-17% of the inhaled dose is absorbed and then excreted through the renal route. Side-effects include cough, sinusitis, diarrhea, nausea, and regurgitation. Patients with a history of pulmonary disease are advised to avoid using this medication. It has a shelf life of approximately 3 years.

## **Oseltamivir**

Oseltamivir was recently made available in Greece under the brand name Tamiflu<sup>®</sup> by Roche. It is also effective when administered within 48 hours from the onset of symptoms. One 75mg capsule is taken orally twice a day. In the United States there is also available a paediatric solution (12 mg/ml) for the treatment of children 1-12 yrs of age, in 2 mg/kg of bodyweight doses (up to 25mg twice a day). The duration of the treatment is 5 days. It is well absorbed and has a bioavailability of about 80%. Half-life duration is 6-10 hours and it is excreted through the renal route. Main side-effects include diarrhea, nausea, regurgitation, headaches.

Both zanamivir and oseltamivir can reduce the duration of uncomplicated influenza illness by approximately one day, should they be administered early on. Their effectiveness in reducing complications has not been confirmed.

## **7.2. Use of Antiviral Medications during a Pandemic**

### **7.2.1. *Amantadine and rimantadine use in pandemic situation***

Amantadine sufficiency during an influenza pandemic would be impossible unless a decision for advance stockpiling was made. It would be necessary to contact the producing company in order to verify delivery delays, if the medication was to be ordered in emergency situations. In similar conditions abroad, there is a delay of several weeks between order and delivery.

Pharmaceutical industries in Greece may provide information on the exact quantities of amantadine in the Greek market in order to predict further needs. Moreover, each company's production capacity for additional quantities in pandemic conditions should be evaluated.

Amantadine can be stored, without compromising efficiency, for up to 5 years (reports mention even 2 decades or more). In the event of an influenza pandemic, continued supply should also be ensured for patients using the medication to treat Parkinson's disease.

Rimantadine is not available in the Greek market therefore no plans for it can be currently developed.

### **7.2.2. *Zanamivir and oseltamivir use in pandemics***

Both these agents have not been approved in Greece for use in prophylaxis against influenza. There are clinical studies showing the short-term benefits derived from their prophylactic use. Reported prophylactic effectiveness is 84% for zanamivir and 82% for oseltamivir. In certain countries, such as Canada and the United States, oseltamivir alone has been approved for prophylaxis. However, individuals under zanamivir or oseltamivir prophylaxis do not develop immunity against influenza and are rendered vulnerable once administration is discontinued.

Considering that their potency covers all virus strains, it is advisable to stockpile certain quantities for use in pandemic conditions. Both medicines have a shelf life of about 4-5 years. It should be noted that neuraminidase inhibitors are considerably more expensive than amantadine.

## **7.3. Defining Necessary Antiviral Medication Quantities**

It is possible that an influenza pandemic would call for the use of significant numbers of antiviral medication doses, compared to those needed to treat more localized influenza epidemics. It is obvious that antivirals should be used only if there are solid epidemiological data to justify this or if an influenza outbreak is laboratory confirmed. Many other issues also need to be taken into account,

such as the storage duration, location and responsibility for a distribution plan, the liability from antiviral medication use, their safety and cost. Antiviral medications are estimated to be necessary for a period of at least 8-12 weeks.

### **7.3.1. Defining necessary antiviral medication quantities for treatment**

According to international data, the effect of an influenza pandemic on a population of 10 million, assuming about 15-25% belonging to high-risk groups, and causing an illness, which would induce about 10% to miss at least half a day's work, would include the following:

- a) increased out-patient visits (400,000-500,000 patients),
- b) increased deaths due to influenza and its complications (1,500-7,000 patients), and
- c) increased hospitalizations due to influenza and its complications (approximately 4,250-16,750 patients).

About 170,000 doses of antivirals would be needed if used for hospitalized patients only (assume 2 doses of amantadine or oseltamivir for 5 days, i.e. 10 doses per patient). Obviously, a higher attack rate would lead to even larger demand. For example, should the attack rate increase to 30%, then about 300,000 doses would be needed.

These calculations, however, do not take into account other factors, such as high-risk groups infection rates, other hospitalization reasons, treatment of milder cases of working individuals (e.g. in healthcare settings, so that they may continue their work), as well as the epidemiologic characteristics of the disease (e.g. "epidemic waves" of influenza infection).

### **7.3.2. Defining necessary antiviral quantities for prophylaxis**

Antiviral medication may not only be used for treatment during a pandemic, but for prophylaxis as well. The quantity of necessary medication for prophylaxis depends also on the availability of an effective vaccine. For instance, if there is a vaccine available, prophylaxis should be administered during at least the first week (or longer should more vaccine doses be needed).

According to international data, if 400,000 people are employed in indispensable services and need to be vaccinated, then 2,800,000 doses of oseltamivir will be needed (assume half the therapeutic dose of oseltamivir for 7 days). If there is no vaccine available, then the necessary quantity of antiviral medications would increase considerably in order to provide prophylaxis throughout the entire duration of circulation of the pandemic influenza strain.

### **7.3.3. Antiviral stockpiling in Greece**

The Ministry of Health and Social Solidarity has already begun the process for stockpiling oseltamivir to cover 5% of the population in case of an influenza pandemic. This amounts to 500,000 therapeutic courses. The HCDCP has proposed the creation of a small amantadine stock as well.

## **7.4. Priorities during a Pandemic**

### **7.4.1. Treatment priorities during a pandemic**

The following population groups should be given treatment priority:

- a) hospitalized patients suffering from severe or complicated influenza (e.g. pneumonia or encephalitis),
- b) patients who belong to high-risk groups (chronic cardiac or pulmonary diseases, immunocompromized patients, etc) exhibiting influenza symptoms, before they are ill enough to be hospitalized, and
- c) healthcare workers in hospitals or the emergency medical services, who exhibit influenza symptoms.

### **7.4.2. Prevention priorities during a pandemic**

The use of antiviral medication as a preventive measure during an influenza pandemic is subject to change due to factors similar to the ones mentioned in the treatment part, i.e. epidemic severity, epidemiologic characteristics in high-risk or vulnerable population groups, and naturally vaccine

effectiveness and availability. The following population groups should be considered for antiviral prophylaxis in priority:

- a) high-risk groups that should have already been vaccinated according to recommendations,
- b) healthcare workers caring for immunocompromized patients or working in closed communities, such as nursing homes, prisons and other institutions,
- c) high-risk patients, hospitalized for other causes, in danger of contracting influenza due to a large number of influenza cases admitted to the hospital,
- d) individuals that cannot be vaccinated (e.g. severe egg allergy) and immunocompromized patients, who cannot develop sufficient immunity after vaccination,
- e) staff working pharmaceutical industries producing vaccine and antiviral medication,
- f) healthcare workers,
- g) important decision-making staff, such as members of the government, certain politicians, public health services, crisis management experts,
- h) staff working in law enforcement services, such as police, fire departments, the military, and
- i) staff providing indispensable services, such as communications, utilities, funeral services.

### **7.5. Side-Effects and Resistance**

Proper documentation and a specific monitoring system are advisable in order to monitor side-effects from the extended use of antiviral medication during a pandemic period.

Resistance testing should also be done routinely during widespread use of antiviral medications and the results should be monitored and analyzed.

### **7.6. Other Medications**

Other medications may be necessary as well for the treatment of patients during an influenza pandemic. These include: antimicrobials to treat bacterial pneumonia, bronchodilators, antipyretics, painkillers, oral and intravenous hydration solutions.

## **8. ACTION PLAN**

### **8.1. Responsibilities of the Health Sector during a Pandemic**

Every institution involved in the management of an influenza pandemic should be familiar with its role and responsibilities, as well as those of others in order to meet the needs arising during each pandemic phase.

#### **8.1.1. *Ministry of Health and Social Solidarity***

- Communication with the government hierarchy, other Centers and international organizations, health professionals, the media and the general public.
- Planning for vaccine and antiviral medication distribution during a pandemic.
- Planning for priority vaccination and antiviral treatment based on vaccine and antiviral medication availability and sufficiency.
- Planning for vaccine and antiviral side-effect monitoring system in collaboration with the National Drug Organization.
- Guidelines to peripheral public health services (prefectures) concerning the preparation of a pandemic plan at their level. Local plans should be harmonized with the National Influenza Pandemic Plan.
- Monitoring of the response (effectiveness, cost etc) of the health sector in each phase and period.
- Organization of healthcare services and personnel.
- Provision of Personal Protective Equipment (PPE), vaccination and antiviral medication policy for health care workers.
- Evaluation of manpower shortages in healthcare services that may arise during the pandemic.
- Provision of indispensable services as a Ministry.
- Collaboration with other agencies and Ministries.
- Provisions of necessary equipment (material and technical infrastructure, personal protection equipment) in healthcare units, as well as other pharmaceutical supplies.
- Coordination and monitoring of bed availability.
- Provision and coordination of home care services.
- Provision for areas/spaces for the collection of dead bodies.

#### **8.1.2. *Hellenic Centre for Disease Control & Prevention***

- Epidemiologic surveillance of influenza (clinical and laboratory) and supply of epidemiological data based on which decisions shall be made by the Ministry of Health and Social Security and other competent institutions to define policies in each phase on national and/or regional level.
- Collection, study, analysis and report of data concerning influenza activity, laboratory results, clinical manifestations and mortality in Greece, as well as other European countries.
- Systematic monitoring of reports from WHO, the European Center for Disease Control (ECDC), the European Influenza Surveillance Scheme (EISS), and the World Organization for Animal Health (OIE), information exchange.
- Investigation of cases, clusters, or epidemics in collaboration with regional public health services (prefectures).
- Guidance for the use of pandemic vaccine.
- Guidance and training of health professionals, the general public, and the media on pandemic-related matters.

- Preparation of guidelines for hospitals, private practicing physicians, and other healthcare services.
- Guidelines to the general public and travelers.
- Guidelines to medical personnel at entrance points (airports, ports, etc.).

### **8.1.3. National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples.
- Typing of influenza strains isolated in clinical samples.
- Antibody detection in serum samples.
- Susceptibility testing for antivirals.

### **8.1.4. National Drug Organisation**

- Procurement of antiviral medication stocks in collaboration with the Ministry for Health and Social Solidarity
- Procurement of the new pandemic vaccine, once available
- Monitoring and reporting of side-effects from the pandemic vaccine and antiviral medications.

### **8.1.5. Regional Public Health Services**

- Preparation of local influenza pandemic plans harmonized to the national plan.
- Preparedness planning and application of emergency measures at a local level.
- Protocols for collaboration with local authorities for the management of influenza pandemic.

### **8.1.6. Hospitals and Other Healthcare Services**

- Preparedness of hospital and other healthcare units in order to meet elevated needs during the pandemic period.
- Planning and provision for hospitalization of increased number of patients.
- Planning in case of staff shortage due to illness.
- Training of personnel for use of Personal Protective Equipment (PPE) and other prophylactic measures.
- Training of personnel to perform rapid diagnostic tests for influenza detection.
- Planning of safe clinical sample transportation to National Influenza Reference Laboratories.

## **8.2. Responsibilities of Non-Health Institutions during a Pandemic**

### **8.2.1. General Secretariat for Civil Protection (and the whole administration)**

- Maintenance of important services and minimizing societal disruption in widespread epidemic conditions in Greece.
- Activation of national contingency plans to enable use of public or private buildings for healthcare.
- Coordination of emergency measures, such as prohibition of assemblies, concerts, theatrical performances etc, school closure, restriction of movement for citizens entering or leaving the country and possible evacuation of Greek citizens from severely affected areas.

### **8.2.2. Ministry of Rural Development & Food**

- Epidemiologic surveillance of influenza in animals (e.g. fowl, pigs, etc.) based on the characteristics of the new viral strain and prevalent conditions.
- Planning and application of necessary control and prevention measures over affected animal farms in danger of influenza infection (e.g. poultry farms, etc.).

### **8.3. National Influenza Pandemic Committee**

The Greek National Influenza Pandemic Committee, based on WHO recommendations, is a permanent body, whose powers vary according to the situation in relation to influenza at international and national level.

During the interpandemic period, the Committee assesses the response of Public Health services to the seasonal influenza activity in the country.

The National Influenza Pandemic Committee plays a significant part once WHO confirms a new virus with pandemic potential that is transmissible to humans. In this case, the Committee is called to make decisions concerning crisis management on all levels.

According to a ministerial decree, the National Influenza Pandemic Committee in Greece consists of the Plenary National Influenza Pandemic Committee and the Executive Influenza Pandemic Committee. The Plenary has a strategic role, while the Executive Committee an operational one.

#### **8.3.1. Members of the Plenary National Influenza Pandemic Committee**

The following participate in the Plenary National Influenza Pandemic Committee in Greece:

- The Minister of Health and Social Solidarity (MoH) presides, assisted by the undersecretaries and the General Secretary for Health of the Ministry.
- The Vice-President of the Health Sector Coordination and Command Centre.
- The Director for Health of the MoH assisted by the Director for Public Health.
- The Director Operational Support and Technical Infrastructure of the MoH assisted by the Director for Human Resources.
- The Director for Social Security of the MoH assisted by the Director for Social Perception and Solidarity.
- The Director for Emergency Planning assisted by the Head of Unit for Emergency Planning.
- The President of the Hellenic Center for Disease Control & Prevention assisted by the Head of the Department for Epidemiological Surveillance and Intervention of the HCDCP.
- Representatives of the National School of Public Health.
- Representatives of the Veterinary Public Health department of the National School of Public Health.
- The President of the National Public Health Council.
- A representative from the National Immunization Committee.
- Representatives of the National Influenza Reference Laboratories in Athens and Thessalonica.
- A representative from the Ministry of Internal Affairs, Public Administration, and Decentralization (responsible for the prefectures).
- The President of the National Drug Organization assisted by the President of the Pharmaceutical Research and Technology Institute.
- Infectious diseases experts.
- Epidemiology experts.
- A representative from the Ministry of Rural Development and Food.
- A representative from the Ministry of Defense (Health Inspection Directorate).

- A representative from the General Secretariat of Civil Protection.
- A representative from the Ministry of Development.
- A representative from the Press Office of the MoH.

### **8.3.2. *Members of the Executive Influenza Pandemic Committee***

The following participate in the Executive Influenza Pandemic Committee:

- The Vice-President of the Health Sector Coordination and Command Centre presides.
- The Director for Health of the MoH assisted by the Director for Public Health.
- The Director Operational Support and Technical Infrastructure of the MoH assisted by the Director for Human Resources.
- The Director for Social Security of the MoH assisted by the Director for Social Perception and Solidarity.
- The President of the Hellenic Center for Disease Control & Prevention assisted by the Head of the Department for Epidemiological Surveillance and Intervention of the HCDCP.
- The President of the National Public Health Council.
- A representative from the Ministry of Internal Affairs, Public Administration, and Decentralization (responsible for the prefectures).
- The President of the National Drug Organization assisted by the President of the Pharmaceutical Research and Technology Institute.

### **8.4. Setting up Other Committees and Working Groups**

The Health Sector Coordination & Command Centre, which has the responsibility for developing the Operational Plan for the Management of Influenza Pandemic has formed several working groups of the abovementioned members of the Committees in order to propose policies on vaccination, antiviral medication use, regional planning, hospital preparedness etc.

## **9. ACTIVITIES PER AUTHORITY AND PANDEMIC PHASE**

### **9.1. Interpandemic Period**

#### **9.1.1. Phase 1**

No new influenza virus subtypes have been detected in humans. An influenza virus subtype may be present in animals, causing epizooties abroad (*Phase 1 outside Greece*) and/or in Greece (*Phase 1 in Greece*). The risk of human infection is considered low.

#### **Ministry of Health and Social Solidarity**

- Establishment of the National Influenza Pandemic Committee.
- Establishment of collaboration with Public Health institutions – Center for Disease Control & Prevention, National Influenza Reference Laboratories, National Drug Organization, National School of Public Health, etc. – as well as other Organizations, Institutions, and Services that may become involved in the management of an influenza pandemic.
- Guidance to regional public health services (prefectures), hospitals and other healthcare units concerning the preparation of local pandemic action plans.
- Contact with pharmaceutical companies producing antiviral medications, antibiotics, etc. with regard to the supply of the aforementioned products.
- Contract with influenza vaccine-producing pharmaceutical companies to ensure vaccine supply once production begins.
- Promotion of pneumococcal vaccination program to the over-65 age group and other high-risk groups.
- Promotion of seasonal influenza vaccination program for healthcare workers.
- Assessment of pandemic plan application cost.
- Regular revision and update of the National Operational Influenza Pandemic Plan.
- Exercises on the National Operational Influenza Pandemic Plan.

#### **Center for Disease Control & Prevention**

- Monitoring through existing influenza surveillance networks in collaboration with National Influenza Reference Laboratories.
- Expansion of existing networks based on international and local conditions.
- Systematic monitoring of reports from the WHO, the European Center for Disease Control (ECDC), the European Influenza Surveillance Scheme (EISS), and the World Organization for Animal Health, information exchange.
- Definition of guidelines concerning vaccination against the pandemic strain and antiviral medication use for chemoprophylaxis and treatment.
- Preparation and publication of instructions/information addressed to health professionals, the general public and the media.
- Guidelines towards individuals working with poultry or other sectors in contact with animals.
- Guidelines towards travelers to and from affected countries.
- Guidelines towards medical services at entrance points concerning suspicious cases.

#### **National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples and strain isolation.
- Typing of influenza strains isolated in clinical samples.
- Close collaboration and information exchange with WHO Collaborating Laboratories.
- Acquisition of reference strains for the timely detection of new strains.

## **National Drug Organization**

- Procurement, storage and distribution of antiviral medications and seasonal influenza vaccines.

## **Regional Public Health Services**

- Preparation of local influenza pandemic plans.
- Regular testing and update of local influenza pandemic plans.

### **9.1.2. Phase 2**

No new influenza virus subtypes have been detected in humans. An influenza virus subtype may be present in animals, causing epizooties abroad (*Phase 2 outside Greece*) and/or in Greece (*Phase 2 in Greece*). The risk of human infection is considered substantial.

## **Ministry of Health and Social Solidarity**

- Assembly of the National Influenza Pandemic Committee.
- Collaboration with Public Health institutions – Center for Disease Control & Prevention, National Influenza Reference Laboratories, National Drug Organization, National School of Public Health, etc. – as well as other Organizations, Institutions, and Services involved in the management of an influenza pandemic for systematic information exchange and application of control and prevention measures.
- Guidance/information to regional public health services (prefectures), hospitals and other healthcare units concerning the transition to the following phase and reevaluation of their preparedness status and plans.
- Promotion of the seasonal influenza vaccination program for healthcare workers.
- Promotion of pneumococcal vaccination program to the over-65 age group and other high-risk groups.

## **Center for Disease Control & Prevention**

- Enhancement of existing influenza surveillance networks in collaboration with National Influenza Reference Laboratories.
- Systematic monitoring of reports from the WHO, the European Center for Disease Control (ECDC), the European Influenza Surveillance Scheme (EISS), and the World Organization for Animal Health and briefing on prevalent conditions in Greece.
- Update of instructions/information addressed to health professionals, the general public, and the media.
- Update of guidelines towards individuals working with poultry or other sectors in contact with animals.
- Update of guidelines towards travelers to and from affected countries.
- Update of guidelines towards medical services at entrance points concerning suspicious cases.

## **National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples and strain isolation.
- Typing of influenza strains isolated in clinical samples.
- Close collaboration and information exchange with WHO Collaborating Laboratories, as well as other laboratories outside of Greece.

## **National Drug Organization**

- Procurement, storage and distribution of antiviral medications and seasonal influenza vaccines.

## **Regional Public Health Services**

- Update of local influenza pandemic plans, identification of gaps.
- Pandemic preparedness evaluation.

## **9.2. Pandemic Alert Period**

### **9.2.1. Phase 3**

Cases of human infection due to a new subtype are reported abroad (*Phase 3 outside Greece*), and/or in Greece (*Phase 3 in Greece*), but there is no human-to-human transmission, except in rare instances, after close contact.

#### **Ministry of Health and Social Solidarity**

- Assembly of the National Influenza Pandemic Committee.
- Collaboration with Public Health institutions – Center for Disease Control & Prevention, National Influenza Reference Laboratories, National Drug Organization, National School of Public Health, etc. – as well as other Organizations, Institutions, and Services involved in the management of an influenza pandemic for the application of control and prevention measures.
- Guidance/information to regional public health services (prefectures), hospitals and other healthcare units concerning action plans to be applied during this phase.
- Intensification of influenza vaccination program for medical and nursing staff coming into contact with patients in hospitals and primary healthcare centers.
- Promotion of the seasonal influenza vaccination program for healthcare workers.
- Guidelines concerning the distribution and use of antiviral medications for influenza.
- Reassessment of antiviral medication stock. New supply contracts if necessary.

#### **Center for Disease Control & Prevention**

- Evaluation of existing influenza surveillance networks.
- Enhancement of influenza surveillance networks.
- Expansion of surveillance to selected hospitals (paediatric hospitals, pulmonary disease hospitals, etc.) when deemed necessary.
- Systematic monitoring of reports from the WHO, the European Center for Disease Control (ECDC), the European Influenza Surveillance Scheme (EISS), and the World Organization for Animal Health and briefing on prevalent conditions in Greece.
- Redefinition of guidelines concerning priority groups for seasonal influenza vaccination and antiviral medication use for chemoprophylaxis and treatment.
- Update of instructions/information addressed to health professionals, the general public, and the media.
- Case definitions for pandemic type influenza and guidelines for its detection and management addressed to hospitals and private physicians.
- Update of guidelines towards travelers to and from affected countries.
- Investigation of reported cases in collaboration with regional public health services; briefing of international organizations on investigation results.
- Update of guidelines towards medical services at entrance points concerning suspicious cases.

#### **National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples and strain isolation.
- Typing of influenza strains isolated in clinical samples.
- Close collaboration and information exchange with WHO Collaborating Laboratories, as well as other laboratories outside of Greece.

#### **National Drug Organization**

- Inventory of available antiviral medications.
- Continued procurement of medications/vaccines to ensure sufficiency.

#### **Regional Public Health Services**

- Update of local influenza pandemic plans, identification of gaps.

- Pandemic preparedness evaluation.

### **9.2.2. Phase 4**

Small clusters with limited human-to-human transmission of the new subtype are reported abroad (*Phase 4 outside Greece*) and/or in Greece (*Phase 4 in Greece*).

#### **Ministry of Health and Social Solidarity**

- Assembly of the National Influenza Pandemic Committee; definition of responsibilities for immediate action by every institution involved according to their plans.
- Collaboration with Public Health institutions – Center for Disease Control & Prevention, National Influenza Reference Laboratories, National Drug Organization, National School of Public Health, etc. – as well as other Organizations, Institutions, and Services involved in the management of an influenza pandemic for systematic information exchange and application of control and prevention measures.
- Guidance/information to regional public health services (prefectures), hospitals and other healthcare units concerning action plans to be applied during this phase.
- Frequent briefing of involved institutions concerning alert level and unexpected developments.
- Promotion of the seasonal influenza vaccination program, especially for high-risk groups.
- Pandemic vaccine distribution when available.
- Reassessment of medication needs to ensure adequate quantities.
- Guidelines concerning antiviral medication use for chemoprophylaxis, whenever necessary.
- Rapid diagnostic test capability in as many primary healthcare units as possible.
- Plan for the possible isolation of cases at entrance points to the country.
- Evaluation of the need for international assistance and its proper procedure, if necessary.
- Request for additional funding, if necessary.

#### **Center for Disease Control & Prevention**

- Continued use of influenza surveillance networks in collaboration with National Influenza Reference Laboratories; increase alert with regard to timely analysis and interpretation of epidemiological findings in suspicious, possible, and confirmed cases.
- Further expansion of surveillance to selected hospitals.
- Systematic monitoring of reports from the WHO, the European Center for Disease Control (ECDC), and the European Influenza Surveillance Scheme (EISS). Briefing of the WHO and ECDC on developments in Greece.
- Redefinition of guidelines concerning priority groups for pandemic influenza vaccination.
- Guidelines towards hospitals concerning the treatment of suspicious, possible, and confirmed cases based on experience.
- Update and distribution of instructions/information addressed to health professionals, the general public, and the media.
- Case definitions for pandemic type influenza and guidelines for its detection and management addressed to hospitals and private physicians.
- Investigation of reported cases in collaboration with regional public health services; briefing of international organizations on investigation results.
- Update of guidelines towards medical services at entrance points concerning suspicious cases.

#### **National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples and strain isolation.
- Typing of influenza strains isolated in clinical samples.

- Close collaboration and information exchange with WHO Collaborating Laboratories, as well as other laboratories outside of Greece.

### **National Drug Organization**

- Distribution of antiviral medications to exposed and infected individuals based on the plan by the Ministry of Health and Social Solidarity.

### **Regional Public Health Services**

- Update of local influenza pandemic plans, identification of gaps.
- Activation of local action plans with regard to this specific phase.

### **9.2.3. Phase 5**

Larger clusters are reported abroad (*Phase 5 outside Greece*) and/or in Greece (*Phase 5 in Greece*), although human-to-human spread remains localized.

#### **Ministry of Health and Social Solidarity**

- Assembly of the National Influenza Pandemic Committee.
- Collaboration with Public Health institutions – Center for Disease Control & Prevention, National Influenza Reference Laboratories, National Drug Organization, National School of Public Health, etc. – as well as other Organizations, Institutions, and Services involved in the management of an influenza pandemic for systematic information exchange and application of control and prevention measures. Increase frequency of meetings between representatives of involved institutions for coordinated action.
- Evaluation of the need for international assistance and define proper procedures for its acceptance, if necessary.
- Regular communication with the Ministries of Health of neighboring and other countries, as well as the European Commission and international organizations (WHO).
- Reassessment of medication needs to ensure adequate quantities.
- Rapid diagnostic test capability in as many primary healthcare units as possible
- Organization of medical check points at entrance and exit points of the country.
- Assessment of health system readiness for response to increased needs.
- Alert hospitals, Healthcare Centers and other healthcare services about the possibility of an influenza pandemic, and recommend revision/update of their influenza pandemic action plans.
- Discontinuation of seasonal influenza vaccine, and supply of pandemic vaccine. Distribution of pandemic vaccine and preparation for mass vaccination (definition of vaccination sites, briefing on ethics) once the pandemic vaccine is made available.
- Local distribution of antiviral medications.

#### **Center for Disease Control & Prevention**

- Continued use of influenza surveillance networks in collaboration with National Influenza Reference Laboratories, increase alert with regard to timely analysis and interpretation of epidemiological findings in suspicious, possible, and confirmed cases.
- Further expansion of surveillance to selected hospitals, and possible application of syndromic surveillance from hospital Emergency departments.
- Systematic monitoring of reports from the WHO, the European Center for Disease Control (ECDC), and the European Influenza Surveillance Scheme (EISS). Briefing of the WHO and ECDC on developments in Greece.
- Redefinition of guidelines concerning priority groups for pandemic influenza vaccination.
- Redefinition of guidelines concerning priority groups for antiviral medication use for chemoprophylaxis and treatment.

- Guidelines towards hospitals concerning the treatment of suspicious, possible, and confirmed cases based on experience.
- Update and distribution of instructions/information addressed to health professionals, the general public, and the media.
- Investigation of reported cases in collaboration with regional public health services; briefing of international organizations on investigation results.
- Start operation of Hotlines for the public and health professionals, and request staff.
- Update of guidelines towards medical services at entrance points concerning suspicious cases and concerning traveler briefing and control.

#### **National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples and strain isolation.
- Typing of influenza strains isolated in clinical samples.
- Close collaboration and information exchange with WHO Collaborating Laboratories, as well as other laboratories outside of Greece.

#### **National Drug Organization**

- Procurement of pandemic vaccine provided its production has begun.
- Discontinuation of seasonal vaccine importation.
- Increase of antiviral stock.

#### **Regional Public Health Services**

- Update of local influenza pandemic plans, identification of gaps.
- Activation of local action plans with regard to this specific phase.

### **9.3. Pandemic Period**

#### **9.3.1. Phase 6**

The transmission of the new virus subtype is increased and sustained throughout the general population abroad (*Phase 6 outside Greece*) and/or in Greece (*Phase 6a-6e in Greece*).

#### **Ministry of Health and Social Solidarity**

- Assembly of the National Influenza Pandemic Committee, and declaration of pandemic.
- Information bulletins to primary healthcare units and regional public health services, concerning the onset of the pandemic in Greece and collaboration for measures at local level
- Regular meetings with other involved institutions and revision of action plans.
- Collaboration with the National Drug Organization to ensure stock sufficiency of antibiotics and other medications.
- Definition of isolation and quarantine procedures.
- Application of pandemic vaccination plan.
- Guidelines towards hospitals for proper bed management in order to meet expected high demand.
- Identification and resolution of particular problems, such as vaccine and antiviral medication availability.
- Constant information to the media, health professionals, and the general public.
- Preparation of protocols concerning conditions for declaring the country in a pandemic emergency state.
- Plan for possible isolation of cases at entrance and exit points of the country and wherever else it may be required.

- Evaluation of the need for international assistance and define proper procedures for its acceptance, if necessary.
- Request for additional funding if necessary.
- Briefing of all agencies/ministries involved on unexpected developments.
- Information to the general public concerning necessary interventions, such as prioritized medical services, travel bans, reduction of basic goods production capacity, etc.

### **Center for Disease Control & Prevention**

- Continued use of influenza surveillance networks in collaboration with National Influenza Reference Laboratories, increased alert with regard to the analysis and interpretation of epidemiological findings in suspicious, possible, and confirmed cases.
- Extensive surveillance, in collaboration with hospital infection committees, of pneumonias and respiratory infections in people that have traveled to areas with epidemic outbreaks due to the new strain, or in people that have come into contact with travelers from these areas. Additional surveillance and information collection systems, such as absenteeism monitoring in schools or other selected areas, unavailability of hospital beds, etc.
- Monitoring of deaths on a weekly basis.
- Intensive laboratory surveillance with as many clinical samples as possible collected from influenza-like illness or pneumonia patients examined in selected hospitals around the country.
- Redefinition of guidelines concerning priority groups for pandemic vaccination.
- Definition of guidelines concerning mass vaccination to cover other groups based on pandemic vaccine availability.
- Definition of guidelines concerning antiviral medication use, as well as preventive measures for those who will not get inoculated.
- Continuing information to health professionals and public health services concerning epidemiological data.
- Guidelines to hospitals concerning the treatment of suspicious, possible, and confirmed cases based on experience.
- Tracing and information of patient contacts in order to seek medical assistance in case of symptoms and take measures to prevent transmitting the virus.
- Update and distribution of instructions/information addressed to health professionals, the general public, and the media.
- Start operation of Hotlines for the public and health professionals (24hrs/7d), and request staff.
- Update of guidelines towards medical services at entrance points concerning suspicious cases and concerning traveler briefing and control.
- Case definitions for pandemic type influenza and guidelines for its detection and management addressed to hospitals and private physicians.
- Systematic monitoring of reports from the WHO, the European Center for Disease Control (ECDC), and the European Influenza Surveillance Scheme (EISS). Constant briefing of the WHO and ECDC on developments in Greece.

### **National Influenza Reference Laboratories**

- Detection of influenza virus in clinical samples and strain isolation.
- Typing of influenza strains isolated in clinical samples.
- Close collaboration and information exchange with WHO Collaborating Laboratories, as well as other laboratories outside of Greece.
- Management of increased number of samples.
- Testing of viral strain resistance to antiviral agents if possible.

### **National Drug Organization**

- Monitoring of new vaccine production and definition of delivery method.
- Issuing of marketing licenses for the pandemic vaccine(s) for circulation in Greece.
- Collaboration with production companies and WHO in regard to clinical studies on vaccination efficiency.
- Monitoring and recording of side-effects from the pandemic vaccine and antiviral medications.

### **Regional Public Health Services**

- Activation and application of local action plans with regard to this specific phase
- Activation of vaccination plans as well as distribution of antivirals and other medications.
- Monitor bed availability, increase bed and personnel capacity to cover needs.

### **Hospital Laboratories**

- Collaboration with National Influenza Reference Laboratories with regard to laboratory tests performed on patients suffering from influenza-like illness and viral pneumonia.
- Recording and reporting to the Hellenic Center for Disease Control & Prevention of the pathogens causing severe or lethal infections as complications, in patients infected with the pandemic strain, as well as their susceptibility or resistance to antibacterial medications.

### **Responsibilities of other agencies/ministries**

It should be noted that in addition to the aforementioned authorities, several other will be called to play important roles throughout the management of an influenza pandemic and during its various phases.

Structures such as the Secretariat for Civil Protection and the services it oversees, will contribute greatly to the application of quarantine measures, should these become necessary, as well as the permission to use public buildings as health care facilities, upon activation of the national contingency plans.

## **9.4. Postpandemic Period**

An influenza pandemic is considered to be over when epidemiological data on influenza activity show activity at prepandemic levels.

Every agency/ministry involved, with a special emphasis in the Health sector, needs to prepare an overall report, presenting all data collected during the pandemic period and all measures taken during its different periods and phases, accompanied by lessons learnt.

The National Influenza Pandemic Committee shall also prepare an overall report describing the effectiveness and gaps in the National Influenza Plan action plans applied and evaluating their effectiveness. The experience acquired during the pandemic is furthermore assessed.

## **Appendix I**

### **MANAGEMENT OF HOSPITAL CONTINGENCIES DURING AN INFLUENZA PANDEMIC**

## **A. EFFECTS OF INFLUENZA PANDEMIC IN HEALTHCARE SETTINGS**

Contingency plans for the management of influenza pandemic are usually based on the hypothesis that the particular strain would cause a morbidity of around 25% of the general population. The attack rate may reach 50% depending on the time needed to develop, test, distribute, and administer the vaccine for the new strain. Even if there is a vaccine against the new strain available, this would most likely require two doses per person to produce an adequate immune response about 6 weeks after the first dose. The effectiveness of the influenza vaccine in general is 70-90%; consequently, a part of the population will not produce antibodies despite inoculation.

As regards chemoprophylaxis with antivirals it seems that it is effective for the management of epidemics of seasonal influenza, but it has not yet been evaluated in pandemic conditions. Successful use of antivirals supposes the existence of adequate stockpile of the particular medicines.

It is obvious that a significant number of hospital beds shall be needed. Thus, it is necessary to plan the distribution and use of existing beds beforehand.

In addition, increased numbers of medical and nursing staff would be needed for the treatment of a large number of patients. For the purposes of the preparedness planning it should also be taken into account that part of the existing staff shall be unable to fulfill their duties due to infection.

### **A.1. BED REQUIREMENTS**

#### **A.1.1. *Determining available hospital beds***

It is necessary to have a register all available bed capacity of state hospitals per district. All available beds in private clinics, at least for the areas of Athens and Thessalonica, should be recorded as well.

#### **A.1.2. *Methods of increasing the number of available beds***

- Increase available beds by reducing the number of non-emergency admissions.
- Use available beds in private clinics for all patients, including from public hospitals.
- Reduction of the number of regular admissions in private clinics.
- Use available beds in military hospitals and rehabilitation centers.
- Use of hotels (or other structures) for healthcare.

Similar arrangements should be made for Intensive Care Unit (ICU) beds.

### **A.2. STAFF REQUIREMENTS**

#### **A.2.1. *Possible sources of medical/nursing and other staff***

In order to deal with hospital staff shortages, the following may be recruited:

- Medical school students.
- Secondary and upper level nursing school students.
- Nurses, registered in nursing associations.
- Specialized privately practicing medical doctors, registered in local Medical Associations and the Greek National Medical Association.
- Other health professionals, such as pharmacists, physiotherapists, etc.
- Volunteers from Non-Governmental Organizations offering supporting or non-medical services, such as preparing and serving meals, etc.

## **B. HOSPITAL EMERGENCY PLAN DEVELOPMENT**

All hospitals should develop emergency plans covering the possibility of an influenza pandemic, such as the ones drafted for the Athens 2004 Olympic Games by hospitals in Olympic prefectures. The following provisions should be taken into account:

### **B.1. PERSONNEL TRAINING**

All personnel should be trained in understanding and applying the hospital pandemic emergency plan, the infection control measures, the vaccination plan (should this become available), etc.

### **B.2. OUT-PATIENT CLINICS**

The appropriate infrastructure and procedures should be created and organized for triage in hospital emergency departments, out-patient clinics and primary healthcare units.

### **B.3. CENTRAL AIR-CONDITIONING**

Considering that influenza is transmitted through droplets, the air-conditioning system supplying air throughout floors, rooms, corridors, Emergency Rooms, and Intensive Care Units should be tested and the possibility of not being able to use it should be considered.

### **B.4. OXYGEN SUPPLY**

- Separate oxygen supply for each bed.
- Oxygen supply of 15-20 liters per minute to several beds at the same time.
- Adequate number of oxygen tanks and portable suction units.
- Possibility to adjust the oxygen flow to each bed separately.

### **B.5. RESPIRATOR CAPACITY**

- Calculate the maximum number of patients able to be hospitalized in Intensive Care Unit setting, based on available staff, number of beds, respirators, etc.
- Calculate the ability to use additional beds in other hospital clinics (ex. ophthalmologic, gynecologic, etc.) with available respirators.

### **B.6. PATIENT DISTRIBUTION**

- Check for empty spaces within the hospital that can be used to house additional beds.
- Register the number of examination beds within the hospital.
- Consider the possible use of a whole floor or ward for the treatment of influenza patients.

### **B.7. HOSPITAL PERSONNEL**

- Consider the possible reinstatement of retired medical and nursing staff, recalling of personnel on leave, and the recruitment of volunteers.
- Inform the personnel about the influenza pandemic and the duties they are to perform in such conditions.

### **B.8. OTHER EQUIPMENT/SUPPLIES**

- Check/register the availability of the following supplies in their specific storage rooms:
  - **Oxygen**

Tubing, masks, nebulizers, oxygen tanks, flow regulators, oxymeters, blood-gas syringes.

- **Infection control (personal protection)**

Gloves, P3 respiratory protection masks, surgical masks, hand antiseptic solution, surgical aprons, uniforms.

- **Parenteral treatment**

Intravenous catheters, central line catheters, needles, syringes, IV solutions, catheter caps, etc.

- **Radiology Department**

Adequate film quantities, development solutions, etc.

- **Microbiological laboratory**

Adequate quantities of culture media, vials for nasopharyngeal swab collection, viral transport medium, materials for antibiotic sensitivity tests, rapid tests for influenza virus etc.

- **Pharmacy**

Adequate quantities of antibiotic and antiviral medication, as well as the provision of additional quantities should it become necessary.

### **B.9. TECHNICAL SERVICES**

In order to increase hospital capacity, preparations should be made to meet the demand for the following services:

- Electricians, plumbers, medical equipment technicians
- Medical waste management
- Consistent water supply
- Electrical generator availability
- Hospital security
- Air-conditioning
- Hospital ambulances
- Storage room for expendables and medical supplies
- Laundry room
- Kitchen, etc.

## **Appendix II**

**PREPARATION FOR AN INFLUENZA PANDEMIC: PRELIMINARY  
PREDICTION OF MORBIDITY**



## A. INTRODUCTION

A preliminary morbidity prediction follows, concerning the effect a possible influenza pandemic will have on healthcare services. The data presented here are based on several factors (see below), but include a large degree of uncertainty; thus, their limitations should also be taken into account.

## B. PRELIMINARY MORBIDITY ESTIMATE

Initial estimates were based on one hand on the distribution of the Greek population by age and geographic location (2001 census) and on the other on the hypotheses used in the Dutch influenza pandemic preparedness plan [1, 2]. All estimates cover the "usual" influenza season (10% attack rate hypothesis), as well as two possibilities of pandemic spread (30% and 50% attack rate), expecting these cases (first epidemic wave) within 3 months and distributing them regularly within this timeframe. Moreover, these estimates are based on the hypotheses of the Dutch plan, as well as some additional parameters: percentage of patients infected with influenza visiting a physician (25%), patients at high risk of influenza complications by age (table 1A), percentage of patients hospitalized for influenza by age and risk group (table 1B), mean duration of hospitalization (8 days) [1-4].

In order to produce more accurate estimates, Greek epidemiologic data should be used (where they exist), while alternative hypotheses should be developed in more detail (e.g. different number of people infected within each age group, etc.). As for the percentage of hospitalized patients and the mortality rate due to influenza, data from the regular influenza seasons are taken into account, which will probably differ greatly in the event of an influenza pandemic (depending on the innate characteristics of the emerging pandemic strain of the virus). Thus, for a more accurate estimate, hypotheses covering such alternatives should also be taken into account. Lastly, estimates for these parameters (and, consequently, for the maximum number of hospital beds needed) depend also on the policy for vaccination of high-risk groups against pneumococcus, as well as for antiviral medication administration[5].

**Table 1.** Assumptions used for morbidity estimates

| <b>A/ Rough preliminary estimate of the number of patients at high risk for complications</b>                               |          |           |  |           |                   |
|---|----------|-----------|--|-----------|-------------------|
| Patient % (1)   |          |           | Number of patients (Greece, 2001 census) |           |                   |
| Age   | Low-risk | High-risk | Low-risk                                 | High-risk | Total             |
| 0-19  | 97.68    | 2.32      | 2,339,815                                | 55,513    | <b>2,395,328</b>  |
| 20-64   | 93.85    | 6.15      | 6,283,557                                | 411,892   | <b>6,695,449</b>  |
| 65+   | 65.05    | 34.95     | 1,218,521                                | 654,722   | <b>1,873,243</b>  |
| Total   | 90.92    | 9.08      | 9,968,060                                | 995,960   | <b>10,964,020</b> |
| <b>B/ Rough preliminary estimate of the number of patients hospitalized for influenza (during regular influenza season)</b> |          |           |  |           |                   |
| Ratio of patients per 100,000 of population (1)   |          |           | Number of patients (Greece, 2001 census) |           |                   |
| Age   | Low-risk | High-risk | Low-risk                                 | High-risk | Total             |
| 0-19  | 0.4      | 100       | 9  | 56        | <b>65</b>         |
| 20-64   | 0.4      | 100       | 25                                       | 412       | <b>437</b>        |
| 65+   | 40       | 185       | 487                                      | 1211      | <b>1,699</b>      |

1) Based on data from international literature [1-4].

**Table 2.** Preparation for an influenza pandemic: rough preliminary estimate of the total number of cases, medical visits and hospital admissions.

| Age   | regular influenza seasons (1) |                |            | 30% attack rate (2) |                |            | 50% attack rate (3) |                |            |
|-------|-------------------------------|----------------|------------|---------------------|----------------|------------|---------------------|----------------|------------|
|       | Cases                         | Medical visits | Admissions | Cases               | Medical visits | Admissions | Cases               | Medical visits | Admissions |
| 0-19  | 293,533                       | 59,883         | 65         | 718,598             | 179,650        | 195        | 1,197,664           | 299,416        | 324        |
| 20-64 | 669,545                       | 167,386        | 437        | 2,008,635           | 502,159        | 1,311      | 3,347,725           | 836,931        | 2,185      |

|       |                  |                |              |                  |                |              |                  |                  |               |
|-------|------------------|----------------|--------------|------------------|----------------|--------------|------------------|------------------|---------------|
| 65+   | 187,324          | 46,831         | 1,699        | 561,973          | 140,493        | 5,096        | 936,622          | 234,155          | 8,493         |
| Total | <b>1,096,402</b> | <b>274,101</b> | <b>2,201</b> | <b>3,289,206</b> | <b>822,302</b> | <b>6,602</b> | <b>5,482,010</b> | <b>1,370,503</b> | <b>11,003</b> |

- 1) regular influenza season (10% attack rate).
- 2) 30% attack rate (in total) hypothesis.
- 3) 50% attack rate (in total) hypothesis.

**Table 3.** Preparation for an influenza pandemic: preliminary estimates for the maximum number of hospital beds needed (during the peak of the epidemic wave).

| Geographic District and Prefecture     | Real population   |             | regular influenza seasons (1) |            | 30% attack rate (2) |             | 50% attack rate (3) |             |
|--|-------------------|-------------|-------------------------------|------------|---------------------|-------------|---------------------|-------------|
|  | 2001              | %           | 0-19 yrs                      | 20+yrs     | 0-19 yrs            | 20+yrs      | 0-19 yrs            | 20+yrs      |
| <b>Greece (total)</b>                  | <b>10,964,020</b> |             | <b>20</b>                     | <b>667</b> | <b>61</b>           | <b>2002</b> | <b>101</b>          | <b>3337</b> |
| <b>CAPITAL DISTRICT</b>                | <b>3,761,810</b>  | <b>34.3</b> | <b>7</b>                      | <b>229</b> | <b>21</b>           | <b>687</b>  | <b>35</b>           | <b>1145</b> |
| ATHENS PREFECTURE                      | 2,664,776         | 24.3        | 5                             | 162        | 15                  | 487         | 25                  | 811         |
| EAST ATTICA PREFECTURE                 | 403,918           | 3.7         | 1                             | 25         | 2                   | 74          | 4                   | 123         |
| WEST ATTICA PREFECTURE                 | 151,612           | 1.4         | 0                             | 9          | 1                   | 28          | 1                   | 46          |
| PIRAEUS PREFECTURE                     | 541,504           | 4.9         | 1                             | 33         | 3                   | 99          | 5                   | 165         |
| <b>REST OF STEREA HELLAS AND EVOIA</b> | <b>829,758</b>    | <b>7.6</b>  | <b>2</b>                      | <b>50</b>  | <b>5</b>            | <b>152</b>  | <b>8</b>            | <b>253</b>  |
| AETOLIA AND AKARNANIA PREFECTURE       | 224,429           | 2.0         | 0                             | 14         | 1                   | 41          | 2                   | 68          |
| VOIOTIA PREFECTURE                     | 131,085           | 1.2         | 0                             | 8          | 1                   | 24          | 1                   | 40          |
| EVOIA PREFECTURE                       | 215,136           | 2.0         | 0                             | 13         | 1                   | 39          | 2                   | 65          |
| EVRYTANIA PREFECTURE                   | 32,053            | 0.3         | 0                             | 2          | 0                   | 6           | 0                   | 10          |
| FTHIOTIDA PREFECTURE                   | 178,771           | 1.6         | 0                             | 11         | 1                   | 33          | 2                   | 54          |
| FOKIDA PREFECTURE                      | 48,284            | 0.4         | 0                             | 3          | 0                   | 9           | 0                   | 15          |
| <b>PELOPONNESUS</b>                    | <b>1,155,019</b>  | <b>10.5</b> | <b>2</b>                      | <b>70</b>  | <b>6</b>            | <b>211</b>  | <b>11</b>           | <b>352</b>  |
| ARGOLIDA PREFECTURE                    | 105,770           | 1.0         | 0                             | 6          | 1                   | 19          | 1                   | 32          |
| ARKADIA PREFECTURE                     | 102,035           | 0.9         | 0                             | 6          | 1                   | 19          | 1                   | 31          |
| ACHAIA PREFECTURE                      | 322,789           | 2.9         | 1                             | 20         | 2                   | 59          | 3                   | 98          |
| ELEIA PREFECTURE                       | 193,288           | 1.8         | 0                             | 12         | 1                   | 35          | 2                   | 59          |
| KORINTHIA PREFECTURE                   | 154,624           | 1.4         | 0                             | 9          | 1                   | 28          | 1                   | 47          |
| LAKONIA PREFECTURE                     | 99,637            | 0.9         | 0                             | 6          | 1                   | 18          | 1                   | 30          |
| MESSENIA PREFECTURE                    | 176,876           | 1.6         | 0                             | 11         | 1                   | 21          | 2                   | 54          |
| <b>IONIAN ISLES</b>                    | <b>212,984</b>    | <b>1.9</b>  | <b>0</b>                      | <b>13</b>  | <b>1</b>            | <b>39</b>   | <b>2</b>            | <b>65</b>   |
| ZAKYNTHOS PREFECTURE                   | 39,015            | 0.4         | 0                             | 2          | 0                   | 7           | 0                   | 12          |
| KERKYRA PREFECTURE                     | 111,975           | 1.0         | 0                             | 7          | 1                   | 20          | 1                   | 34          |
| KEFALLONIA PREFECTURE                  | 39,488            | 0.4         | 0                             | 2          | 0                   | 7           | 0                   | 12          |
| LEFKADA PREFECTURE                     | 22,506            | 0.2         | 0                             | 1          | 0                   | 4           | 0                   | 7           |
| <b>EPIRUS</b>                          | <b>353,820</b>    | <b>3.2</b>  | <b>1</b>                      | <b>22</b>  | <b>2</b>            | <b>65</b>   | <b>3</b>            | <b>108</b>  |
| ARTA PREFECTURE                        | 78,134            | 0.7         | 0                             | 5          | 0                   | 14          | 1                   | 24          |
| THESSPOTIA PREFECTURE                  | 46,091            | 0.4         | 0                             | 3          | 0                   | 8           | 0                   | 14          |
| IOANNINA PREFECTURE                    | 170,239           | 1.6         | 0                             | 10         | 1                   | 31          | 2                   | 52          |
| PREVEZA PREFECTURE                     | 59,356            | 0.5         | 0                             | 4          | 0                   | 11          | 1                   | 18          |
| <b>THESSALY</b>                        | <b>753,888</b>    | <b>6.9</b>  | <b>1</b>                      | <b>46</b>  | <b>4</b>            | <b>138</b>  | <b>7</b>            | <b>229</b>  |
| KARDITSA PREFECTURE                    | 129,541           | 1.2         | 0                             | 8          | 1                   | 24          | 1                   | 39          |
| LARISSA PREFECTURE                     | 279,305           | 2.5         | 1                             | 17         | 2                   | 51          | 3                   | 85          |
| MAGNESIA PREFECTURE                    | 206,995           | 1.9         | 0                             | 13         | 1                   | 38          | 2                   | 63          |
| TRIKALA PREFECTURE                     | 138,047           | 1.3         | 0                             | 8          | 1                   | 25          | 1                   | 42          |
| <b>MACEDONIA</b>                       | <b>2,424,765</b>  | <b>22.1</b> | <b>4</b>                      | <b>148</b> | <b>13</b>           | <b>443</b>  | <b>22</b>           | <b>738</b>  |
| AGHION OROS                            | 2,262             | 0.0         | 0                             | 0          | 0                   | 0           | 0                   | 1           |
| GREVENA PREFECTURE                     | 37,947            | 0.3         | 0                             | 2          | 0                   | 7           | 0                   | 12          |
| DRAMA PREFECTURE                       | 103,975           | 0.9         | 0                             | 6          | 1                   | 19          | 1                   | 32          |
| EMATHIA PREFECTURE                     | 143,618           | 1.3         | 0                             | 9          | 1                   | 26          | 1                   | 44          |
| THESSALONICA PREFECTURE                | 1,057,825         | 9.6         | 2                             | 64         | 6                   | 193         | 10                  | 322         |
| KAVALA PREFECTURE                      | 145,054           | 1.3         | 0                             | 9          | 1                   | 26          | 1                   | 44          |
| KASTORIA PREFECTURE                    | 53,483            | 0.5         | 0                             | 3          | 0                   | 10          | 0                   | 16          |
| KILKIS PREFECTURE                      | 89,056            | 0.8         | 0                             | 5          | 0                   | 16          | 1                   | 27          |
| KOZANE PREFECTURE                      | 155,324           | 1.4         | 0                             | 9          | 1                   | 28          | 1                   | 47          |
| PELLA PREFECTURE                       | 145,797           | 1.3         | 0                             | 9          | 1                   | 27          | 1                   | 44          |
| PIERIA PREFECTURE                      | 129,846           | 1.2         | 0                             | 8          | 1                   | 24          | 1                   | 40          |

| Geographic District and Prefecture | Real population |            | regular influenza seasons (1) |           | 30% attack rate (2) |            | 50% attack rate (3) |            |
|------------------------------------|-----------------|------------|-------------------------------|-----------|---------------------|------------|---------------------|------------|
|                                    | 2001            | %          | 0-19 yrs                      | 20+yrs    | 0-19 yrs            | 20+yrs     | 0-19 yrs            | 20+yrs     |
| SERRES PREFECTURE                  | 200,916         | 1.8        | 0                             | 12        | 1                   | 37         | 2                   | 61         |
| FLORINA PREFECTURE                 | 54,768          | 0.5        | 0                             | 3         | 0                   | 10         | 1                   | 17         |
| CHALCHIDIKE PREFECTURE             | 104,894         | 1.0        | 0                             | 6         | 1                   | 19         | 1                   | 32         |
| <b>THRACE</b>                      | <b>362,038</b>  | <b>3.3</b> | <b>1</b>                      | <b>22</b> | <b>2</b>            | <b>66</b>  | <b>3</b>            | <b>110</b> |
| EVROS PREFECTURE                   | 149,354         | 1.4        | 0                             | 9         | 1                   | 27         | 1                   | 45         |
| XANTHE PREFECTURE                  | 101,856         | 0.9        | 0                             | 6         | 1                   | 19         | 1                   | 31         |
| RODOPE PREFECTURE                  | 110,828         | 1.0        | 0                             | 7         | 1                   | 20         | 1                   | 34         |
| <b>AEGEAN ISLES</b>                | <b>508,807</b>  | <b>4.6</b> | <b>1</b>                      | <b>31</b> | <b>3</b>            | <b>93</b>  | <b>5</b>            | <b>155</b> |
| DODECANISOS PREFECTURE             | 190,071         | 1.7        | 0                             | 12        | 1                   | 35         | 2                   | 58         |
| KYKLADES PREFECTURE                | 112,615         | 1.0        | 0                             | 7         | 1                   | 21         | 1                   | 34         |
| LESVOS PREFECTURE                  | 109,118         | 1.0        | 0                             | 7         | 1                   | 20         | 1                   | 33         |
| SAMOS PREFECTURE                   | 43,595          | 0.4        | 0                             | 3         | 0                   | 8          | 0                   | 13         |
| CHIOS PREFECTURE                   | 53,408          | 0.5        | 0                             | 3         | 0                   | 10         | 0                   | 16         |
| <b>CRETE</b>                       | <b>601,131</b>  | <b>5.5</b> | <b>1</b>                      | <b>37</b> | <b>3</b>            | <b>110</b> | <b>6</b>            | <b>183</b> |
| HERAKLION PREFECTURE               | 292,489         | 2.7        | 1                             | 18        | 2                   | 53         | 3                   | 89         |
| LASITHION PREFECTURE               | 76,319          | 0.7        | 0                             | 5         | 0                   | 14         | 1                   | 23         |
| RETHYMNON PREFECTURE               | 81,936          | 0.7        | 0                             | 5         | 0                   | 15         | 1                   | 25         |
| CHANIA PREFECTURE                  | 150,387         | 1.4        | 0                             | 9         | 1                   | 27         | 1                   | 46         |

1) regular influenza season (10% attack rate).

2) 30% attack rate (in total) hypothesis.

3) 50% attack rate (in total) hypothesis.

## BIBLIOGRAPHY

- 1) Genugten MLL, Heijinen MLA, Jager JC. Scenario analysis of the expected number of hospitalizations and deaths due to pandemic influenza in the Netherlands. RIVM Report 217617004. 2002
- 2) Genugten MLL, Heijinen MLA, Jager JC. Pandemic influenza and healthcare demand in the Netherlands: scenario analysis. *Emerging Infectious Diseases* 2003; 9: 531-8.
- 3) Baltussen RMPM, Reinders A, Sprenger MJW, Postma MJ, Jager JC, Ament AJHA, Leidl RM. Estimating influenza related hospitalization in the Netherlands. *Epidemiology and Infection* 1998; 121: 129-38.
- 4) Sprenger MJW, Mulder PGH, Beyer WEP, Strik R van, Masurel N. Impact of influenza on mortality in relation to age and underlying disease, 1967-1989. *International Journal of Epidemiology* 1993; 22: 334-40.
- 5) WHO. Influenza pandemic preparedness and response. EB115/44/20-01-2001.
- 6) WHO consultation on priority public health interventions before and during an influenza pandemic, Geneva, Switzerland 16-18 March 2004.
- 7) National Influenza Pandemic Plans of the United States, Switzerland, Canada, United Kingdom, New Zealand, Ireland, Australia, Netherlands, Norway, Slovakia, Czech Republic, Hungary available at: <http://www.who.int/csr/disease/influenza/nationalpandemic/en>
- 8) Kiso M, Mitamura K, Sakai-Tagawa Y, Shiraishi K, Kawakami C, Kimura K, Hayden FG, Sugaya N, Kawaoka Y. Resistant influenza A viruses in children treated with oseltamivir: descriptive study. *Lancet*. 2004 Aug 28; 364 (9436): 759-65.
- 9) Dolin R, Reichman RC, Madore HP, Maynard R, Linton PN, Webber-Jones J. A controlled trial of amantadine and rimantadine in the prophylaxis of influenza A infection. *N Engl J Med* 1982 Sep 2; 307 (10): 580-4.
- 10) Treanor J, Hayden F, Vrooman P, Barbarash R, Bettis R, Riff D, et al. Efficacy and safety of the oral neuraminidase inhibitor oseltamivir in treating acute influenza: A randomized controlled trial. *JAMA* 2000; 283: 1016-1024.
- 11) Hayden FG, Osterhaus ADME, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in treatment of influenza virus infections. *N Engl J Med* 1997; 337: 874-80.
- 12) Influenza Pandemic Preparedness Plan. Responding to an Influenza Pandemic or its Threat: the role of WHO and Guidelines for National or Regional Planning. World Health Organization, Geneva, Switzerland, 1999.
- 13) Blick TJ, Sahasrabudhe A, McDonald M, Owens IJ, Morley PJ, Fenton RJ, McKimm BJ. The interaction of neuraminidase and hemagglutinin mutations in influenza virus in resistance to 4-guanidino-Neu4Ac2en. *Virology* 1998; 246 (1): 95-103.
- 14) Hayden FG, Couch RB. Clinical and Epidemiological Importance of Influenza A Viruses Resistant to Amantadine and Rimantadine. *Reviews in Medical Virology* 1992; 2: 89-96.
- 15) Monto AS, Arden NH. Implications of viral resistance to amantadine in control of influenza A. *Clin. Infect. Dis.* 1992; 15: 362-7; discussion 368-9.
- 16) The WHO global influenza preparedness plan. Available at [http://www.who.int/csr/resources/publications/influenza/WHO\\_CDS\\_CSR\\_GIP\\_2005\\_5/en/index.html](http://www.who.int/csr/resources/publications/influenza/WHO_CDS_CSR_GIP_2005_5/en/index.html)
- 17) Avian influenza contingency plan. Hellenic Ministry of Rural Development and Food. FEK (Government Newspaper) 1760, 2004.