Influenza A (H1N1)--a new communicable disease

Role and activities of the Health Authorities and International Organizations in relation to the current H1N1 influenza pandemic

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List of Abbreviations

BLA	Biologics License Application
CBER	Center of Biologics Evaluation and Research
CDC	Centre for Disease Control
CDER	Center for Drug Evaluation and Research
CFR	Code of Federal Regulations
CFSAN	Center for Food Safety and Applied Nutrition
CDRH	Center for Devices and Radiological Health
CMC	Chemistry, Manufacturing and Control
CVM	Center for Veterinary Medicine
CP	Centralized Procedure
DNA	Deoxyribonucleic Acid
EC	European Commission
EMEA	European Agency for the Evaluation of Medicinal Products
EU	European Union
EOC	FDA's Emergency Operations Center
EVM	European Vaccine Manufactures association
FDA	Food and Drug Administration
GISN	Global Influenza Surveillance Network
GOARN	Global Outbreak Alert & Response Network
HHS	Department of Health and Human Service, USA
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IND	Investigational New Drug
MAH	Marketing Authorization Holder
NIC	National Influenza Centres

NIH	National Institutes of Health, USA
OCM	Office of Crisis Management
OER	Office of External Relations
ORA	Office of Regulatory Affairs
OIP	Office of International Programs
PhVWP	Pharmacovigilance Working Party
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
URTI	Upper Respiratory Tract Infection
USA	United States of America
VWP	Vaccine Working Party1
WHO	World Health Organization
WWI	World War I

1. Introduction

A new communicable disease influenza A (H1N1) affected geographically diverse areas around the world in 2009. Person to person transmission has led to increase the numbers of patients. The current influenza A (H1N1) virus, which was previously referred as Swine Flu is totally a new virus subtype. This new virus subtype is efficiently able to be transmitted from human to human which may cause Pandemic Influenza.

Influenza virus infection, one of the most common infectious diseases, is a highly contagious airborne disease that causes an acute febrile illness and results in variable degrees of systemic symptoms, ranging from mild fatigue to respiratory failure and death. These symptoms contribute to significant loss of workdays, human suffering, mortality, and significant morbidity.

Actually influenza A(H1N1) is a common respiratory disease of pigs caused by type “A” influenza viruses. As of 2009, the known influenza virus strains include influenza “C” and the subtypes of influenza “A” known as H1N1, H1N2, H3N1, H3N2, and H2N3. Transmission of the virus from pigs to humans is not common and does not always lead to human influenza, often resulting only in the production of antibodies in the blood. If transmission does cause human influenza, it is called Zoonotic swine flu. Symptoms of Zoonotic swine flu in humans are similar to those of influenza and of influenza-like illness in general, namely chills, fever, sore throat, muscle pains, severe headache, coughing, weakness and general discomfort. People with regular exposure to pigs are at increased risk of swine flu infection. The meat of an infected animal poses no risk of infection when properly cooked. Infact, it is a literature work. So, the objective of this paper is to study the present global situation of swine flu with its historical perspective (Islam R. and Rehman M. 2009).

The differential diagnosis of influenza A or B infection based solely on clinical criteria is difficult because of the overlapping symptoms caused by the various viruses associated with upper respiratory tract infection (URTI). In addition, several serious viruses, including adenoviruses, enteroviruses, and paramyxoviruses, may initially cause influenza like symptoms. The early presentation of mild or moderate cases of flavivirus infections (e.g., dengue) may initially mimic influenza. For example, some cases of West Nile fever acquired in New York in 1999 were clinically misdiagnosed

as influenza. The CDC recommends real time RT-PCR as the method of choice for diagnosing H1N1. This method allows a specific diagnosis of novel influenza (H1N1) as opposed to seasonal influenza.

Patients infected with influenza virus frequently present with various symptoms shared by many other viral infections. In the northern and southern hemispheres, these symptoms are more common in the winter months. As a result, during the winter, clinics and emergency department waiting rooms fill with patients who have influenza or other URTIs. (Derlet R.W. 2010).

The three big worldwide outbreaks (pandemic) of influenza occurred in the 20th century: in 1918, 1957, and 1968. All 3 have been informally identified by their presumed sites of origin as Spanish, Asian, and Hong Kong influenza, respectively (Kilbourne, 2006). The influenza pandemic of 1918-1919 killed more people than the Great War, known today as World War I (WWI), at somewhere between 20 and 40 million people. It has been cited as the most devastating epidemic in recorded world history. More people died of influenza in a single year than in four-years of the Black Death Bubonic Plague from 1347 to 1351. Known as "Spanish Flu" or "La Grippe" the influenza of 1918-1919 was a global disaster. The 1918-1919 H1N1 type influenza pandemic killed an estimated 20-50 million persons, with 549,000 deaths in the United States alone (CDC, 2009).

In 2009 a new strain of H1N1 influenza virus, often referred to as "swine flu" was a global outbreak of the Influenza A. First described in April 2009, the virus appeared to be a new strain of H1N1 which resulted when a previous triple reassortment of bird, pig, and human flu viruses further combined with a Eurasian pig flu virus. Unlike most strains of influenza, H1N1 does not disproportionately infect adults older than 60 years; this was an unusual and characteristic feature of the H1N1 pandemic (CDC, 2009).

Strategies to shorten the time between emergence of a human influenza pandemic virus and the availability of safe and effective pandemic influenza vaccines are of the highest priority in global health security. The current regulatory approaches for pandemic influenza vaccines in European Union United States Australia, Canada, and the Japan have defined regulatory pathways for the licensure of influenza vaccines for use in a pandemic situation. Emergency options have also been

identified should a pandemic influenza vaccine be needed before the vaccine has been licensed.

There are limited immunogenicity and safety data, and no efficacy data would be available when human pandemic influenza vaccines are first administered after a pandemic is declared. The risks and benefits of pandemic influenza vaccine will need to be studies post marketing. Clear post marketing surveillance data has to be evaluated for effectiveness and safety of pandemic influenza vaccine. The sharing of post-market information (e.g. safety signals) is important, especially for those countries that do not conduct routine post-market surveillance (WHO Regulatory preparedness 2007). Post-marketing preparedness requires collaboration between all stakeholders, WHO, Public Health Authorities, industry to provide safe and effective therapy to the effected peoples.

Several sources are available to them to keep current knowledge up-to-date with developments during a influenza pandemic. The guidelines and situations can change rapidly with time and development and the web sites of national authorities are frequently updated, especially when a pandemic is declared. The first Web site contains an update written for the public and caregivers; the government and World Health Organization (WHO) sites provide detailed information that are updated as guidelines and developments occur.

1.1 Aim of this Thesis

The aim of this thesis is to illustrate the role of health authorities and organizations in relation to the current H1N1 influenza pandemic as well as the have an overview on the pandemic of influenza 2009.

The challenges faced during the pandemic of influenza A (H1N1) in 2009 have opened the doors of new research and strategic plans to control and prevent unexpected disasters. Influenza A undergoes frequent antigenic changes that require new vaccines to be developed and people to obtain a new vaccination every year. Much of the illness and death caused by conventional or seasonal influenza can be prevented by annual influenza vaccination.

In the frame of above statement the chapter 1 give an overview of what is known to date about this H1N1 influenza and the nature and value of the currently available treatment options. Additionally, this chapter summarises the results of a comprehensive literature search on the mechanisms of action suspected to play a major role in the underlying pathology of the disease.

In chapter 2 the pandemic of H1N1 Influenza in 2009 is structured as well as the role of European Medicine Agency (EMA), Food and Drug Administration (FDA) and WHO is explained to understand the position of authorities and their strategy towards pandemic of H1N1 Influenza in 2009.

In Chapter 3 regulatory guidance provided by the EMA as well as by the FDA is discussed. Moreover the different registration process as explained by health authorities and availability of vaccines in pandemic of influenza is discussed.

Furthermore, chapter 4 summarises the pharmacovigilance and monitoring of safety regarding the approved H1N1 vaccines as well as demonstrates quick influenza H1N1 vaccine regulatory strategies.

In this context it should be noted that all explanatory documents i.e. guidelines, position papers etc. regarding the new legislation which have been published until the 31 May 2010 are taken into consideration.

1.2 Historical Background of H1N1 Influenza

Influenza is the contagious respiratory illness caused by Influenza viruses. Influenza A (H1N1) is currently the greatest pandemic disease threat to humankind. It could potentially infect 30% of the world's population within a matter of months. Even at a conservative overall mortality rate of 2%, it would result in around 135 million deaths worldwide within the first year of a new pandemic outbreak. This is about 4 times the total mortality attributed to HIV-1 in the last 30 years (Gatherer, 2009).

In 2009, an influenza pandemic was caused by a new H1N1 virus. The virus began causing illness in Mexico in March 2009 and it reached Canada at the end of April; it had spread world-wide by June.

In the last century, there were three pandemics:

- Spanish influenza, 1918–19
- Asian influenza, 1957–58
- Hong Kong influenza, 1968–69

Spanish influenza, 1918–19

Well known as "Spanish Flu" of 1918–1920 is the earliest known pandemic for which hard molecular evidence exists for the involvement of influenza A. This first influenza pandemic killed 40 million people worldwide, is informative as a "worst case scenario" for a flu pandemic. The H1 haemagglutinin in this pandemic may have been of avian origin, and the disease was first detected in the USA in prisons and military bases.

Asian influenza, 1957–58

In Asia, , an influenza strain was identified in Asia that people less than 65 years of age were not immune to, and a pandemic was predicted in February 1957. This pandemic was much milder illness than that of 1918, the global death toll was estimated to be around 2 million. The virus was quickly identified in 1957 due to advance science technology. The virus was identified as a form of avian influenza, normally found in wild ducks, which has crossed with a human virus.

Hong Kong influenza, 1968–69

In Hong Kong, the influenza pandemic was first detected In early 1968. The first cases in North America were detected in the United States in September of that year, but illness did not become widespread until December. Deaths from this virus peaked in December 1968 and January 1969. Those over the age of 65 were most likely to die. An estimated 500,000 people died in the Hong Kong Flu pandemic. The same virus returned in 1970 and 1972. This was the mildest pandemic in the 20th century. People who survived the 1957-58 Asian Flu pandemic had developed resistance to the H2N2 virus responsible for the outbreak.

Fig. 1 on the next page shows a phylogenetic tree of the haemagglutinin proteins of all H1N1 strains circulating in humans since the Spanish Flu. The 1918 protein is an out group, and the remainder of the sequences are either seasonal H1N1 from the 1934/1977 lineage or zoonotic strains.

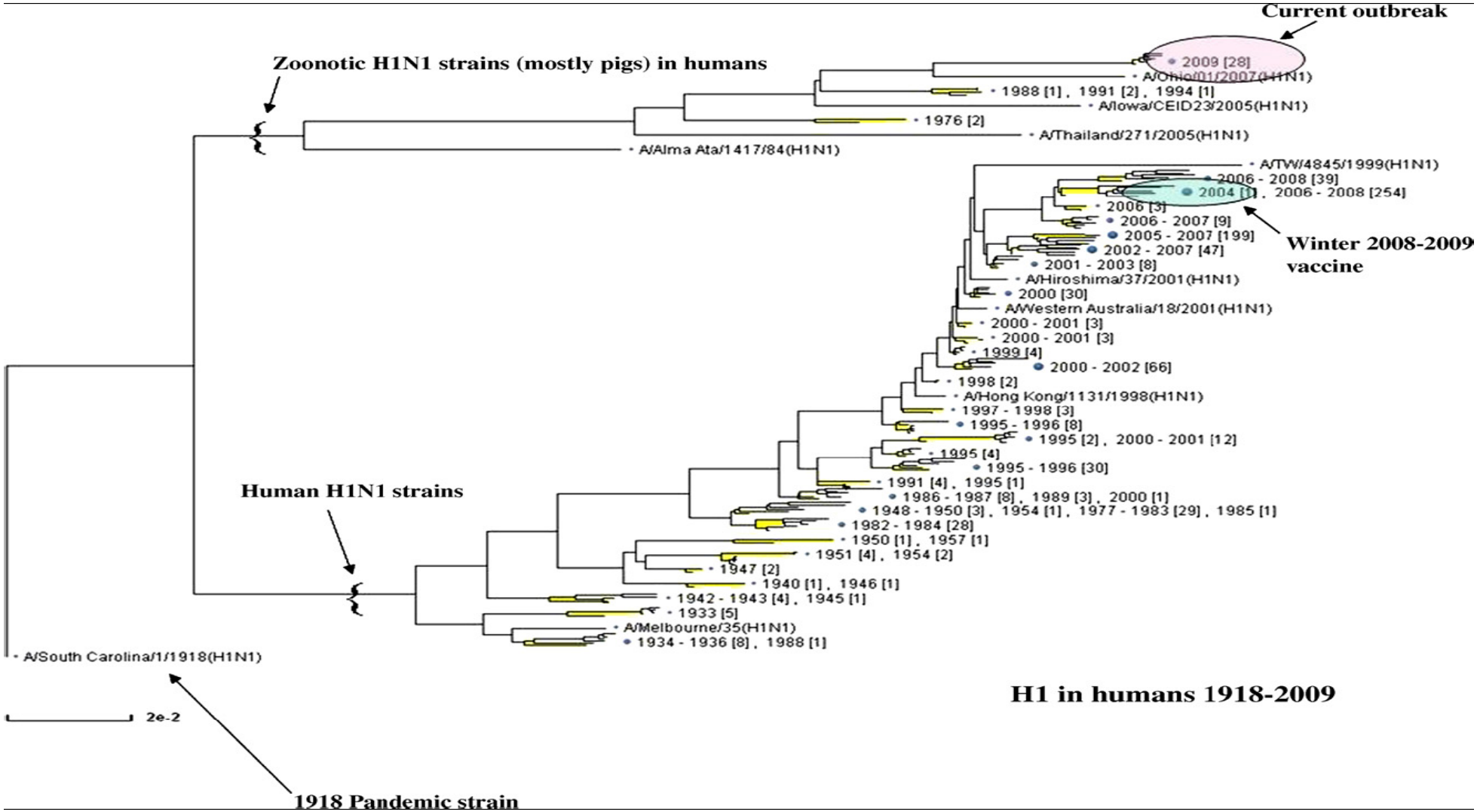


Fig. 1. Phylogenetic tree of H1 haemagglutinin sequences in influenzaAH1N1strains infecting humans from 1918 to the present day. 3 clades can be seen: (1) the 1918 pandemic strain which is an outlier; (2) strains circulating seasonally since at least the 1930s (lower of 2 major clades); (3) zoonotic strains (upper clade). The positions of the current outbreak and the most recent vaccine strains are indicated. Tree drawn using the NCBI Influenza Virus Resource tools: (Gatherer 2009).

During the flu pandemic in 1918, swine influenza was first proposed to be a disease, related to human influenza when pigs became sick as well as human. The first identification of an influenza virus as a cause of disease in pigs occurred about ten years later, in 1930.

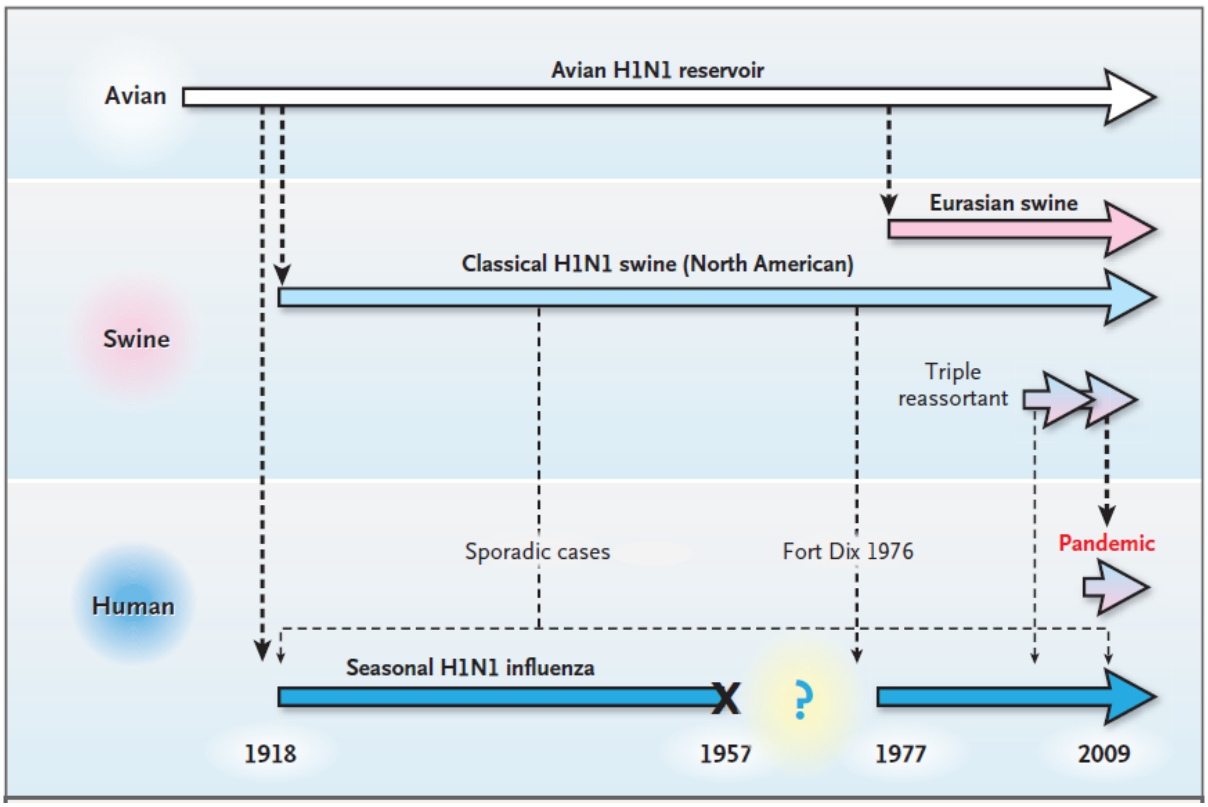
For the following 60 years, swine influenza strains were almost exclusively H1N1. Then, between 1997 and 2002, new strains of three different subtypes and five different genotypes emerged as causes of influenza among pigs in North America. In 1997-1998, H3N2 strains emerged. These strains, which include genes derived by re-assortment from human, swine and avian viruses, have become a major cause of swine influenza in North America. Re-assortment between H1N1 and H3N2 produced H1N1.

In 1999 in Canada, a strain of H4N6 crossed the species barrier from birds to pigs, but was contained on a single farm. As well as persisting in pigs, the descendants of the 1918 virus have also circulated in human through the 20th century, contributing to the normal seasonal epidemics of influenza. However, direct transmission from pigs to human is rare, with only 12 cases in the U.S. since 2005.

Nevertheless, the retention of influenza strains in pigs after these strains have disappeared from the human population might make pigs a reservoir where influenza viruses could persist, later emerging to reinfect humans once human immunity to these strains has waned. Swine flu has been reported numerous times as a Zoonosis in human, usually with limited distribution, rarely with a widespread distribution. Outbreaks in swine are common and cause significant economic losses in industry, primarily by causing stunting and extended time to market. For example, this disease costs the British meat industry about £65 million every year. (Islam and Rehman 2009).

The following Figure 2 (Emergence of Influenza A (H1N1) viruses from Birds and Swine into Humans) of influenza pandemic describes the important events and processes in the emergence of influenza virus during the past 91 years.

Figure 2 Emergence of Influenza A (H1N1) viruses from Birds and Swine into Humans (Zimmer and Burke 2009).



The diagram shows the important events and processes in the emergence of influenza A (H1N1) viruses during the past 91 years. Avian, swine, and human populations are represented in the top, middle, and bottom of the diagram, respectively. Epidemic or zoonotic viruses are shown as wide horizontal arrows (white for avian viruses, light blue or pink for swine viruses, and dark blue for human viruses). Crossspecies transmissions are shown as vertical dashed lines, with thick lines for transfers that gave rise to sustained transmission in the new host and thin lines for those that were transient and resulted in a selflimited number of cases. Principal dates are shown along the bottom of the diagram. The disappearance of H1N1 in 1957 most likely represents competition by the emerging pandemic H2N2 strain in the face of population immunity to H1N1. The reemergence in 1977 is unexplained and probably represents reintroduction to humans from a laboratory source.

The influenza virus is thought to have emerged almost simultaneously from birds into humans and swine. It is not known whether low levels of cross immunity against historically remote shared epitopes might confer some clinical protection against the newly emerging virus (Zimmer and Burke 2009).

1.3 Current Understanding of the Pathology of H1N1 Influenza

Influenza or flu is a viral infection that affects mainly the nose, throat, bronchi and, occasionally, lungs and commonly occurs in winter. Infection usually lasts for about a week, and is characterized by sudden onset of high fever, aching muscles, headache and severe malaise, non-productive cough, sore throat and rhinitis.

The virus usually appears in epidemic form and transmitted easily from person to person via droplets and small particles produced when infected people cough or sneeze. Influenza tends to spread rapidly in seasonal epidemics.

The greatest severity is in young children, elderly people, immune-suppressed people, and those with chronic diseases. Most infected people recover within one to two weeks without requiring medical treatment. However, in the very young, the elderly, and those with other serious medical conditions, infection can lead to severe complications of the underlying condition, pneumonia and death.

Pandemic (H1N1) 2009 is a new influenza virus that has never circulated among humans before. After outbreaks in North America early in 2009, the virus spread rapidly around the world. Pandemic influenza is transmitted like seasonal influenza but people have virtually no immunity to it. Mitigating its effects is a public health priority.

There are three types of flu viruses existing

- influenza A
- influenza B
- influenza C

Types A and B viruses cause seasonal epidemics which hit the USA and Europe virtually every winter. The type C influenza virus causes mild respiratory illness and is not responsible for epidemics.

There are no B virus subtypes, but there are different influenza B virus strains. Of the three genuses of influenza viruses that cause human flu, two also cause influenza in pigs. With influenza “A” is being widespread in pigs and influenza “C” being rare. These two are briefly in below:

Influenza “C” virus infects both human and pigs, but does not infect birds. Transmission between pigs and human was occurred in the past. For example, influenza “C” caused small outbreaks of a mild form of influenza amongst children in Japan and California. Due to its limited host range and the lack of genetic diversity in influenza “C”, this form of influenza does not cause pandemics in human (Islam and Rehman 2009).

Influenza A is generally more pathogenic than influenza B. Influenza A is a zoonotic infection, and more than 100 types of influenza A infect most species of birds, pigs, horses, dogs and seals. Indeed, the 1918 pandemic that resulted in millions of human deaths worldwide is believed to have originated from a virulent strain of H1N1 from pigs or birds.

Influenza “A” (H1N1)

Influenza A (Family Orthomyxoviridae, Genus Influenza virus A) is currently the greatest pandemic disease threat to humankind. Its rivals for this title (HIV-1, Ebola, SARS, pneumonic plague) have higher mortality if untreated, but either lack influenza’s rapid inter-personal transmission (HIV-1) or its widespread seasonal distribution (Ebola, SARS, pneumonic plague). Influenza A is unique among the major pandemic threats in that it could potentially infect 30% of the world’s population within a matter of months. Even at a conservative overall mortality rate of 2%, it would result in around 135 million deaths worldwide within the first year of a new pandemic outbreak. This is about 4 times the total mortality attributed to HIV-1 in the last 30 years (Gatherer 2009).

Influenza A (H1N1) virus is a subtype of influenza virus A and the most common cause of influenza (flu) in humans. Some strains of H1N1 are endemic in humans and cause a small fraction of all influenza-like illness and a large fraction of all seasonal influenza.

Swine flu influenza is known to be caused by influenza “A” of subtypes H1N1, H1N2, H3N1, H3N2, and H2N3. In pigs, three subtypes of influenza “A” virus (H1N1, H3N2, and H1N2) are the most common strains worldwide. In the United States, the H1N1 subtype was exclusively prevalent among swine populations before 1998; however, since late August 1998, H3N2 subtypes have been isolated from pigs. As of 2004, H3N2 virus was isolated in US swine and turkey stocks were triple re-assortments,

containing genes from human (HA, NA, and PB1), swine (NS, NP, and M), and avian (PB2 and PA) lineages (Islam and Rehman 2009).

Recently, scientists obtained and sequenced the 1918 H1N1 strain from a frozen corpse found in Alaska. The virus was reconstructed at the Centers for Disease Control and Prevention (CDC) laboratory in Atlanta and was found to be highly lethal when tested in mice; the virus was also found to be lethal to chicken embryos. This unique N1 neuraminidase is being studied in order to provide better insight into the N1 found in H5N1, the type responsible for avian influenza (also known as bird flu).(Derlet, 2006).

The pathologic and imaging findings with 2009 influenza A (H1N1) infection progressed to pneumonia shows diffused alveolar damages, and ARDS. Clinical management was further complicated by pulmonary interstitial emphysema and by subsequent development of pneumomediastinum, pneumothoraces, and subcutaneous emphysema. Whereas most 2009 influenza A (H1N1) infections in healthy individuals are self-limited, it is not entirely clear which pathologic factors caused the progression to fatal disease in this case and in other cases (Guo H. et al 2010).

1.4 Prevention, Vaccination and Treatment of H1N1 Influenza

Prevention

Influenza A (H1N1) is an infection caused by a virus and an influenza pandemic occurs when a novel influenza virus appears against which the human population has limited or no immunity, and which transmits efficiently from person to person, resulting in several simultaneous epidemics worldwide with the potential for considerable morbidity and mortality. With the increase in global transport and communications, as well as in urbanization and overcrowded conditions, epidemics caused by the new influenza virus are likely to quickly take hold around the world (WHO Pandemic influenza preparedness 2008). The impact of a novel pandemic influenza virus on refugee and displaced populations is expected to be severe. Risk factors for increased morbidity and mortality from pandemic influenza in these populations include:

- high prevalence of malnutrition;
- overcrowding, particularly in camp settings;
- poor links to national disease surveillance systems;
- high incidence/prevalence of other communicable diseases, e.g. acute respiratory illnesses,
- possible exclusion from national influenza preparedness and response activities;
- poor access to basic health-care services that will be accentuated by a pandemic;
- limited or no access to hospitals for supportive care and treatment of complications;
- logistic challenges resulting from often remote locations or ongoing active conflict;
- lack of adequate surveillance/early warning systems to detect cases or clusters;
- malaria, diarrhoeal diseases;

- lack of trained and equipped staff to investigate outbreaks and manage ill persons.

To avoid the flu from spreading the following care should be taken into account by everyone

- Wash your hands often with soap and water for 15 - 20 seconds, especially after you cough or sneeze. You may also use alcohol-based hand cleaners.
- Avoid close contact with sick people.
- Cover your nose and mouth with a tissue when you cough or sneeze. Throw the tissue away after using it.
- Avoid touching your eyes, nose, or mouth, to avoid getting infected by germs.
- Wear a facemask , if possible, when sharing common spaces with other household members
- If you do get sick, consider staying home from work or school for 7 days after your symptoms begin, or until you have been symptom-free for 24 hours, whichever is longer.

Prevention is better than cure. Influenza A (H1N1) virus spread worldwide and WHO has already declared the disease as alert level, one step short of full flagged pandemic. Therefore the preventive measures are required in place so that the virus does not spread.

Vaccines

Antiviral for influenza prophylaxis and treatment have been available for many years. With the recognition of the 2009 H1N1 influenza A strain, influenza antiviral have taken center stage as health care providers and pharmacists plan and implement a response for safe and effective patient care.

Vaccines are the best tool we have to prevent influenza. Health authorities and organizations recommend vaccination against seasonal and 2009 H1N1 flu to prevent the influenza this year. The seasonal flu vaccine is unlikely to provide protection against 2009 H1N1 influenza. The 2009 H1N1 vaccine is not intended to replace the seasonal flu vaccine – it is intended to be used along-side seasonal flu vaccine.

Some vaccines contain inactivated (or killed) viruses. These vaccines are given by injection into the upper arm for most people. In infants and younger children the thigh is the preferred site for the vaccine shot.

Another type of vaccine is made with live viruses, and it is administered by nasal spray. Both are protective against influenza.

In European Union, the following vaccines have received a positive recommendation from the Agency for use in the EU against the virus causing the current pandemic:

- Celvapan
- Focetria
- Humenza
- Pandemrix

The following table 1 gives an overview of vaccines against pandemic influenza A (H1N1) available in the European Union in October 2009 with their description.

Table 1: Overview of vaccines against Influenza A (H1N1)

Name Producer	Product description	Culture Medium	Haemagglutinin content	Adjuvant emulsion	Number of doses
Celvapan, Baxter	Inactivated, whole wild-type virus A/California/7/2009 (H1N1)v	Cell-culture	7.5 µg	None	All > 6 months 2 x 0.5 mL
Pandemrix, GSK	Inactivated, split-influenza, reassortant, A/California/7/2009 (H1N1)v-like strain	Egg-culture	3.75 µg (per adult dose)	AS03	>10 years 2 x 0.5 mL
			1.875 µg (per pediatric dose)		6 months – 9 years 2 x 0.25 mL
Focetria, Novartis	Inactivated, surface-influenza antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (H1N1)v-like strain	Egg-culture	7.5 µg	MF59	All > 6 months 2 x 0.5 mL
Fluval P, Omninvest	Inactivated, whole reassortant virus A/California/7/2009 (H1N1)v-like strain	Egg-culture	6 µg (per adult dose) 3 µg (per pediatric dose)	aluminium phosphate	Adults and adolescents > 12 years 1 x 0.5 mL Children 3-12 years 1 x 0.25 mL Children 6 months - 3 years* 1 x 0.25 mL (*decision pending)

Recommendations and guidance of various bodies concerning priority groups / target groups for specific pandemic vaccines against pandemic influenza A(H1N1) 2009 shown in table 2 of the next page:

Table 2 Recommendations and guidance of various health authorities against H1N1 vaccines

Key contents from the three organizations	World Health Organization strategic Advisory Group of Experts (7 July 2009)	United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practice (28 August 2009) Limited Supply	United States Centers for Disease Control and Prevention Advisory Committee on Immunization Practice (28 August 2009) Supply Option	European Union Health Security Committee (25 August 2009)
General considerations and criteria for selecting the priority and target groups	'SAGE suggests the following groups for consideration, noting that countries need to determine their order of priority based on country-specific conditions:'	'ACIP recommends that vaccination efforts should focus initially on persons in five target groups (below). In the event that vaccine availability is unable to meet initial demand, priority should be given to a subset of the five target groups (below).' No priority order between the categories below	ACIP recommends that vaccination efforts should focus initially on persons in five target groups (below).' No priority order between the categories below	'It should be stressed that it is within the mandate and responsibility of Member States to develop a vaccination strategy for influenza A(H1N1) 2009.' No priority order between the categories below
Priority and target groups	Healthcare workers - all countries should immunise their healthcare workers as a first priority to protect the essential health infrastructure	Healthcare workers and emergency medical services personnel - who have direct contact with patients or infectious material	Healthcare and emergency medical services personnel	Healthcare workers
	Pregnant women – since this group appears to be at increased risk for severe disease.	Pregnant women	Pregnant women	Pregnant women
	Individuals aged >6 months with one of several chronic medical conditions – in order to reduce morbidity and mortality	Children and adolescents aged 5—18 years who have medical conditions that put them at higher risk for influenza-related complications	Persons aged 25-64 years who have medical conditions that put them at higher risk for influenza-related complications.	All persons from 6 months of age up with underlying chronic conditions - increasing the risk for severe disease, starting with the ones who have a severe underlying condition (e.g. severe asthma, unstable coronary heart disease, uncompensated heart failure, etc.)
	Healthy young adults (aged >15 years and <49 years) to reduce morbidity and mortality	Persons who live with or provide care for infants aged <6 months	Persons who live with or provide care for infants aged < 6 months (e.g. parents, siblings and daycare providers)	
	Healthy children	Children aged 6 months to 4 years	Persons aged 6 months to 24 years	
	Healthy adults aged >49 years and <65 years to reduce morbidity and mortality			
	Healthy adults aged >65 years to reduce morbidity and mortality			

Immunization experts recommend a single dose of vaccine in adults and adolescents from 10 years of age and above, provided this use is consistent with regulatory authorities' indications. More study is advised on effective dosage regimens for immuno-suppressed persons for whom two doses of vaccine may be needed. Where national authorities have made children a priority for early vaccination, experts are advising one dose of vaccine to as many children as possible over the age of 6 months and younger than 10 years of age. Recommendations on numbers of dosages may need to be adapted rapidly as new data emerges (WHO Pandemic influenza preparedness 2008).

Treatment

The health care professionals should give all of their patient's guidance on how to recognize signs of progressive illness, and when to seek medical attention.

In general, antiviral treatment recommendations are:

- Patients who have severe or progressive illness should be treated with antiviral medication as soon as possible.
- People with mild symptoms but who are at higher risk for severe illness (e.g. pregnant women, infants and young children, and those with chronic lung problems) should start antiviral treatment as soon as possible.
- Antiviral treatment is not necessary for people have uncomplicated, or mild, illness and are not in a high risk group for severe illness.

Cautions should be taken before the start of Influenza A (H1N1) treatment in some special population such as pregnant and breastfeeding women, infants and very young children and adults over 65 years of age.

In hospital settings, health providers should monitor oxygen levels closely and supplement oxygen as needed, following guidelines. When pneumonia is present patients should be treated with both antiviral medication and antibiotics as early as possible.

Most people who get H1N1 flu will likely recover without needing medical care or special antiviral medications. It is necessary to be sure whether you should take antiviral medications to treat the H1N1 flu.

The special populations are on high risk and the health professional should take care of prescribing the antiviral drug in these groups which are on high risk for flu complications. The following people may be at high risk:

- Children younger than 5 years old, especially those younger than age 2
- Adults 65 years of age and older
- People with chronic lung (including asthma) or heart conditions (except high blood pressure), kidney, liver, neurologic, and neuromuscular conditions, blood disorders (including sickle cell disease), diabetes and other metabolic disorders and an immune system that does not work well, such as AIDS patients or cancer patients receiving chemotherapy

Other high risk people include:

- Pregnant women
- Anyone younger than age 19 receiving long-term aspirin therapy
- Residents of nursing homes and other chronic-care facilities

The following table 3 listed the antiviral agents for treatment of and Prophylaxis against Influenza

Table 3: Antiviral agents for the treatment of H1N1 (W.Paul Glezen 2008)

Drug	Formulation	Adult Dose Treatment	Adult Dose Prophylaxis	Common Side effect
Oseltamivir (Tamiflu, Roche)	75-mg capsule	1 capsule twice a day for 5 days	1 capsule/day	Nausea, vomiting
Zanamivir (Relenza, GlaxoSmithKline)*	5 mg per inhalation (Diskhaler)	2 inhalations twice a day for 5 days	2 inhalations/day	Bronchospasm
Amantadine (Symmetrel, Endo Pharmaceuticals)†‡	100-mg tablet	1 tablet twice a day for 3–5 days§	1 tablet/day§	Central nervous system effects (e.g., seizures in patients with seizure disorder, insomnia, anorexia)
Rimantadine (Flumadine, Forest Laboratories)†	100-mg tablet	1 tablet twice a day for 5 days	1 tablet/day	-
Ribavirin (Virazole, Valeant Pharmaceuticals)	60 mg/ml in reservoir	Aerosol for 2 hr every 8 hr for 5 days or as indicated	Not applicable	-

* Zanamivir is contraindicated for persons with reactive airway disease and for children younger than 7 years of age.
† This drug is not currently recommended for use in United States, because most influenza A (H3N2) viruses are resistant to them.
‡ Amantadine is contraindicated for persons with a seizure disorder.
§ The dose may be adjusted in the case of renal insufficiency.
¶ Ribavirin aerosol is licensed for treatment of respiratory syncytial virus; it is not currently approved by the Food and Drug Administration for influenza virus but has been used in hospitalized immunocompromised patients with influenza virus infections.

The older adamantanes, amantadine and rimantadine, are currently not recommended for use in the United States because almost all influenza A (H3N2) viruses are resistant to them, and they are not effective against influenza B viruses. When influenza A (H1N1) viruses predominate, however, these drugs may still be useful if they are used in combination with a neuraminidase inhibitor. An increasing proportion of influenza A (H1N1) virus is resistant to oseltamivir, the oral neuraminidase inhibitor, but not to zanamivir. Zanamivir is a neuraminidase inhibitor that is administered by active inhalation, a method that may not be practical for debilitated patients or for children younger than 7 years of age, and is contraindicated for those with reactive airway disease. Influenza B viruses have decreasing sensitivity to both of these neuraminidase inhibitors in Japan, where oseltamivir is used extensively (Glezen 2008).

The use of combination therapy may be considered. Ribavirin, a broad-spectrum antiviral drug delivered in aerosol form, which is licensed for use against respiratory syncytial virus infection, has been effective in clinical trials involving young adults with influenza A or B infection, although it is not currently approved for this indication. The use of ribavirin in combination with appropriate adamantanes or neuraminidase inhibitors has been proposed in immunocompromised patients with influenza, although this therapy has not been tested in controlled clinical trials (Glezen 2008)

2. Pandemic of H1N1 Influenza in 2009

A pandemic is a worldwide epidemic of infectious diseases caused by a novel virus that affects most or all age groups within a period of months. It may be viewed as hundreds of large epidemics occurring in many different countries at the same time. Further, flu pandemics exclude seasonal flu, unless the flu of the season is a pandemic. More recent pandemics include the HIV pandemic and the H1N1 virus flu pandemic.

A flu pandemic may occur if three conditions are met:

- a new influenza virus emerges (such as influenza H1N1);
- the virus infects humans (this has occurred with H1N1);
- the virus spreads efficiently and in a sustained manner from human to human.

When these prerequisites are present, the virus has become a human influenza virus, and humans will no longer require contact with swine or birds to be infected. The disease may spread widely and rapidly around the world as humans have no immunity against the new virus. It is influenza pandemic (WHO Pandemic influenza preparedness 2008).

Before the t H1N1 pandemic an influenza virus had never been identified as a cause of infections in people. Genetic analyses of this virus have shown that it originated from animal influenza viruses and is unrelated to the human seasonal H1N1 viruses that have been in general circulation among people since 1977. Antigenic analysis has shown that antibodies to the seasonal H1N1 virus do not protect against the pandemic H1N1 virus. However, other studies have shown that a significant percentage of people age 65 and older do have some immunity against the pandemic virus. This suggests that some people in the older age group may have some cross protection from exposure to viruses that have circulated in the more distant past.

After early outbreaks in North America in April 2009 the new influenza virus spread rapidly around the world. By the time WHO declared a pandemic in June 2009, a total of 74 countries and territories had reported laboratory confirmed infections. To date, most countries in the world have confirmed infections from the new virus.

North America

According to the WHO declaration and CDC report the first novel H1N1 patient in the United States was confirmed by laboratory testing at CDC on April 15, 2009. The second patient was confirmed on April 17, 2009. It was quickly determined that the virus was spreading from person-to-person. On April 22, CDC activated its Emergency Operations Center to better coordinate the public health response. On April 26, 2009, the United States Government declared a public health emergency and has been actively and aggressively implementing the nation's pandemic response plan.

By June 19, 2009, all 50 states in the United States, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands have reported novel H1N1 infection. While nationwide U.S. influenza surveillance systems indicate that overall influenza activity is decreasing in the country at this time, novel H1N1 outbreaks are ongoing in parts of the U.S., in some cases with intense activity.

Table 4: H1N1 cases occurred in North America between April 2009 and April 10, 2010.

2009 H1N1	Mid Level Range*	Estimated Range*
Cases		
0-17 years	~20 million	~14 million to ~28 million
18-64 years	~35 million	~25 million to ~52million
65 years and older	~6 million	~4 million to ~9 million
Cases Total	**~61 million**	**~43 million to ~89 million**
Hospitalization		
0-17 years	~87,000	~62,000 to ~128,000
18-64 years	~160,000	~114,000 to ~235,000
65 years and older	~27,000	~19,000 to ~40,000
Hospitalization total	**~274,000**	**~195,000 to ~403,000**
Deaths		
0-17 years	~1,280	~910 to ~1,888
18-64 years	~9,570	~6,800 to ~14,040
65 years and older	~1,620	~1,160 to ~2,380
Deaths total	**~12,470**	**~8,870 to ~18,300**

*Deaths have been rounded to the nearest ten. Hospitalizations have been rounded to the .nearest thousand and cases have been rounded to the nearest million. Exact numbers also are available on the CDC website.(http://www.cdc.gov/h1n1flu/)

The Numbers:

- CDC estimates that between 43 million and 89 million cases of 2009 H1N1 occurred between April 2009 and April 10, 2010. The mid-level in this range is about 61 million people infected with 2009 H1N1.
- CDC estimates that between about 195,000 and 403,000 2009 H1N1-related hospitalizations occurred between April 2009 and April 10, 2010. The mid-level in this range is about 274,000 H1N1-related hospitalizations.
- CDC estimates that between about 8,870 and 18,300 2009 H1N1-related deaths occurred between April 2009 and April 10, 2010. The mid-level in this range is about 12,470 2009 H1N1-related deaths.

Europe

In Europe, widespread and increasing transmission of pandemic influenza virus was observed across much of the continent but the most intense circulation of virus occurred in northern, eastern, and southeastern Europe. Transmission appears to have peaked in few countries of Western Europe including Iceland, Ireland, the UK (Northern Ireland), and Belgium after a period of sustained intense transmission. Further east, a number of countries reported sharp increases in the rates of ILI (Serbia, Moldova, Norway, Lithuania, Georgia) or ARI (Belarus, Bulgaria, Romania, and Ukraine). A moderate or greater impact on the healthcare system was reported in parts of northern and southeastern Europe. Greater than 20% of all sentinel respiratory specimens tested positive for influenza in at least 20 countries, with ≥ 50% of samples testing positive for influenza in Spain, Portugal, Estonia, Slovenia, Slovakia, Moldova, Bosnia and Herzegovina, Greece, Norway, Finland, Denmark, Belgium, Iceland, and Ireland. Over 99% of subtyped influenza A viruses in the Europe were pandemic H1N1 2009.

Table 5: Reported number of confirmed 2009 pandemic influenza A (H1N1) cases admitted to hospitals and intensive care, by country, as of 04 January 2010, 14.00 CEST in EU and EFTA countries.

Country (date of report)	Number of cases currently hospitalized	Comulative number of cases admitted in hospitals	Number of cases currently in intensive care	Comulative number of cases admitted to intensive care
Austria (17.12.)	172	-	-	-
Belgium (24.12.)	-	-	-	-
Bulgaria (13.12)	-	-	-	-
Cyprus(23.11)	-	-	-	6
Czech Republic (23.12.)	-	-	-	-
Denmark (30.12.)	-	-	2	70
Estonia (29.12.)	-	-	-	-
Finland (02.01.)	49	-	21	-
France (29.12.)	-	-	209	985
Germany (22.12.)	-	-	-	-
Greece (30.12.)	-	-	-	-
Hungary (30.12.)	-	-	-	-
Iceland (10.12.)	3	180	1	20
Ireland (31.12.)	149	1034	10	87
Italy (31.12.)	-	923	-	446
Latvia (17.12.)	-	-	-	-
Liechtenstein (30.12.)	-	-	-	-
Lithuania (21.12.)	-	-	-	-
Luxembourg (27.12.)	-	-	0	0
Malta (04.09.)	-	46	-	1
Netherlands (28.12.)	31	2156	6	209
Norway (23.12.)	5	1310	4	170
Poland (22.12.)	-	-	-	-
Portugal (31.12.)	58	-	20	-
Romania (31.12.)	-	-	-	-
Slovakia (22.12.)	51	260	18	94
Slovenia (17.12.)	76	-	-	-
Spain (30.12.)	-	-	-	-
Sweden (30.12.)	-	1286	-	-
Switzerland (31.12.)	7	430	-	77
United Kingdom (31.12.)	496	-	122	-

Source: ECDC Daily update, 2009 Influenza A (H1N1) Pandemic 4 Jan 2010

World wide

Worldwide the number of human cases of pandemic (H1N1) 2009 is increasing substantially, even in countries that have already been affected for some time. This

disease continues to evolve as new countries become affected, as community-level spread extends in already affected countries, and as information is shared globally. Many countries with widespread community transmission have moved to testing only samples of ill persons and have shifted surveillance efforts to monitoring and reporting of trends. This shift has been recommended by WHO, because as the pandemic progresses, monitoring trends in disease activity can be done better by following trends in illness cases rather than trying to test all ill persons, which can severely stress national resources. It remains a top priority to determine which groups of people are at highest risk of serious disease so steps to best to protect them can be taken.

Unlike typical seasonal flu patterns, the new virus caused high levels of summer infections in the northern hemisphere, and then even higher levels of activity during cooler months in this part of the world.

The new virus has also led to patterns of death and illness not normally seen in influenza infections. Most of the deaths caused by the pandemic influenza have occurred among younger people, including those who were otherwise healthy. Pregnant women, younger children and people of any age with certain chronic lung or other medical conditions appear to be at higher risk of more complicated or severe illness. Many of the severe cases have been due to viral pneumonia, which is harder to treat than bacterial pneumonias usually associated with seasonal influenza. Many of these patients have required intensive care.

Table 6: 2009 flu pandemic (number of confirmed deaths)

Area	Confirmed deaths
Worldwide (total)	**14,286**
European Union and EFTA	2,290
Other European countries and Central Asia	457
Mediterranean and Middle East	1,450
Africa	116
North America	3,642
Central America and Caribbean	237
South America	3,190
Northeast Asia and South Asia	2,294
Southeast Asia	393
Australia and Pacific	217

Source: "ECDC Daily Update – Pandemic (H1N1) 2009 – 18 January 2010". European Centre for Disease Prevention and Control.
Note: The ratio of confirmed deaths to total deaths due to the pandemic is unknown

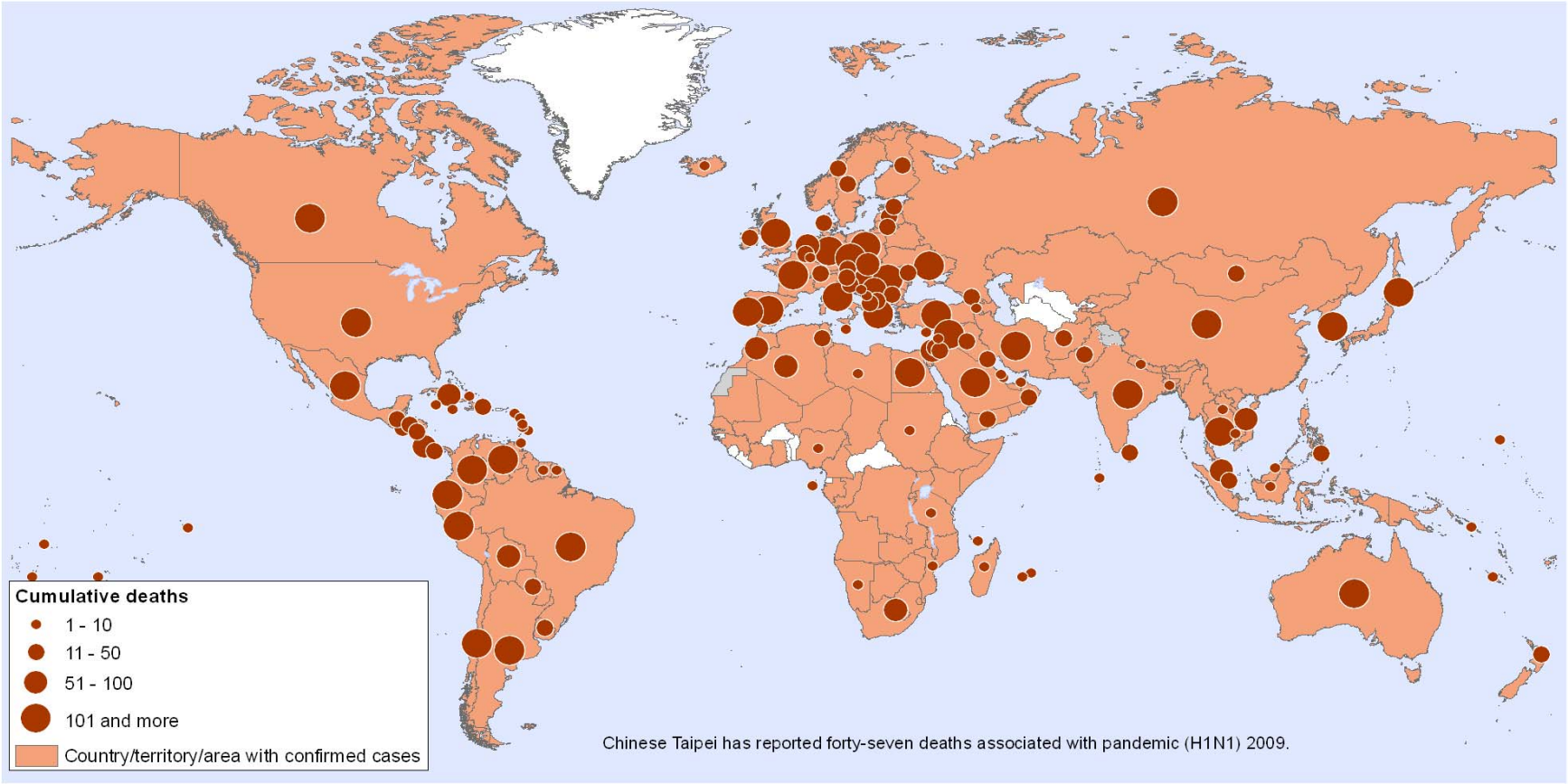
In Central and Western Asia, increasing diseases activity and pandemic influenza virus isolations continues to be reported in several countries. A high intensity of respiratory diseases with increasing trend was reported in Kazakhstan. Recent increases in rates of ILI or ARI have been observed in Uzbekistan and in parts of Afghanistan (particularly in the capital region and in southern and northeastern provinces). In Israel, sharp increases in rates of ILI and pandemic virus detections have been reported in recent weeks.

In East Asia, influenza transmission remains active. Intense influenza activity continues to be observed in Mongolia with a severe impact on the healthcare system; however, disease activity may have recently peaked in the past 1-2 weeks. In Japan, influenza activity remains elevated but stable nationally, and may be decreasing slightly in populated urban areas. A small number of seasonal H3N2 and H1N1 influenza viruses continue to be detected in China and South East Asia, though the proportion of seasonal viruses is declining in relation to the proportion of pandemic influenza H1N1.

An integrated global alert and response system for epidemics and other public health emergencies based on strong national public health systems and capacity and an effective international system for coordinated response.

The map below display information on the qualitative indicators reported. Information is available for approximately 60 countries each week. Implementation of this monitoring system is ongoing and completeness of reporting is expected to increase over time.

Figure 3. Countries, territories and areas with lab confirmed cases and number of deaths as reported by WHO (Pandemic H1N1 2009)



A description of WHO pandemic monitoring and surveillance objectives and methods can be found in the updated interim WHO guidance for the surveillance of human infection with pandemic (H1N1) virus (WHO Guidance on Global surveillance 2009).

2.1 Role of European Medicine Agency

The European Medicines Agency is responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. The website of EMA provides news updates to the H1N1 influenza pandemic. The website also provides information about the role and activities of the EMA in relation to the pandemic and, in addition, outlines how medicines being used in the European Union (EU) during the pandemic were developed and approved.

The Agency's specific responsibilities in relation to the current H1N1 influenza ('swine flu') pandemic are to:

- review data submitted as part of the procedure for authorisation of pandemic-influenza vaccines or antiviral medicines in all European Union (EU) Member States (centralised procedure);
- continuously monitor the safety of centrally authorised pandemic-influenza vaccines and antivirals, and to recommend changes to the use or authorisation status of these medicines, where necessary;
- monitor information received from EU Member States about the safety of antivirals authorised in individual countries;
- liaise with European partners, including the European Commission, the competent authorities of the Member States, sister agencies such as the European Centre for Disease Prevention and Control, and international partners, such as the World Health Organization and regulatory bodies of non-EU countries, to ensure timely exchange of information and coordination of activities relating to the ongoing pandemic;
- communicate relevant information about these activities to the public, healthcare professionals and the media.

The European Medicines Agency has developed a pandemic influenza crisis-management plan, which allows the Agency to respond rapidly and efficiently to the challenges of a potential outbreak of pandemic influenza (EMEA/214301/2006).

The primary objective of the crisis management plan is to define and implement the EMEA policy and, consequently the strategy for the rapid and efficient handling of

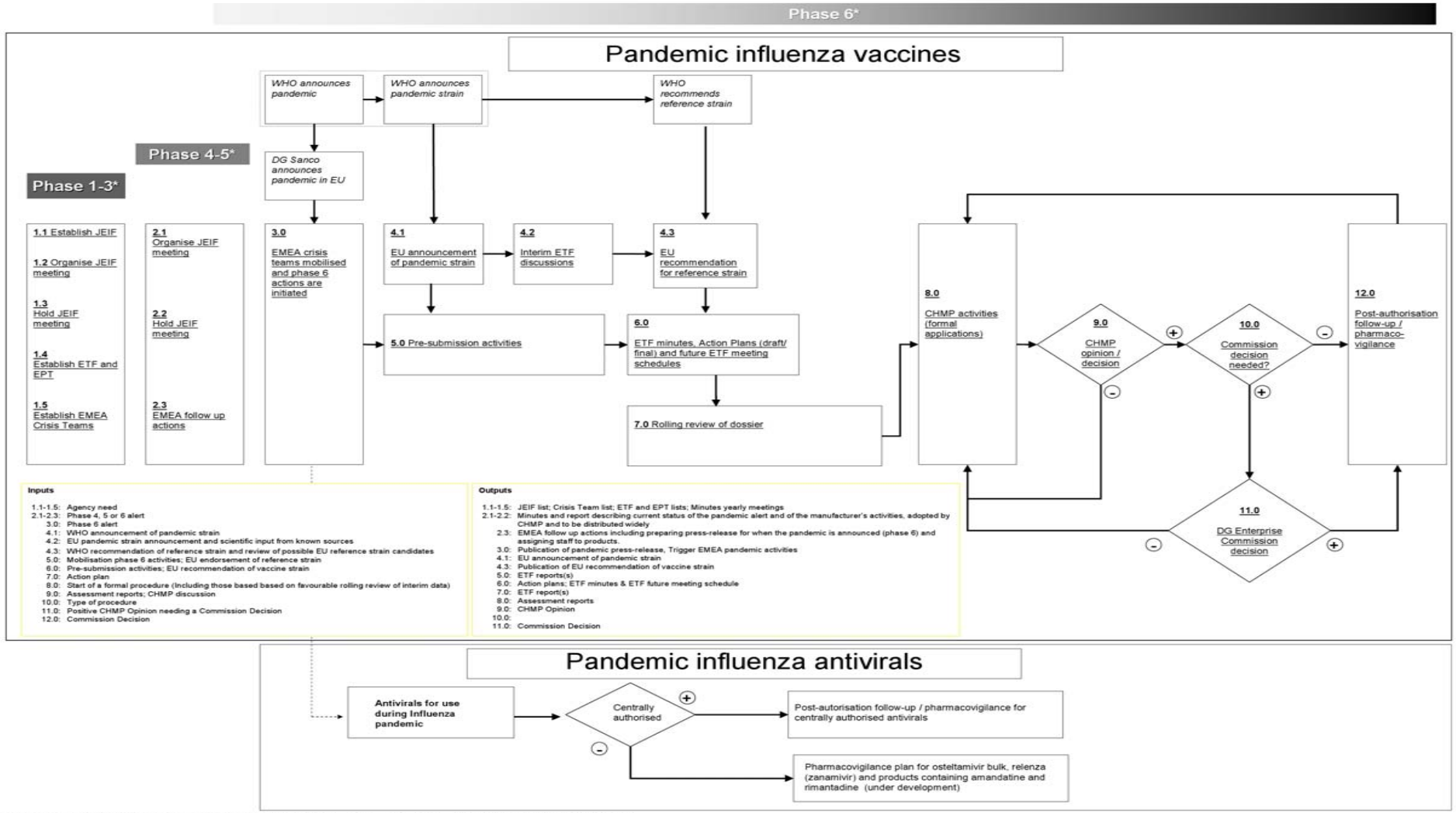
actions required by the EMEA Secretariat related to pandemic influenza vaccines and antivirals, in liaison with the CHMP, (Co-) Rapporteurs, competent authorities of the Member States, the European Commission (DG Sanco and DG Enterprise), ECDC and the Marketing Authorisation Holders, or Applicants.

The key objectives of the EMEA pandemic influenza crises plan are to handle the crises situation in case of influenza pandemic and integration of the various EMEA activities to deal with the crises. In order to deal successfully with crises, the crises teams and CHMP expert groups (EMEA task force and evaluation project teams) have been created.

The EMEA Task Force is established specifically to deal with pre- and post authorisation activities related to pandemic influenza vaccines, and are established during the Pandemic Alert Period (at the latest in Phase 4). The Evaluation project teams will be involved in the fast track assessment of the pandemic variation as described in the work instructions. The EMEA will provide support to the activities of the EMEA Task Force as described in the work instructions.

An EMEA pandemic influenza crisis communications plan has been developed. The plan describes a set of actions that help the Agency to respond to the communication's need arising from the outbreak of a pandemic. The specific work instructions to this EMEA Pandemic Influenza Crisis Management Plan include details of the EMEA communications during this crisis as below in the process map.

Figure 4 EMEA Pandemic Influenza process map and associated work instructions and SOPs dealing with the EMEA responsibilities for Influenza Pandemic Vaccines and Antivirals.



* Phases as defined in the WHO Global influenza preparedness plan (doc. WHO/CDS/CSR/GIP/2005.5)

Source: EMA website http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/11/WC500015462.pdf

2.2 Role of U. S. Food and Drug Administration

The FDA plays a vital role on the team led by the U.S. Department of Health and Human Services in the fight against the 2009 H1N1 virus. The agency works closely with the Centers for Disease Control and Prevention, National Institutes of Health, other federal government agencies, and global partners such as the World Health Organization and foreign governments to protect public health during the 2009 H1N1 pandemic.

The FDA has approved 2 classes of influenza drugs: adamantanes and neuraminidase inhibitors. The ada-mantane class has been available since 1976, when amantadine was approved for the prevention and treatment of influenza A and B virus infections. Because 2009 H1N1 influenza virus is resistant to adamantanes, only the neuraminidase inhibitors, oseltamivir and zanamivir, are currently recommended as first-line treatments (see table 1)

Table 7: First line Antiviral treatments for 2009 H1N1 Influenza (Valenti 2010)

Antiviral	Influenza A	Influenza B	Prophylaxis	Treatment
Osteltamivir	Yes	Yes	Yes; age>1 Year	Yes; age>1 Year
Zanamivir	Yes	Yes	Yes; age>5 Year	Yes; age>7 Year

To prepare for an influenza pandemic, the Food and Drug Administration (FDA) developed FDA Pandemic Influenza Preparedness Strategic Plan. The FDA Pandemic Influenza Preparedness Strategic Plan coordinates with and complements the President's National Strategy for Pandemic Influenza, the Implementation Plan for the National Strategy for Pandemic Influenza, and the Department of Health and Human Service's (HHS's) Pandemic Influenza Plan and the HHS Pandemic Influenza Implementation Plan.

To increase the Nation's preparedness for an influenza pandemic, in November 2005, the (then Acting) Commissioner for Food and Drugs, Andrew von Eschenbach, M.D., established an FDA Task Force on Pandemic Influenza Preparedness to set into operation FDA's participation in the President's National Strategy for Pandemic Influenza and the HHS Pandemic Influenza Plan.

The following principles guided FDA development of this plan:

- Good coordination is required among Federal departments and agencies, State, local, and tribal governments, foreign governments, and private sector parties (such as industry, healthcare professionals, and academia).
- Communication is essential to minimizing the health effects of an influenza outbreak and for preparing for such an outbreak.
- Domestic vaccine production capacity sufficient to provide vaccines for the entire United States population is critical, as is the development of a vaccine against each circulating influenza virus with pandemic potential and, ideally, the development of a vaccine that confers cross-protective immunity.
- Development of anti-viral drug products, other biologic products, and diagnostics, PPE, and other devices is important in preparing for, and responding to, an influenza outbreak.
- Protection of human food and animal feed will include identifying food and feed at risk of AI contamination and identifying methods to inactivate influenza viruses.
- Protecting consumers from fraudulent or counterfeit products is also important in preparing for an influenza outbreak.
- Ensuring that our workforce has appropriate administrative and technological support and the best available public health information to remain effective throughout a pandemic influenza period is necessary.

Pandemic Influenza Preparedness Strategic Plan of FDA provides a solid foundation for a cross-cutting initiative involving many of our centers and offices. The principal centers and offices, and their roles, are as follows:

- The Center for Biologics Evaluation and Research (CBER) leads the Task Force's Vaccine and Other Biologics Development, Production, and Regulatory Review Subgroup
- The Center for Drug Evaluation and Research (CDER) leads the Task Force's Anti-Viral Drug Development, Production, and Regulatory Review Subgroup
- The Center for Devices and Radiological Health (CDRH) leads the Task Force's Device Development, Production, and Regulatory Review Subgroup

- The Center for Food Safety and Applied Nutrition (CFSAN) and the Center for Veterinary Medicine (CVM) share the lead roles in the Task Force's Food and Feed Safety Subgroup
- Coordinating food and feed safety activities and plans with Federal and State agencies, industry, and others;
- The Office of Crisis Management (OCM)/Office of Emergency Operations manages FDA's Emergency Operations Center (EOC) which will coordinate our emergency response activities for an influenza pandemic. As with all emergency response efforts, our EOC will serve as FDA's focal point for communication and coordination activities with the Secretary's Operations Center (SOC) and HHS agencies. The EOC uses the Incident Command Structure to maintain situational awareness, enhance collaboration and coordination, communicate critical information, and make and implement decisions during emergencies. OCM developed an FDA Pandemic Influenza Emergency Response Plan which further identifies the EOC's role and responsibilities and its relationships with other FDA, HHS, and government entities during an influenza pandemic.
- OCM and the Office of External Relations (OER) share lead roles for the Task Force's Emergency Preparedness, Response, and Communication Subgroup
- The Office of Regulatory Affairs (ORA) leads the Task Force's Enforcement Subgroup. Compliance experts, including members from ORA and OGC, compose the Task Force's Enforcement Subgroup and are responsible for identifying enforcement roles and responsibilities, including the implementation of enforcement actions to curtail illegal activity, such as the marketing of counterfeit pandemic influenza anti-viral drug products, vaccines, devices, or other therapeutics. However, the Enforcement Subgroup will not address compliance issues associated with legally-marketed or legitimate pandemic influenza products; such issues will be considered by the vaccine, anti-viral and diagnostics subgroups (mentioned in the preceding bullets).
- The Office of International Programs (OIP) leads, manages, and coordinates FDA's international pandemic influenza preparedness activities and also coordinates our international activities with the Office of the Secretary, HHS, and other Federal departments, as necessary.

2.3 Role of World Health Organization

On June 11, 2009 the Director-General of the WHO, declared the Swine Flu a pandemic. That's the highest phase - phase 6. The declaration of phase six means that emergency procedures are put into motion which bypass established systems designed to safeguard the public health. The result of this is described in part six of this DeepJournal series on the Swine Flu. Conclusion: the vaccine is being tested while being administered to the public. The definition of what a pandemic is, is therefore of great import.

WHO continues to help all Member States respond to pandemic influenza. The goal is to reduce the impact of the pandemic on society. A primary focus is support to health systems in countries with less resources to help them prevent, detect, treat and mitigate cases of illness associated with this virus.

To help countries protect people from developing severe disease from pandemic influenza H1N1 infection, the World Health Organization (WHO) is coordinating the distribution of donated pandemic influenza vaccine to eligible countries.

Several activities as a biggest Health organization of World have been performed by WHO and continuing monitoring and preparedness of outbreak of communicable diseases. Some of major activities are described as follows:

Surveillance activities (Information about WHO regional influenza surveillance)

WHO conducts surveillance of seasonal influenza in the Region and publishes a weekly regional bulletin on seasonal influenza. The bulletin contains epidemiological and virological data from the countries in the Region that report their influenza surveillance data to WHO. The data are collected by clinicians' networks and laboratory networks, consisting primarily of WHO-recognized national influenza centres (NICs).

Member States collect data on:

- the epidemiology and virology of seasonal epidemics;
- outbreaks of avian influenza in animals and humans; and
- outbreaks of other influenza viruses with pandemic potential.

The regional surveillance network also participates in the WHO Global Influenza Surveillance Network (GISN), mainly through the 50 NICs in 39 European countries. Data and viruses are submitted through the NICs and the surveillance focal points to one of the four global WHO collaborating centres for reference and research on influenza (for the European Region, the centre is located in the United Kingdom). This enables WHO to recommend the composition of the influenza vaccine for the following season, which it does twice a year, for the northern and southern hemispheres. In addition, the collaborating centres determine patterns of antiviral susceptibility of circulating strains and update reagents. GISN also acts as a global alert mechanism for the appearance of influenza viruses with pandemic potential.

Technical advisory consultation on oseltamivir resistant influenza viruses (Organized by the European Centre for Disease Prevention and Control and WHO/Europe)

The prevalence of high-level oseltamivir-resistant influenza A(H1N1) virus was first detected in European countries by the European Union's European surveillance network for vigilance against viral resistance (VIRGIL), the WHO collaborating centre in London and the WHO/Europe national influenza centres. Subsequently, the viruses were found in many countries across the rest of the world through the Global Influenza Surveillance Network.

The European Centre for Disease Prevention and Control (ECDC) and WHO/Europe convened a global consultation of specialists to review the situation and discuss the public health implications of the phenomenon.

A global meeting of health professional has been held to review the situation and discuss the public health implication of the phenomenon. The specialists addressed what was known about the virological, epidemiological and clinical features of infections caused by these viruses, their genetic and biologic properties and the options for prevention and treatment. The participants agreed on the public health questions that needed to be addressed – questions that will shape the future research agenda – and a meeting was planned to develop protocols to improve clinical data collection on infections caused by these and other novel viruses.

Workshops and training (On pandemic preparedness, laboratory work, surveillance and avian influenza)

A pandemic influenza preparedness meetings held on regular basis in each WHO regional and sub regional offices all around the world.

Pandemic preparedness assessments (Information and reports on assessment visits)

Since 2005, WHO/Europe, with the European Centre for Disease Prevention and Control (ECDC) and the European Commission (EC), has made pandemic preparedness assessments of European countries using the methodology described by ECDC. It plans and carries out assessment missions jointly with Member States.

The aims of these missions are:

- to establish the current level of preparedness;
- to provide expertise on issues identified by the Member State; and
- to guide further activities.

Assessments have now been performed in 40 Member States. ECDC published a status report based on assessments in the European Union/European Economic Area (EU/EEA) countries in 2007.

3. Marketing Authorization for H1N1 Vaccines

3.1 Europe

Vaccines are universally regarded as the most important medical intervention for preventing influenza and reducing its health consequences during a pandemic. Influenza vaccines are used to immunize an influenza virus that is circulating in population. They are one of the most effective means for preventing people from becoming infected and, thus, for controlling the spread of the disease.

In a pandemic situation, it is important to make suitable vaccines available quickly and in large quantities. However, as with all medicines, vaccines still need to be assessed before they can be authorised for use, to ensure that their benefits outweigh any risks associated with their use.

Different procedures have been put in place in the European Union to speed up the availability of vaccines that can be used to protect the population against pandemic influenza. These procedures, managed by the European Medicines Agency, allow an influenza vaccine to be authorised more quickly than the 18 to 24 months usually required for the authorisation of a medicine in the EU.

The two main procedures for authorisation of pandemic influenza vaccines are:

- the 'mock-up procedure', which allows a vaccine to be developed and authorised in advance of a pandemic, based on information generated with a virus strain that could potentially cause a pandemic. Once the actual virus strain causing the pandemic is identified, the manufacturer can include this strain in the mock-up vaccine and apply for it to be authorised as a 'final' pandemic vaccine;
- the 'emergency procedure', which allows for fast-track approval of a new vaccine developed after a pandemic has already been declared. Authorisation of these pandemic vaccines is quicker than for a normal vaccine, as the information submitted by the manufacturer is assessed in an accelerated timeframe (around 70 days instead of 210 days).

A third procedure allows vaccines authorised for use against non-pandemic, 'seasonal flu' to be modified so that they afford protection against pandemic flu.

Special procedures are also in place to monitor the effectiveness and safety of authorised pandemic vaccines once they are being used in the European population.

The mock-up authorisation procedure

A mock-up vaccine contains an influenza virus from a subtype such as H5 to have pandemic potential. Pharmaceutical companies can gain authorisation for mock-up vaccines after they have carried out full studies looking into how the vaccine is made (its 'quality'), as well as its safety and its immunogenicity (its ability to trigger the production of antibodies against the virus) (www.ema.europa.eu).

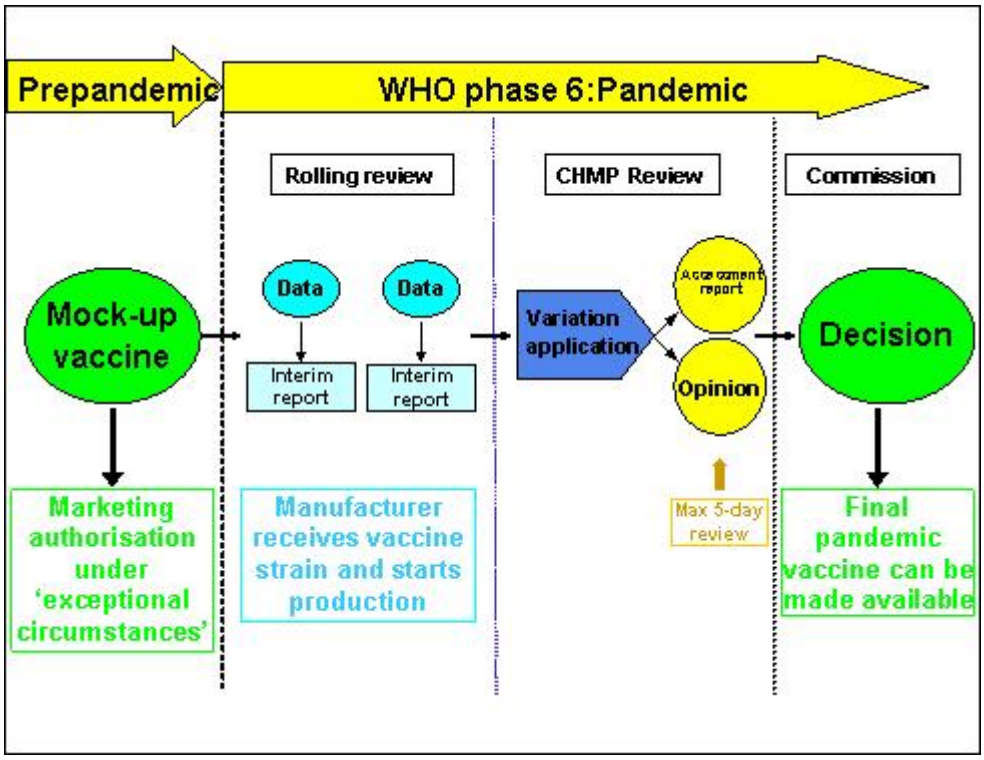
To gain authorisation for a mock-up vaccine, the company needs to submit the information from its studies to the European Medicines Agency. In particular, the mock-up vaccine must show that it brings about an appropriate level of protection: according to criteria laid down by the Agency, at least 70% of the people in which the vaccine is studied must develop protective levels of antibodies for the vaccine to be approvable. If the vaccine's benefits are judged to outweigh its risks, the vaccine will be authorised, but this authorisation will be under 'Exceptional Circumstances'. This is because full information on the final vaccine's safety and effectiveness during a pandemic will only be available once a pandemic has started and the flu virus responsible has been included in the vaccine (www.ema.europa.eu).

Because of the emergency nature of flu pandemics, the amount of information collected on the final pandemic vaccine is limited at the time of authorisation. Although a company needs to demonstrate that that its vaccine can be manufactured appropriately with the new flu virus strain, only preliminary data from clinical studies of the final vaccine may be available at the time of authorisation of the final vaccine. Further testing of the vaccine's safety and effectiveness will continue to take place after administration of the vaccine has begun. The CHMP will continue to evaluate all of the data generated from the ongoing trials once the vaccine is being used (www.ema.europa.eu).

To confirm that the final vaccines are as safe and effective as expected, their effects will be closely monitored after they have been authorised. This is especially important for certain groups of patients for whom limited data are expected to be available at

the time of the final pandemic vaccine's authorisation, such as children and pregnant women.

Figure 5 Authorisation of pandemic flu vaccines using the 'mock-up' approach



Source EMA: Vaccines authorisation procedures (www.ema.europa.eu).

The emergency authorisation procedure

In the emergency procedure, companies utilise the 'rolling review' process, supplying data on vaccines under development as they become available, rather than waiting until they have collected the full dossier of data. This allows the CHMP to evaluate the data in real time, so that the final vaccine can be approved as quickly as possible.

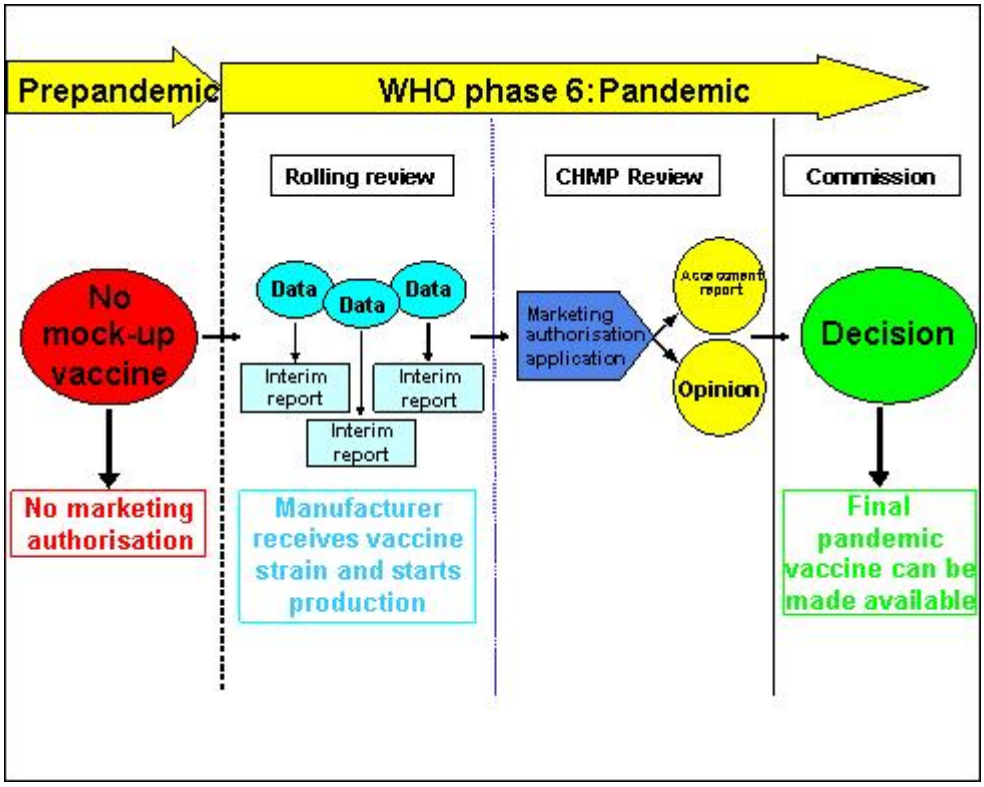
Once enough data has been gathered to show that the vaccine's benefits outweigh its risks, the company is obliged to make a formal application to the European Medicines Agency, so that the vaccine can be authorised for use. The CHMP then carries out an accelerated assessment of the full dossier of information, issuing an opinion after around 70 days. This opinion is transmitted to the European Commission, which is expected to take around 25 to 45 days to issue a decision. The vaccine can then be made available for use.

Vaccines authorised using the emergency procedure are given 'Conditional Approval'. This means that, although the vaccine's benefits outweigh its risks, the

data used to support the authorisation are not yet comprehensive. The authorisation is granted on the condition that the company will supply the additional information requested, such as the results of further studies, once the vaccine is on the market.

Once they have been authorised, further steps are taken to monitor the safety and effectiveness of pandemic flu vaccines.

Figure 6 Authorisation of pandemic flu vaccines using the 'emergency' procedure



Source EMEA: Vaccines authorisation procedures (www.ema.europa.eu).

Authorised Vaccines

Five vaccines that have benefited from these procedures, and which will thus be available for use in the current H1N1 influenza pandemic, are:

1. Arepanrix, which was recommended on 20 January 2010 by the European Medicines Agency for an EU-wide marketing authorisation.
2. Celvapan, which was recommended on 1 October 2009 by the European Medicines Agency for an EU-wide marketing authorisation.
3. Focetria, which was recommended on 24 September 2009 by the European Medicines Agency for an EU-wide marketing authorisation.

4. Humenza which was recommended on 18 February 2010 by the European Medicines Agency for an EU-wide marketing authorisation.
5. Pandemrix, which was recommended on 24 September 2009 by the European Medicines Agency for an EU-wide marketing authorisation.

One other vaccine, Daronrix, has been authorised as a 'mock up' vaccine for potential use during an influenza pandemic, but has not yet been approved for use in the current H1N1 pandemic.

The following specific regulatory guidelines are available on EMA website for development and approval of pandemic influenza vaccines:

- Guideline on submission of marketing authorisation applications for pandemic influenza vaccines through the centralised procedure
- Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (revision)
- Standard paediatric investigation plan for non-adjuvanted or adjuvanted pandemic influenza vaccines during a pandemic
- Guideline on influenza vaccines prepared from viruses with the potential to cause a pandemic and intended for use outside of the core dossier context
- Core SPC for pandemic influenza vaccines

3.2 United States

All initial licences of pandemic influenza should be submitted as Biologics License Application (BLA) in accordance with either the provisions in 21 CFR 601.2 or the accelerated approval provisions in 21 CFR Part 601 Subpart E.

Biological products are licensed under the authority of section 351 of the Public Health Service Act (PHS Act) (42 U.S.C. 262). Under section 351, BLAs are approved only upon a showing that the product is "safe, pure and potent," and that the manufacturing facility meets standards designed to assure that the biological product "continues to be safe, pure, and potent." In previously issued guidance entitled, "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products" dated May 1998 (section II.A.), FDA stated, "*Potency* has long been interpreted to include effectiveness (21 CFR 600.3(s)). In 1972, FDA initiated a review of the safety and effectiveness of all previously licensed biologics. The Agency stated then that proof of effectiveness would consist of controlled clinical investigations as defined in the provision for 'adequate and well-controlled studies' for new drugs (21 CFR 314.126), unless waived as not applicable to the biological product or essential to the validity of the study when an alternative method is adequate to substantiate effectiveness (21 CFR 601.25(d)(2))."

According to Giudance of Industry published on FDA website the following different authorizations procedures of pandemic vaccine can be followed according to rules and regulations applied for obtaining the license of vaccines (FDA Guidance for Industry 2007):

Approval of a Pandemic Influenza Vaccine for Manufacturers of a U.S. Licensed Seasonal Inactivated Influenza Vaccine where the Process for Manufacturing the Pandemic Influenza Vaccine is the Same

If a manufacturer holds a U.S. license for an approved BLA for a seasonal inactivated influenza vaccine under either the provisions in 21 CFR 601.2 or the accelerated approval provisions with the vaccine's clinical benefit having been confirmed in a postmarketing study, and the manufacturing process used for the production of the pandemic vaccine is the same as for the licensed product, clinical immunogenicity trials would be needed to determine the appropriate dose and regimen of a pandemic influenza vaccine candidate. These trials should also include an assessment of

safety. Sponsors can expect that authorities will seek their involvement on plans to collect additional effectiveness and safety information when the vaccine is used (discussed below).

All submissions for the initial licensure of a pandemic influenza vaccine should be submitted as BLAs, which will provide for a trade name and labeling specific to the pandemic vaccine. For sponsors with existing licensed seasonal inactivated influenza vaccines who intend to file a BLA for a pandemic influenza vaccine that utilizes the same manufacturing process, we would expect that the BLA would reference the original BLA, including the nonclinical and chemistry, manufacturing, and controls (CMC) data in their original BLA.

Approval of a Pandemic Influenza Vaccine for Manufacturers of a U.S. Licensed Seasonal Live Attenuated Influenza Vaccine where the Process for Manufacturing the Pandemic Influenza Vaccine is the Same

As for inactivated pandemic influenza vaccines discussed in above, clinical trials to determine the appropriate dose and regimen of a live attenuated pandemic influenza vaccine would be needed and should include an assessment of immunogenicity and safety. Sponsors can expect FDA to seek their involvement in plans to collect additional effectiveness and safety information, such as through epidemiological studies, should a pandemic influenza situation be declared or if use occurs in persons at high risk of exposure to the virus.

Sponsors with licensed seasonal live attenuated influenza vaccines who intend to seek licensure for a pandemic influenza vaccine that utilizes the same manufacturing process should submit a new BLA, which will provide for a trade name and labeling specific to the pandemic vaccine. We would expect that the new BLA would reference the BLA for the seasonal vaccine, including the nonclinical and CMC data in their original BLA.

Accelerated Approval of a Pandemic Influenza Vaccine Manufactured by a Process not U.S. Licensed

Accelerated approval may be granted for certain biological products such as pandemic influenza vaccines that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments. For pandemic vaccines, the accelerated approval pathway will be available at least until adequate supplies of

such vaccines are available. (See Accelerated Approval of Biological Products for Serious or Life Threatening Illnesses (21 CFR 601 Subpart E)).

Such an approval will be based on adequate and well-controlled clinical trials establishing that the biological product has an effect on a surrogate endpoint that is reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit (21 CFR 601.41). Approval under this section will be subject to the requirement that the sponsor study the biological product further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit (21 CFR 601.41).

Postmarketing studies must also be adequate and well-controlled and should be conducted with due diligence (21 CFR 601.41). The protocols for these studies should be submitted with the original BLA. Marketing approval for biological products approved under these regulations may be withdrawn, for example, if the postmarketing clinical study fails to verify clinical benefit or the sponsor fails to perform the required postmarketing study with due diligence (21 CFR 601.43(a)(1) and (2)).

For pandemic influenza vaccines, the immune response elicited following receipt of the vaccine may serve as a surrogate endpoint that is likely to predict clinical benefit, that is, prevention of influenza illness and its complications. Influenza virus hemagglutinins, present on viral surfaces, are important for cell-receptor binding. The immune response to these hemagglutinins as measured by the presence of serum HI antibodies is an important protective component following vaccination and/or infection.

To date, prospectively designed studies to evaluate the effectiveness of influenza vaccines have not identified a specific HI antibody titer associated with protection against culture-confirmed influenza illness. Some studies of influenza infection, including human challenge studies following vaccination, have suggested that HI antibody titers ranging from 1:15 to 1:65 may be associated with protection from illness in 50% of subjects and that protection from illness is increased with higher titers. Evaluations of seroconversion and GMT have been used as measures of vaccine activity (FDA Guidance for Industry 2007).

For the purposes of accelerated approval of inactivated pandemic influenza vaccines, the HI antibody response may be an acceptable surrogate marker of activity that is

reasonably likely to predict clinical benefit. Currently immune response data following receipt of live attenuated influenza vaccines are limited. Accelerated approval of new live attenuated pandemic influenza vaccines will depend on the identification of an immune surrogate that is reasonably likely to predict clinical benefit.

To be considered for accelerated approval, a BLA for a pandemic inactivated influenza vaccine should include results from one or more adequate and well-controlled studies designed to meet immunogenicity endpoints and a commitment to conduct confirmatory postmarketing studies. In addition, all sponsors who seek licensure of a pandemic influenza vaccine through accelerated approval should expect FDA to seek their involvement in working with FDA and other governmental agencies on plans to collect additional effectiveness and safety information, such as through epidemiological studies, when the vaccine is used. Since each vaccine candidate is unique (e.g., particular product characteristics, manufacturing process, etc.), we recommend that you discuss with CBER early in development the adequacy of the manufacturing methods and product testing and the extent of the clinical data needed to license your candidate vaccine (FDA Guidance for Industry 2007).

Influenza A (H1N1) 2009 Monovalent

FDA approved these vaccines as a strain change to each manufacturer's seasonal influenza vaccine. There is considerable experience with seasonal influenza vaccine development and production and influenza vaccines produced by this technology have a long and successful track record of safety and effectiveness in the United States. The Influenza A (H1N1) 2009 Monovalent vaccines will undergo the usual testing and lot release procedures that are in place for seasonal influenza vaccines.

Injectable Vaccines

- Influenza A (H1N1) 2009 Monovalent Vaccine (CSL Limited)
- Influenza A (H1N1) 2009 Monovalent Vaccine (ID Biomedical Corporation of Quebec)
- Influenza A (H1N1) 2009 Monovalent Vaccine (Novartis Vaccines and Diagnostics Limited)
- Influenza A (H1N1) 2009 Monovalent Vaccine (Sanofi Pasteur, Inc.)

Intranasal Vaccine

- Influenza A (H1N1) 2009 Monovalent Vaccine (MedImmune LLC)

4. Pharmacovigilance of H1N1 Vaccines

Vaccines are considered the safest tools of modern medicine that help in protecting disease by inducing immunity. Since majority of vaccines are administered to children as well as healthy population, a strict safety supervision of vaccines is essential. Therefore the Pharmacovigilance plan and activities of vaccines must be excellent to make vaccine strategy acceptable, after their marketing. So naturally a very high standard of safety is to be expected.

The absence of data can generate fear in the general population that is broadcast by anti-vaccination lobby. Vaccines are not separate health products but anti-infectious medicines administered for the large part prophylactically and for which the effect is immunological and not pharmacological. They should be evaluated by the usual methods of clinical pharmacology and pharmacovigilance, taking into account certain specificities (mechanism of action, manufacture, frequent administration to healthy subjects, particular recommendations, etc.) (Le Louvet et.al. 2007).

In addition to postmarketing surveillance data, national authorities and organisations are relying on the results of special research and clinical studies and other data provided by countries directly through frequent expert teleconferences on clinical, virological and epidemiological aspects of the pandemic, to gain a global overview of the evolving situation.

Thus pharmacoepidemiology studies are necessary to confirm the alerts identified by spontaneous reporting. ADRs can be specific, related to the antigen of an attenuated alive virus vaccine (lymphocyte meningitis after anti-mumps vaccine) or non-specific, related to a component different from the antigen (aluminium hydroxide involved in the "macrophagic myofasciitis", allergic reactions to neomycin, latex, egg or gelatine) (Autret-Leca et.al. 2006).

Although the pharmacovigilance of vaccines is important, yet it is given much less attention. There rae no different systems and regulatory guidelines in most of the countries for this activity. Lot of research is going on for vaccine development in infectious disease like HIV, Malaria, H1N1 etc that have a high patient load. For the last two decades, pharmacovigilance has been gaining an increasing attention. It is now, high time that vaccines also receive their due attention (Budhiraja 2010).

The goal of vaccine pharmacovigilance is the early detection and timely response to adverse events following immunization, in order to minimize negative effects to the health of individuals and lessen the potential negative impact on immunization of population.

Planning for the prospect of pandemic influenza is one of the most effective steps to mitigate the impacts of such an event. Moreover, preparing and maintaining the pharmacovigilance plan and activities for the influenza pandemic requires support and collaboration from multiple partners at the state, national, and international levels. As limited safety data on novel H1N1 influenza vaccines are currently available, additional pharmacovigilance activities are essential to monitor and assess their safety with widespread use.

Pharmacovigilance Plan

The CHMP Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (EMA, Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application CPMP/VEG/4717/03) specifies that, as part of the post-approval commitments, Marketing Authorisation Holders (MAHs) should have protocols in place at the time of authorisation of the mock-up vaccine to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field (i.e. during the pandemic), since there will be only limited immunogenicity and safety data and no efficacy data at the time of licensing.

CHMP has published a guideline which provides recommendations on how routine and additional pharmacovigilance activities should be conducted during the pandemic period, as well as the preparatory activities to be undertaken in the pre-pandemic period to achieve a high level of preparedness (Annex 1 CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine EMEA/359381/2009).

These recommendations have been drafted following discussions between representatives from the Pharmacovigilance Working Party (PhVWP), the Vaccine Working Party (VWP), the European Vaccine Manufactures association (EVM), the CHMP, EMEA and ECDC

- specific activities performed during a pandemic in relation to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions (see section 4.2);
- the format and content of the simplified PSUR (see section 4.3);
- specific activities performed for signal detection (see section 4.4);
- the post-authorisation safety study (see section 4.5) ; the protocol of the prospective cohort study should be presented in Annex 5 of the Risk Management Plan
- additional activities related to the:
    - detection of cases of Guillain-Barré syndrome
    - the monitoring of immunocompromised subjects exposed to the vaccine
    - the monitoring of pregnant women exposed to the vaccine.

The pharmacovigilance guidelines drawn up by the European Commission in accordance with Article 106 of Directive 2001/83/EC of the European Parliament and the Council are published as Volume 9A of The Rules Governing Medicinal Products in the EU.

The objectives of pharmacovigilance for vaccines are to identify rare or new adverse events, identify those that are causally related to the vaccine /vaccination and estimate their rate of occurrence. In addition, any change in the frequency or severity of a known safety concern requires prompt evaluation. Evidence of causality is inter alia based on biological plausibility supported by laboratory evidence and/or statistically significant excess of events in the post-vaccination period. Passive reporting systems have methodological limitations, particular for ascertaining reliable adverse event/reaction rates and investigating causal relationship.

5. Summary and Conclusion

Influenza A (H1N1) are emerging or re-emerging as a major public health problem in Europe, USA and other parts of the world. It is important to understand the strategy to prevent the pandemic, their transmission and virus densities in an affected area. The challenge of reversing the trend of emergent of influenza virus is quite difficult but not impossible. The past changes in public health including decay in infrastructure, lack of vaccination, resistance, increasing travel, increasing trade, urbanization, deforestation, agricultural practice, climate change, and the complacency among public health officials, policy makers, and the public contributed a dramatic resurgence of Influenza A (H1N1) virus.

This thesis summarized the current patho-physiological understanding, historical pandemic outbreak of H1N1 virus, their distribution and public health importance in European countries. The pandemic influenza is a new virus, and virtually everyone is susceptible to infection from it. It shows the emerging/ remerging of influenza A (H1N1) with significant public health impact in affected areas of Europe, USA and other parts of the world.

One of the main objectives of the thesis is to know about the challenging role of authorities facing and controlling the pandemic outbreak of this virus. The Pandemic (H1N1) 2009 is a strain of influenza A which can be transmitted from person to person. New strains of seasonal influenza A circulate every year in flu season. Moreover, the available Influenza vaccines are one of the most effective ways to protect people from contracting illness during influenza epidemics and pandemics. These vaccines will boost immunity against the new influenza, and help ensure public health as the pandemic evolves.

This thesis summarized the roles and responsibilities of different health authorities in an outbreak situation of influenza and to monitor the post marketing activities. The Health authorities and organizations are well prepared to respond to potential disruptions to their operations and protect the well-being of peoples whether caused by pandemic or other unforeseen events. In most of the countries the Ministry of Health is piloting the vaccination plan. However in countries where service delivery is fully decentralized the authorities in charge of healthcare are leading the response. In other countries specific agencies have been charged to prepare the plan. On front

line, vaccination is performed mainly by general Practitioners for the population and health care providers have to vaccinate their staff.

To monitor influenza strains in preparation of an outbreak, various systems are existing. Mainly the WHO Global Influenza Surveillance Network was established in 1952 and consists of over 120 National Influenza Centres in over 90 countries that monitor influenza activity and isolate influenza viruses in every region of the world. This network feeds into the Global Outbreak Alert & Response Network (GOARN) which is a WHO-led technical collaboration of existing institutions and networks who pool human and technical resources for the rapid identification, confirmation and response to outbreaks of international importance.

Although no viruses are better understood or more intensively studied than the viruses of influenza, if the next influenza pandemic occurs within the next 5-10 years its control will depend on innovations in vaccine production developed more than 40 years ago, but not yet applied to the full extent demanded by our present hard-won knowledge of the epidemiology of the disease. We have become so enamored of the brilliant advances made in the interim in understanding the molecular biology of both virus and host that common sense and inexpensive implementation of proven and older methods of control have been neglected as an interim barricade. In this review, I have advocated a return to first principles, while embracing the promise and returns of contemporary research. With the assumption that the next pandemic virus will contain one of the 13 influenza A virus hemagglutinin subtypes not currently causing epidemic human disease, high-yield reassortant viruses of each of these subtypes should be produced with all dispatch and, in collaboration with industry, tested for production stability and immunogenicity in humans. From this archive, an appropriate reassortant could be selected within days or weeks, and production could ensue. If not a perfect match with the imminent pandemic virus, this "barricade vaccine" could stand as a first line of defense until supplanted by a definitive "rampart vaccine," matching better the emergent, potentially pandemic virus.

Only limited data on safety and immunogenicity of influenza A/H1N1 vaccines will be available when Member States start using them. In addition, due to the continuous mutation of the influenza virus, the effectiveness of vaccines will need to be constantly measured.

The Pharmacovigilance of vaccines after their marketing is crucial because, prior to its availability on the market, the size of clinical trials is insufficient to identify rare or deferred adverse effects. Therefore a Risk Management Plan (RMP) for vaccines is essential. Article 8 (3) (ia) of directive 2001/83EC, as amended, requires the applicant to submit "a detailed description of the pharmacovigilance and, where appropriate, of the risk management system which the applicant will introduce.

For a more optimal pharmacovigilance of vaccines, it is necessary to:

- improve the coherence between the evaluating authorities;
- set up, in addition to the usual risk management plan, an active microbiological and epidemiological surveillance and to follow up exposed populations;
- have programmes of education of the medical community regarding vaccination and health education for the general public.

6. References

- Autret-Leca, E, Bensouda-Grimaldi, Jonville-Bera, and Beau-Salinas. Pharmacovigilance of Vaccines. Archives de Pédiatrie Volume 13, Issue 2, February 2006, Pages 175-180
- Budhiraja S, Akinapelli R. Pharmacovigilance in vaccines. Indian J Pharmacol 2010;42:117-117
- CDC Estimates of 2009 H1N1 influenza cases

  http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm
- CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine EMEA/359381/2009
- Derlet Robert W, MD, Professor of Emergency Medicine, University of California at Davis School of Medicine; Chief Emeritus, Emergency Department, University of California at Davis Health System. eMedicine, Influenza. Updated: Aug 19, 2010.

  http://emedicine.medscape.com/article/219557-overview
- ECDC Daily Update – Pandemic (H1N1) 2009 – 18 January 2010". European Centre for Disease Prevention and Control

  http://www.ecdc.europa.eu/en/healthtopics/H1N1/Pages/home.aspx
- EMEA/214301/2006. EMEA Pandemic Influenza Crisis Management Plan for the Evaluation and Maintenance of Pandemic Influenza Vaccines and Antiviral. London, 21 August 2006 Doc. Ref. EMEA/214301/2006
- EMEA, Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application CPMP/VEG/4717/03 (Revision) London, 30 May 2008
- Food and Drug Administration Guidance for Industry Clinical Data Needed to Support the Licensure of Pandemic Influenza Vaccines. U.S. Department of Health and Human Services. Center for Biologics Evaluation and Research MAY 2007

- Gatherer Derek. The 2009 H1N1 influenza outbreak in its historical context. Journal of Clinical Virology 45 (2009) 174–178
- Glezen, W Paul. MD, Prevention and treatment of seasonal Influenza. N Engl J Med 2008; 359:2579-85
- Gou H. Henry, MD, PhD, Robert T. Sweeney, MD, Donald Regula, MD and Ann N. Leung, MD. Fatal 2009 Influenza A (H1N1) Infection, Complicated by Acute Respiratory Distress Syndrome and Pulmonary Interstitial Emphysema. January 12, 2010, doi: 10.1148/rg.302095213
- Islam R & Rahman M.: H1N1 Flu: Swine Flu: A Global Perspective. The Internet Journal of Health. 2010 Volume 10 Number 2
- Kilbourne ED. Influenza pandemics of the 20th century. Emerg Infect Dis. 2006 Jan http://www.cdc.gov/ncidod/EID/vol12no01/05-1254.htm
- Le Louët, Hervé, Elisabeth Loupi and Françoise Haramburu. Which Pharmacovigilance for Vaccines? Thérapie 2007 Mai-Juin; 62 (3): 245-247
- Valenti, William M. MD 2010. 2009 H1N1 Influenza: Antiviral Use for Prevention and Treatment. Drug Benefit Trends. 2010;22:10-14
- World Health Organization (WHO) 2007. Regulatory preparedness of Human Pandemic Influenza Vaccines. WHO/BS/07.2074
- World Health Organization (WHO) 2008. Pandemic influenza preparedness and mitigation in refugee and displaced populations. WHO guideline for humanitarian agencies. Second edition Geneva 2008
- World Health Organization (WHO) 2009. Human infection with pandemic (H1N1) 2009 virus: updated interim WHO guidance on global surveillance. 10 July 2009
- Zimmer Shanta M., M.D., and Burke Donald S., M.D. Historical Perspective — Emergence of Influenza A (H1N1) Viruses N Engl J Med 2009; 361:279-85

7. Annexes

Annex 1. CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine EMEA/359381/2009

European Medicines Agency
Post-authorisation Evaluation of Medicines for Human Use

London, 25 September 2009
Doc. Ref: EMEA/359381/2009

CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine

Adopted by CHMP in November 2006
Revision 1.0 adopted by CHMP on 25 June 2009

Revision 1.1 adopted by CHMP on 24 September 2009

1. INTRODUCTION

The CHMP Guideline on dossier structure and content for pandemic influenza vaccine marketing authorisation application (CPMP/VEG/4717/03) specifies that, as part of the post-approval commitments, Marketing Authorisation Holders (MAHs) should have protocols in place at the time of authorisation of the mock-up vaccine to ensure that immunogenicity, effectiveness and safety of the final pandemic vaccine are adequately documented during use in the field (i.e. during the pandemic), since there will be only limited immunogenicity and safety data and no efficacy data at the time of licensing. Marketing Authorisation Holders may seek scientific advice from European competent authorities, and should collaborate with European health authorities to assure adequate performance of post-marketing surveillance. In 2005, all European influenza vaccine manufacturers agreed to collaborate in the preparation of a common core risk management to be submitted with the Marketing Authorisation Application for a pandemic influenza vaccine.

This document provides recommendations on how routine and additional pharmacovigilance activities should be conducted during the pandemic period, as well as the preparatory activities to be undertaken in the pre-pandemic period to achieve a high level of preparedness. These recommendations have been drafted following discussions between representatives from the Pharmacovigilance Working Party (PhVWP), the Vaccine Working Party (VWP), the European Vaccine Manufactures association (EVM), the CHMP, EMEA and ECDC.

Revision 1.0 has been prepared by EMEA in collaboration with the PhVWP, EVM and individual vaccine manufacturers in the context of the influenza A/H1N1 pandemic. The A/H1N1 influenza pandemic and the likelihood of a mass vaccination with A/H1N1 pandemic influenza vaccines have highlighted the need to revise this document taking into account differences between the situation in 2009 and the one foreseen in 2006. The following elements have been taken into account:

- the influenza pandemic has already been declared;
- the epidemiological characteristics of the A/H1N1 pandemic may differ from those foreseen for the H5N1 pandemic, with a lower case-fatality rate; in benefit-risk assessment, greater attention may therefore be given to less severe adverse reactions;
- the pilot testing of the simplified PSUR (S-PSUR) showed there was a need to revise its content and format.

Revision 1.1. includes changes mainly related to:

- the simplified PSUR, following the re-testing of the revised version
- the definition of vaccination failure to include a documented laboratory confirmation.

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2. SCOPE

This document applies to the pharmacovigilance plan as part of the risk management plan introduced with the authorisation application of mock-up pandemic influenza vaccines according to the CHMP Guideline on dossier structure and content of pandemic influenza vaccine marketing authorisation application (CPMP/VEG/17/17/03). It also applies to the pharmacovigilance plan of vaccines authorised outside the context of the mock-up dossier and to be used during an influenza pandemic.

This document specifies additional pharmacovigilance activities to be carried out during an influenza pandemic, as soon as the pandemic has been announced by WHO (Phase 6 of the WHO global Influenza preparedness plan) or by the European Commission in the framework of Decision 2119/98/EC. The pandemic influenza pharmacovigilance plan will terminate when it has been agreed with national competent authorities that it is no more necessary.

In addition to these activities, Applicants may propose further measures considered appropriate for the evaluation of the efficacy and safety of their product. These measures should be discussed and agreed with national competent authorities. This document does not address the safety specification, the need for additional risk minimisation measures and the risk minimisation plan itself.

The risk management plan for pandemic influenza vaccines will be an evolving document. It should be amended whenever new significant information arises, e.g. a change in the profile of adverse events of interest, results of studies, or change in benefit-risk balance.

3. LEGAL FRAMEWORK

The Guideline on risk management systems for medicinal products for human use (EMEA/CHMP/96268/2005) provides guidance on how Marketing Authorisation Applicants (MAAs) should meet the requirements for a description of a risk management system that they will introduce for a new medicinal product.

According to Article 24(3) of Regulation (EC) No 726/2004, the timing/periodicity of submission of periodic safety update reports (PSURs) may be specified as a condition of the marketing authorisation, and may deviate from the periodicity specified in that article. The format of the PSUR can also be specified in the conditions of the marketing authorisation. These conditions should be laid down in Annex II of the Opinion and justified in public health terms.

The content of the Individual Case Safety Reports is described in the draft Volume 9A of the Rules Governing Medicinal Products in the European Union. Section I.4.1. (Requirements for Expedited Reporting of Individual Case Safety Reports) requires that all available clinical information relevant to the evaluation of the reaction should be provided.

4. RECOMMENDATIONS FOR THE PANDEMIC INFLUENZA PHARMACOVIGILANCE PLAN

4.1. Content of the pharmacovigilance plan

In the Pharmacovigilance plan, the Applicant should describe:

- specific activities performed during a pandemic in relation to the collection, collation, assessment and reporting of spontaneous reports of adverse reactions (see section 4.2);
- the format and content of the simplified PSUR (see section 4.3);
- specific activities performed for signal detection (see section 4.4);
- the post-authorisation safety study (see section 4.5) ; the protocol of the prospective cohort study should be presented in Annex 5 of the Risk Management Plan
- additional activities related to the:
    - detection of cases of Guillain-Barré syndrome

- the monitoring of immunocompromised subjects exposed to the vaccine
- the monitoring of pregnant women exposed to the vaccine.

4.2. Spontaneous reporting

4.2.1. General principles

The possible disruption of the postal system and limited time available to health care professionals may require the development or strengthening of alternative channels of reporting suspected adverse reactions by health care professionals, such as fax, telephone or electronic transmission (e.g. web-based system). Depending on the circumstances, postal reporting may need to be discouraged in order to avoid loss of data at a critical time due to postal back-logs.

Consideration should be given to national systems already in place for reporting adverse drug reactions to vaccines. Discussions with regulatory authorities should be initiated if additional channels are developed, in order to ensure compatibility of reporting systems. Functioning of these additional reporting channels should be tested.

MAHs should be prepared to use an alternative system of ADR reporting in case of disruption of the main system.

4.2.2. Spontaneous reporting from health care professionals

i) It is recommended that MAHs and National Competent Authorities actively encourage health care professionals to report at least a minimum set of criteria needed for a proper evaluation of the suspected adverse events/reactions. An optional standardised reporting form is proposed in Annex 1 as an example of the elements to be reported. Each MAH should preferably develop an electronic format of the report form. In order to minimise data entry errors, consideration should be given to pre-fill the form with the tradename of the vaccine authorised and marketed in the EU.

ii) It is recommended that MAHs and National Competent Authorities (NCAs) actively encourage health care professionals to report the following adverse reactions:

   - Fatal or life-threatening adverse reactions
   - Serious unexpected adverse reactions
   - Adverse events of special interest (AESI): neuritis, convulsions, anaphylaxis, encephalitis, vasculitis, Guillain-Barré syndrome, Bell's palsy, demyelinating disorders, laboratory-confirmed vaccination failure.

   Standard case definitions should be used for the classification of cases of AESIs, as they will need to be reported in the simplified PSUR.

   - For anaphylaxis, convulsion, Guillain-Barré syndrome and encephalitis, the MAH and NCAs should use standard case definitions from Brighton Collaboration: http://www.brightoncollaboration.org/internet/en/index/definition___guidelines/document_download.html
   - For Bell's palsy, a Brighton Collaboration case definition is being developed.
   - For neuritis, vasculitis and demyelination, for which Brighton Collaboration definitions do not exist, an operational definition should be proposed by the Applicant in the Risk Management Plan. The narrow MedDRA SMQs for demyelination and vasculitis may be used to classify cases in these two categories.
   - For laboratory-confirmed vaccination failure, Applicants should propose a definition taking into account the Concept Paper on Vaccination Failure developed by the CIOMS/WHO Working Group on Vaccine Pharmacovigilance (http://www.cioms.ch). Vaccination failure would qualify as an AESI only if there is a documented laboratory confirmation. A narrative

documenting the laboratory confirmation should be included in all ADR reports of laboratory-confirmed vaccination failure.

iii) The list of AESIs and the Risk Management Plan may be updated if a signal of severe safety issue is observed in pre-authorisation studies or from post-authorisation surveillance.

iv) The basis for the assessment of an association between A/H1N1 influenza vaccines and severe adverse events should be Observed-to-Expected analyses. For this purpose, data will be needed on vaccine exposure and the expected number of cases. It is therefore crucial that background incidence rates on AESIs are collected as early as possible, before the vaccine is introduced on the market. Vaccine manufacturers should actively liaise with public health and regulatory authorities in countries where its vaccine(s) will be used in order to explore the availability of such data. Use of large electronic databases could be used if available. If data are not available, they could be extrapolated from other countries. Background incidence rates should be provided with any specific signal evaluation.

v) In the context of the A/H1N1 influenza, specific attention should be given to the active detection and investigation of cases of Guillain-Barre syndrome (GBS). Vaccine manufacturers should actively liaise with public health and regulatory authorities in countries where their vaccine(s) will be used in order to identify sources of information such as networks of specialists or other programmes that may help identify early cases of GBS. Applicants should also propose methodologies to further investigate the incidence of GBS following vaccine administration in other sources of information such as large computerised databases (see section 4.6).

4.2.3. Spontaneous reporting from patients

In the pandemic situation, patients' reports should be accepted and followed-up, as appropriate, as they may be the source of a large amount of information. However, experience regarding their usefulness is limited, especially for influenza vaccines.

Only medically confirmed reports should be expedited by MAHs to regulatory authorities. Non-medically confirmed reports should be compiled for signal detection. They should be analysed and reported separately to regulatory authorities (section 4.3.3).

4.2.4. Expedited reporting from MAHs to regulatory authorities

Expedited reporting should follow the timelines defined in Volume 9A of the Rules Governing Medicinal Products in the European Union, but it is recommended that reporting of fatal, life-threatening reactions and AESIs should take place as soon as possible.

4.3. Periodic Safety Update Reports

During a pandemic situation, the resources must be concentrated on a timely and effective monitoring of the safety profile of the influenza vaccines used during the pandemic. Moreover, a 6-monthly cycle may be too long to allow assessment of the safety of a vaccine for which high levels of exposure are expected within a short period of time. Therefore, 6-monthly or annual PSURs falling within the pandemic period will be replaced by monthly simplified PSURs (S-PSUR) accompanied by a summary of vaccine distribution.

4.3.1. Objectives of the simplified PSUR

- To notify regulatory authorities of ADRs that have been received within a pre-specified time period and that may have the greatest implications for risk-benefit balance in a pandemic.
- To flag any preliminary safety concerns and prioritise them for further evaluation within the appropriate timeframe.

4.3.2. Frequency of submission

- The clock should start from the first Monday after shipment of the first batch of vaccine.
- First data-lock point is 28 days later and Day 0 of S-PSUR submission is 14 days later.

- Day 0: S-PSUR submission to the Rapporteur and CHMP members.
- Day 5: Preliminary Rapporteur's assessment report is circulated to CHMP members.
- Day 7: Deadline for comments on the preliminary assessment report
- Day 9: Written procedure for agreement of the final assessment report
- Day 10: Final assessment report approved
- Day 11: The MAH receives the final assessment report.

- Reporting to be monthly for the first 6 months.
- Periodicity should be reviewed by the MAH and the (Co-)Rapporteur at 6 monthly intervals.

When it has been agreed by the CHMP that the S-PSUR is no longer necessary, a full PSUR covering the period since the data lock point of the last routine PSUR will be submitted within a time frame to be agreed with the Rapporteur.

4.3.3. Format of the simplified PSUR

Only spontaneously reported data should be included in the PSUR. The report should include the following Tables of aggregate data (using the pre-defined templates attached in Annex 2).

1. An overview for all spontaneous reports per country, stratified according to type of report (medically confirmed or non-medically confirmed) and seriousness, for the period covered by the report and cumulatively.

2. An overview for all spontaneous adverse reactions by SOC, High Level Term (HLT) and Preferred Term (PT), stratified according to type of report (medically confirmed or non-medically confirmed) and including the number of fatal reports, for the period covered by the report and cumulatively. MAHs should exlore ways to present such cases without double counting if SMQs include overlapping terms.

3. Adverse Events of Special Interest stratified according to type of report (medically confirmed or non-medically confirmed). AESIs will be defined as follows:

    - Neuritis: PT "Neuritis"
    - Convulsion: narrow SMQ "Convulsions"
    - Anaphylaxis: narrow SMQ "Anaphylactic reaction" and narrow SMQ "Angioedema"
    - Encephalitis: narrow SMQ "Non-infectious encephalitis"
    - Vasculitis: narrow SMQ "Vasculitis"
    - Guillain-Barré syndrome: narrow SMQ "Guillain-Barré syndrome"
    - Demyelination: narrow SMQ "Demyelination" (as GBS is also included in this SMQ, there will be an overlap in the number of cases for these two categories).
    - Bell's palsy: PT "Facial palsy"
    - Laboratory-confirmed vaccination failure: PT "Vaccination failure" (a report should be classified as medically confirmed based on a narrative documenting the laboratory confirmation).

4. Serious unlisted adverse reactions (SOC, HLT, PTs) stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

5. All spontaneous adverse reactions by age group, per SOC, HLT and PT, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by

the report and cumulatively. The following age groups will be used: < 2 years, 2-8 years, ≥ 9 years.

6. All spontaneous adverse reactions (SOC, HLT, PT) occurring in pregnant women, stratified according to type of report (medically confirmed or non-medically confirmed), for the period covered by the report and cumulatively.

The following principles should be followed when compiling the data:

- Table 1 will be based on the number of reports, while all other tables will be based on number of reactions (presented on PT level, sorted by System Organ Class [SOC] and High Level Term [HLT]).
- All tables will be based on generic and not product-specific data[1]. Product-specific data can be evaluated during signal work-up.
- "Cumulatively" means all adverse reactions since the use of the vaccine..
- All non-medically confirmed events are those that have been entered into the database by the data-lock point. Those which have not yet been entered should be reported in the following S-PSUR.
- "Serious" refers to the seriousness using regulatory criteria based on outcomes. This definition should be used consistently in all tables.
- Narratives of fatal cases and cases of Guillain-Barré syndrome will be provided in Annex.

A short summary should be provided in which the total number of new ADRs since the last S-PSUR is outlined and validated signals and areas of concern are highlighted, taking into account information arising from the prospective cohort study described in 4.5. In the event of multiple signals, signal work-up may be prioritised and appropriate timelines for submission of a full signal evaluation report should be provided.
Signals occurring in pregnant women should be described in terms of gestational age at time of vaccination, gestational age at time of occurrence of adverse event, adverse event, outcome.

4.3.4. Vaccine distribution report

To put the safety report into context, a summary of vaccine distribution should be included and should provide details of the number of doses of vaccine distributed in

i) EU member states for the reporting period by batch number,
ii) EU member states cumulatively and
iii) the rest of the world.

4.3.5. Testing of the production of the S-PSUR

The S-PSUR should be used as soon as the vaccine is used post-authorisation. It is therefore important to test the production and evaluation of the S-PSUR before the authorisation. The testing can be performed on a single S-PSUR based on another vaccine product. The Applicant should liaise with the EMEA Product Team Leader for practical aspects of the testing.

4.4. Signal detection

It is likely that potential safety issues will emerge when pandemic influenza vaccines are used in a large population. It is important for MAHs to identify them and this activity should be performed at least on a weekly basis. Identified signals should be validated and assessed using an Observed to Expected analysis as recommended in the Draft Guideline on the Conduct of Pharmacovigilance for

[1] Based on the assumption that product name will not be provided in a significant proportion of cases.

Vaccines for Pre- and Post-Exposure Prophylaxis against Infectious Diseases (http://www.emea.europa.eu/pdfs/human/phvwp/50344907en.pdf).

Newly identified signals should be highlighted in the S-PSUR. Furthermore, any signal leading to a change in the balance of risks and benefits of the vaccine should be immediately notified to the competent authorities.

The method(s) used for the detection and investigation of new safety signals should be presented in the description of the pharmacovigilance system and summarised in the pharmacovigilance plan, especially if specific activities are established for the pandemic vaccine.

Whenever a prioritisation of the evaluation is needed, the choice of the events to be considered for primary review should be guided by their potential impact on Public Health. If prioritisation is required, it is proposed to use the following criteria:

- seriousness of the adverse event
- incidence of the adverse event.

If further prioritisation is needed, the following MedDRA SOC should be examined in a first stage:
- Nervous system disorders
- Vascular disorders
- Immune system disorders
- Blood and lymphatic system disorders.

4.5. Post-Authorisation Safety Study

Very limited knowledge on safety will be available from A/H1N1 influenza vaccines before use. Additional pharmacovigilance activities for the vaccines used during pandemic are therefore needed to assess safety. Given differences in the vaccination policy between member states in terms of type of vaccine used, target population prioritised for vaccination, setting of vaccination and surveillance systems already in place, it is considered that a single method cannot be proposed.

A minimum requirement is that each MAH puts in place a prospective cohort study for each vaccine, for which specifications are described below. The design of the prospective cohort study of exposed subjects and of other additional pharmacovigilance activities should be presented in the risk management plan.

i) General principles

The following principles should be included in proposals for additional pharmacovigilance activities by Applicants:
- rapid generation and communication of data (e.g. through a web-based system) is essential as a basis for operational decisions
- proposals should be detailed enough to show that they are feasible and may be started as soon as vaccination begins
- the work plan for preparation and implementation should be described in the risk management plan
- adequate human resources should be secured in order to maintain and access the database during the pandemic period
- additional pharmacovigilance activities will not be requested in all Member States where the vaccine is used, provided the required sample size is obtained
- wherever possible, e.g. in countries where different vaccines will be used, it is desirable that the concerned MAHs agree on a common protocol or perform a common study.

ii) Objectives

A prospective non-interventional cohort study will be conducted for all vaccines in at least one European Member State and started as soon as the vaccine is used post-authorisation. Concurrent cohorts of non-exposed patients are not required given the conditions of a pandemic situation.

The primary objective of the study will be to investigate the incidence of adverse events in different age groups following an active surveillance of all vaccinated subjects. Primary endpoints and solicited events should be proposed in the study protocol and agreed with the competent authorities. Secondary objectives will include the collection of data on any AESIs and unexpected severe adverse events occurring in the study.

Effectiveness endpoints could also be included in the PASS provided they do not delay its implementation. The feasibility of their inclusion should be assessed and balanced with the advantages of conducting a specific effectiveness study (see section 5.1).

Immunological endpoints (except results of the investigation of cases of laboratory-confirmed vaccination failure reported in the study) should be included only if they do not delay the study implementation and do not impact on the speed of recruitment and availability of safety data. If needed, immunological data should be collected in specific studies (see section 5.2).

iii) Setting

The prospective cohort study will not need to be carried out in all Member States where the vaccine will be used. In selecting the setting(s) where the study will be initiated, Applicants should pay attention to feasibility criteria, such as the recruitment of an adequate number of high-risk subjects (e.g. health care workers), and the collection of data in a short period of time. MAHs should seek agreement from Ethics Committees in the pre-pandemic period according to national requirements. The countries and settings where the study is to be performed should be presented in the pharmacovigilance plan.

In Member States where Applicants will concomitantly market a number of vaccines, they are encouraged to perform common studies.

Cohorts to be included in prospective cohort studies should be identified early. National pandemic plans should be investigated in the countries where the vaccine is likely to be used, in order to identify groups of subjects prioritised for vaccination with the pandemic influenza vaccines and for consideration for recruitment into the study as soon as vaccination begins. Subjects may also be recruited in centres with at risk patients.

Systems used for the surveillance of seasonal influenza vaccination should also be investigated in order to evaluate their potential as a source of subjects for a prospective cohort study of the pandemic influenza vaccine.

iv) Target population and sample size

The recruitment procedure should ensure that an adequate number of subjects are included in each age category. The following numbers of subjects to be studied are considered a minimum sample size:

- 2 - 23 months: 500
- 2 - 8 years: 500
- 9 - 17 years: 3,000
- 18 - 44 years: 1,500
- 45 - 60 years: 1,500
- >60 years: 2,000.

For practical reasons, flexibility in the age categories is allowed if specific child groups with different age categories are targeted by national immunisation programmes.

The total sample size of 9,000 subjects would be able to rule out events occurring with a frequency of 1 per 3,000 if no event is observed (provided the event may occur in all age categories).

For all subjects, medical information should be obtained at the time of entry in order to allow stratified analysis of incidence rate. Medical information to be collected includes at least: asthma in children,

chronic obstructive pulmonary disease (COPD) in elderly patients, whether immunocompromised, cardiovascular disorders, diabetes, chronic neurological diseases.

Pregnancy information should be collected at baseline and during the course of the study. MAHs should also consider studying the safety of their pandemic influenza vaccine in women vaccinated during pregnancy using specific sources of data (section 4.4.3.).

Subjects already vaccinated with another pandemic vaccine should be excluded from the study population. However, subjects who were primed in the pre-pandemic period may be included.

v) Duration of follow-up

Subjects enrolled in the cohort should be follow-up for at least 6 months after the last dose of the vaccine.

vi) Analysis and reporting

Procedures should be put in place to allow rapid communication of data to the MAH, taking into account potential difficulties occurring during the pandemic. Web-based or other automated procedures for active follow-up of subjects and data collection are encouraged.

The database should be dynamic, allowing an analysis of available data in real time when a signal is detected from the spontaneous system, in order to give a preliminary estimate of incidence.

Analyses should include an estimation of the proportion of subjects (95% CI) presenting the primary endpoint, SAEs and/or AESI after the first and second vaccinations. For new safety concerns, Observed-to-Expected analyses should be performed (in different age categories if relevant). It is therefore important that background rates in countries where the vaccine will be used are collected as early as possible before the vaccine is introduced on the market.

Analyses should take into account the time period between different doses.

Milestones for interim and final reports should be presented in the study protocols and agreed with competent authorities. New signals should be highlighted in the S-PSUR. Serious adverse reactions arising from such studies should also be reported on an expedited basis according to the same criteria and timelines as adverse reactions reported spontaneously by healthcare professionals.

4.6. Other activities

i) For rare events such as Guillain-Barré syndrome, MAHs should investigate the possibility of constituting case series through the participation of specialist centres or clinics. Aggregated analyses could be performed to investigate potential risk factors; such series could also be a source of cases for further investigations (such as case-control analyses) performed after the pandemic. During the pandemic, the choice of the study design should take into account the time needed to obtain results.

ii) Safety monitoring of vaccinated immunocompromised subjects (either due to an underlying disease or due to treatment with immunosuppressants) should be considered; such patients could be recruited in specialised settings like dialysis or transplant centres.

iii) In order to document the safety of vaccines in pregnant women, the company should investigate whether a national pregnancy registry or another source of information exist in the countries where its vaccine will be used, in order to identify pregnancies exposed to the A/H1N1 vaccine and determine their outcome. Pregnancies occurring during the prospective cohort study should also be followed up. Activities undertaken to identify and access these sources of data should be reported in the pharmacovigilance plan in order to facilitate the coordination of efforts.

5. OTHER ACTIVITIES TO BE PRESENTED IN THE RISK MANAGEMENT PLAN

5.1. Effectiveness of the pandemic influenza vaccine should be studied in collaboration with regulatory authorities, in particular to have access to laboratory data and for laboratory confirmation. Applicants should actively liaise with public health and regulatory authorities in countries where its vaccine(s) will be used in order to agree on activities to be performed to assess effectiveness. Possible options are the inclusion of effectiveness outcomes in the prospective observational safety study, use of other sources of data such as local networks or sentinel physicians, or specific studies. Recommendations from ECDC for effectiveness studies should be consulted. Concerted efforts by vaccine manufacturers could facilitate the surveillance of the effectiveness of different vaccines in a same country. Effectiveness studies proposed to be carried-out post-authorisation should be described in the risk management plan.

5.2. A specific immunological study may be conducted to collect serum samples in a subset of vaccinated subjects to be tested for cross-reactivity against potential drifted variants of the A/H1N1 virus. Sera might also be used for cross-protection experiments in non-clinical models. Vaccine immunogenicity in a subset of immunosupressed subjects may help evaluate whether alternate vaccination schedules should be applied, including more than 2 doses (or higher HA antigen content in the vaccines).
Immunological studies proposed to be carried-out post-authorisation should be described in the risk management plan.

ANNEX 1

Optional adverse event reporting form

ADVERSE EVENT FOLLOWING FLU IMMUNISATION REPORTING FORM

Please forward completed form to……by fax :……or mail :……or Email : ……@……

Date of report: |__|__|__|__|__|__|__|__| Country : _____
D D M M Y Y Y Y

Source : ❒ Physician ❒ Pharmacist ❒ Nurse ❒ Patient ❒ RA ❒ Other

VACCINEE DETAILS

Name: |__|__| Date of birth : |__|__|__|__|__|__|__|__| or Age : …… Sex : ❒ M ❒ F
Initials *D D M M Y Y Y Y*

Pregnanc : ❒ YES ❒ NO ❒ Unknown *If YES, specify gestational age at the time of immunization* :……..

Pre-existing conditions/Relevant medical history : ❒ YES ❒ NO ❒ Unknown *If YES, specify* :……

……
……..

Ongoing treatment: ❒ YES ❒ NO ❒ Unknown *If YES, specify* :
……..

……

FLU VACCINES ADMINISTERED

Vaccine (*Name*)	Manufacturer	Batch number	N°Doses	Date given	Route of administration
1. _____	_____	_____	❒ 1st dose ❒ 2nd dose ❒ Unknown |__|__|__|__|__|__|__|__|	❒ IM ❒ SC ❒ Unknown
2. _____	_____	_____	❒ 1st dose ❒ 2nd dose ❒ Unknown |__|__|__|__|__|__|__|__|	❒ IM ❒ SC ❒ Unknown
3. _____	_____	_____	❒ 1st dose ❒ 2nd dose ❒ Unknown |__|__|__|__|__|__|__|__|	❒ IM ❒ SC ❒ Unknown

DETAILED ADVERSE EVENT INFORMATION

Adverse event	Start date	Stop date	Description of Adverse event (clinical examinations, lab tests) and treatment, if any

Seriousness : ❒ YES ❒ NO ❒ Unknown
If YES : ❒ Life-threatening ❒ Hospitalization ❒ Resulted in permanent disability/incapacity ❒ Congenital anomaly ❒ Other (e.g. medically significant)

Outcome : ❒ Recovered ❒ Improving ❒ Not yet recovered

❒ Sequelae : ❒ YES ❒ NO, *If YES, Describe* :
……

❒ Fatal : Autopsy ❒ YES ❒ NO Cause of death :
……

REPORTER (Health professional or consumer)

Name : _____ Postcode : _____ Profession (only health professional) :
_____

Phone number : _____ Fax number : _____ Email :
_____@_____

Address :
_____
_____

Signature : ……

ANNEX 2. Format and content of the simplified PSUR

Table 1 – All spontaneous reports per country

Country	Medically confirmed				Non-medically confirmed*			
	Serious		Non-serious		Serious		Non-serious	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number	No in reporting period	Cumulative number	No in reporting period	Cumulative number

*Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 2 – All spontaneous adverse reactions

SOC HLT PT	Medically confirmed				Non-medically confirmed*			
	No in reporting period		Cumulative number		No in reporting period		Cumulative number	
	All	Fatal	All	Fatal	All	Fatal	All	Fatal
Total								

*Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 3 – Adverse Events of Special Interest

Term (SMQ or PT)	Medically confirmed		Non-medically confirmed*	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
Total				

*Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 4 – All serious unlisted adverse reactions

SOC	Medically confirmed	Non-medically confirmed*

HLT PT				
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
Total				

*Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 5a, 5b, and 5c– All spontaneous adverse reactions per age category

SOC HLT PT	Medically confirmed		Non-medically confirmed*	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
Total				

*Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Table 6 – All spontaneous adverse reactions in pregnant women

SOC HLT PT	Medically confirmed		Non-medically confirmed*	
	No in reporting period	Cumulative number	No in reporting period	Cumulative number
Total				

*Only those cases that have been entered onto the database at data-lock. X non-medically confirmed reports remain outstanding.

Annex 1: Narratives of fatal cases.

Annex 2: Narratives of cases of Guillain-Barré syndrome.

Hiermit erkläre ich an Eides statt, die Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

Bekkerzeel, Belgium,

28 August 2010

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(Syed Irshad Rizvi)