Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 6.2
Pandemic Influenza

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Executive Summary

The threat of an influenza pandemic and its potential impact on health, social and economic conditions has long been recognized by the WHO and EU. The 2004 pandemic influenza background paper from the Priority Medicines Report highlighted several priority research areas including: low vaccine uptake and production capacity; expensive antiviral agents; and the need for increased EU funding towards influenza virus, vaccine and antiviral agents research. These research areas were identified as critical in the ability of Europe to respond to the next influenza pandemic.

In April 2009, a new influenza A (H1N1) virus emerged in Mexico and the United States. The virus quickly spread worldwide and was officially declared a global epidemic, the first one of the 21st century. Box 6.2.1 outlines a generally accepted understanding of the 2009 influenza pandemic.

Box 6.2.1: General summary of the 2009 H1N1 influenza pandemic

- The pandemic virus was less virulent than was anticipated in many pandemic preparedness plans.
- Highest disease incidence was in 0-4 year old age group although cumulative incidence of infection was in school-aged children.
- Deaths associated with virologically confirmed influenza were lower than the number of excess deaths typically associated with interpandemic influenza.
- Majority of deaths occurred at a younger age than typically seen with seasonal influenza.
- Although older adults had lower morbidity rates, this population had the highest case fatality ratio.
- Pregnant and post-partum women and indigenous populations, recognized risk groups during interpandemic influenza seasons, were also at increased risk for a severe outcome.
- Intensive care units were burdened by the increase in the number of young adults with severe disease due to the pandemic virus, though this was not experienced in all countries.
- Although the 2009 pandemic influenza A (H1N1) seems to have replaced all seasonal influenza A (H1N1) subtypes, it has not replaced influenza A (H3N2) subtypes which have continued to co-circulate as a small proportion of all types influenza A viruses. This is in contrast to previous pandemics where the pandemic virus replaced all influenza A viruses.
- Unlike the pattern for interpandemic influenza A (H1N1) viruses, no significant neuraminidase resistance of the 2009 pandemic influenza A (H1N1) has been reported to date, although variants with reduced oseltamivir sensitivity may be emerging in the Asia-Pacific region.
Although the 2009 H1N1 influenza virus was only moderately severe, it revealed the many areas surrounding the prevention and mitigation of influenza that require continued focus and research. The pathogenic and transmissibility mechanisms of the influenza virus are not yet fully understood. Improvements in the current methodologies of assessing the health and economic burdens are needed. Global and country surveillance systems need modification to more accurately estimate morbidity and mortality. Moreover, barriers to immunization should be identified and addressed. Despite increased global vaccine production capacity between 2006 and 2009, the number of available pandemic vaccine was insufficient during the 2009 influenza pandemic. However, increasing vaccine production capacity is not enough as universal access to these vaccines must also be assured during a pandemic. Vaccine effectiveness studies should be conducted in order to determine recommendations for vaccine use by specific age and risk groups. Strengthening global and country vaccine coverage monitoring systems will provide further insight into vaccine provision and the impact of immunization policies.

Current influenza control strategies include vaccination and the use of antiviral agents. The development of safe and effective vaccines with cross-strain and long-lasting protection against influenza will be imperative to reducing influenza-related morbidity and mortality. Antiviral therapy remains unchanged since 2004. Given the likelihood that influenza virus strains will confer resistance to monotherapy, novel antiviral agents will need to have broad spectrum activity and improved pharmacological profiles. During the 2009 H1N1 pandemic, rapid influenza diagnostic tests (RIDTs) had not been developed to specifically detect influenza A (H1N1). Numerous RIDTs have since been developed however comprehensive studies should be conducted on their diagnostic accuracy and cost-effectiveness.

Over the past 10 years, the EU has established a wide range of influenza-related surveillance networks, consortiums and research projects. These efforts are critical as pandemic preparedness is a monumental task that requires diligence, commitment and cooperation at the national and international levels in order to ensure adequate capacity in responding to the next influenza pandemic.
1. The Influenza Virus

1.1 Biological properties

The influenza viruses belong to the family Orthomyxoviridae and are classified into three types (A, B and C) according to antigenic differences among their nucleoprotein (NP) and matrix (M) proteins.1 Influenza A viruses circulate naturally in a global avian reservoir; however, some viral strains have crossed the species barrier establishing in pigs, horses and most notably, infecting humans. Influenza B viruses almost exclusively infect humans although they present a less pathogenic profile than influenza A viruses. Influenza C viruses are rare and have been known to infect humans, dogs and swine.

Influenza A viruses are enveloped negative-stranded RNA viruses comprised of eight gene segments that encode 10 proteins: hemagglutinin (HA), neuraminidase (NA), matrix proteins (M1 and M2), nonstructural proteins (NS1 and NS2), the nucleocapsid (NP), and the three polymerases (PB1, PB2 and PA).2 Influenza A viruses are further classified based on the rod-shaped HA trimer and mushroom-shaped NA tetramer antigens, two glycoproteins that serve as prominent features of the virus envelope. These two proteins are critical for the infection of susceptible cells of a host as the HA proteins facilitate viral attachment and the NA proteins are responsible for viral release. Together the HA and NA antigens elicit immune responses that prevent infection or reduce viral replication, respectively. Until recently, a total of 16 HA subtypes (H1-H16) and 9 NA subtypes (N1-N9) had been identified in avian hosts. Of the 144 total possible combinations, only three combinations of the HA/NA subtypes have been established as human influenza (H1N1, H2N2, and H3N2).3 More recently, H7 and H9 subtypes have been known to cause infection in humans.4

RNA polymerases lack the proofreading ability of DNA polymerases resulting in high mutation rates, specifically point mutations of the HA or NA antigens. These mutations from its predecessors, known as “antigenic drift”, can lead to new, distinct antigenic variants and is well characterized in human and poultry influenza viruses.1 Further research on the magnitude of antigenic difference among variants and specific amino acids directly related to antigenic difference may provide insight on how best to develop and utilize vaccinations as a control strategy. Additionally, the eight individual gene segments of the influenza virus allows for genetic reassortment when two influenza viruses infect the same cell. The host animal consequently serves as a “mixing vessel” and the result is an “antigenic shift” with generations of novel influenza viruses acquiring characteristics of both parent viruses.2 These two mechanisms permit a genetic diversity among influenza viruses that describe the recurring seasonal influenza epidemics of varying pattern and severity as well as the continuing risk of the emergence of a novel pandemic strain.

1.2 Pathogenicity and transmissibility

Avian influenza viruses are divided into highly pathogenic avian influenza (HP) or low pathogenic avian influenza (LP). The distinction between LP and HP avian influenza is their local versus system replication, respectively. Although multiple studies have demonstrated that the virulence of influenza viruses is polygenic, the complete pathogenic mechanism is not yet fully understood.3
In 1997, avian H5N1 influenza appeared in the poultry markets of Hong Kong, infecting 18 humans, six of whom died. However, avian influenza viruses do not efficiently infect and replicate in humans therefore host range restriction was disabled by that particular virus strain. The viral and host factors that determine host range restriction are poorly understood; determining the genetic mechanism that confers interspecies transmissibility could provide an important marker for identifying virus strains capable of human transmission.

### 1.3 Risk for a pandemic

The 1997 H5N1 influenza outbreak in Hong Kong was the first known incidence of a purely avian virus causing severe human disease and death. By 2006, the H5N1 virus had spread across 54 countries spanning three continents. Interestingly, as of 2013, despite large outbreaks and considerable human exposure to the H5N1 virus since 2003, only 615 confirmed cases have been reported. The inefficient human-to-human transmission is the only factor inhibiting H5N1 from transforming a zoonotic disease to be a pandemic virus. In the presence of the correct combination of genetic modifications, there is a substantial possibility for the enormous replicative capacity of a highly mutable virus, such as H5N1, to emerge as a pandemic virus. The potentially devastating health and economic impacts of a pandemic gives cause for further research into the ecology, virology, and pathogenesis of the avian influenza viruses.

### 2. Interpandemic Influenza Disease Burden

Every year, influenza accounts for large numbers of cases and deaths worldwide. The number of cases in any given year depends largely on the infection rate, morbidity and mortality rates associated with that particular influenza infection as well as the size of the population affected. Weather conditions, especially humidity and temperature are also factors that influence virus survival and transmission. The populations typically most affected are the elderly and those with high-risk medical conditions. The World Health Organization (WHO) estimates that annual influenza epidemics result in approximately three to five million cases of severe illness and 250 000-500 000 deaths globally.

### 2.1 Excess influenza-associated morbidity and mortality

Estimating the health and economic burdens of influenza is essential to framing influenza preventions and control policies; however, accurately documenting the burden of influenza is often compromised by several factors. Ambulatory and hospitalized adults tend to exhibit different clinical presentations and virological courses. Patients are also admitted to the hospital with a wide range of diagnoses, including non-respiratory diagnoses. Symptoms typical of influenza such as fever, myalgia, sore throat, and cough may be subdued or absent at the time of admission, resulting in some influenza cases going undiagnosed. Even when influenza symptoms are recognized as such, only a small percentage of cases are virologically confirmed. Still, these diagnostic tests are never 100% sensitive or specific. Finally, morbidity resulting from influenza infection can be complicated by additional medical conditions, such as acute myocardial infections, secondary bacterial infections, pulmonary disease, cardiovascular disease, diabetes, and compromised immunity.
As stated in the original background paper, few studies had been conducted on estimates of excess influenza-associated mortality in European countries. Studies have since underlined varying methods divided into two broad categories that have been used to estimate the burden of influenza. One such method is to calculate excess outcomes including general practice consultations, hospitalization and deaths that occur during epidemic influenza periods above a “baseline” incidence. Baseline measurements can be defined as incidence of influenza during the summer, incidence during the winter of non-epidemic years or also when there are no influenza virus strains circulating. A study conducted in Portugal measured excess mortality associated with influenza activity during the 2008 influenza season. Influenza activity data consisted of weekly estimates of influenza-like illnesses (ILI) incidence rates obtained by the Portuguese general practitioners sentinel network. Weekly aggregated mortality data was generated by the Daily Mortality Monitoring (VDM) System. Results from the study include an overall impact of 1,961 excess deaths or an excess death rate of 18 per 100,000 inhabitants. Impact was higher in women than men and 82% of total deaths occurred in persons 75 years and older. Another study conducted in the Netherlands estimated influenza-associated mortality and hospitalization, looking also at low-risk individuals under 65 years of age. Influenza-associated hospitalization was highest in 0–1 year olds and the elderly as compared to low-risk (under 65 years of age) adults. Within the low-risk population of persons under the age of 65, hospitalization was highest for 0–4 year olds and was also significant for 5–64 year olds. Excess influenza-associated mortality was also demonstrated among 50–64 year olds and the elderly, though not in the younger age categories.

The alternative method used to estimate the burden of influenza is the development of statistical techniques utilizing underlying temporal patterns in the occurrence of individual organisms to attribute non-specific incidence data to various causative agents. This method may be able to provide more robust estimates of disease burden. A study conducted in England and Wales aimed to estimate the burden of influenza in terms of general practice consultations, hospital admissions and deaths using this statistical method. Results showed that in primary care, those younger than 45 year of age comprised the majority of the burden while the elderly are more likely to be hospitalized and to die.

Data from these studies highlight several aspects of the methods used to estimate the burden of disease that should be addressed in future studies. Improved official influenza surveillance data is needed to ensure accurate estimation of morbidity and mortality during a pandemic. There is a degree of uncertainty in the accuracy of the excess outcomes approach as these estimates depend on the definition of a particular year’s influenza season, which can lead to an overestimated influenza burden especially if other causes of morbidity or mortality are prevalent at the same time as influenza. Likewise, if these causes are absent during the influenza season, the influenza burden may be underestimated. These methods also use different definitions of viral seasons and end-points, variations of the study period and differences in healthcare systems, all of which result in lack of comparability across studies. Additionally, these statistical models are not easily applied to tropical and subtropical regions where influenza seasons are variable and spread over many months during the year.
2.2 Economic burden

As recognized in the 2004 background paper, influenza also imparts an economic burden on affected communities and countries. New studies have since been published on this economic impact, which includes direct health care costs and indirect costs (e.g. work absenteeism and loss of productivity).\textsuperscript{15} The majority of health care costs lie within physician visits and hospitalization. A study in the United States estimates that approximately 50\% of the 50-60 million people affected with influenza visit their doctor while between 114 000 and 142 000 people are hospitalized each year.\textsuperscript{15} This amounts to annual direct medical costs between US$ 3 and 5 billion per year.\textsuperscript{15} However, the most significant costs are the indirect costs of work absenteeism and the associated costs of loss of productivity, accounting for more than 80\% of the total societal cost of seasonal influenza epidemics.\textsuperscript{16} Site studies conducted in North America, Western Europe, Asia and Australia revealed that the mean number of working days lost ranged between 1.5 and 4.9 days per influenza episode for those with laboratory-confirmed influenza.\textsuperscript{16} Studies in France and Germany estimate a US$ 10-15 billion cost due to loss of productivity alone.\textsuperscript{16} Aside from the acute infection phase, full recovery can take up to one to two weeks.\textsuperscript{16} Moreover, 80\% of adults state that they find their work performance impaired upon returning to work.\textsuperscript{16} As the healthy adult working population is the largest group affected by influenza, exploring the vaccination of working population is warranted.

2.3 Vulnerable populations

2.3.1 Children

Although several studies conducted in Europe have described the impact of influenza and common infective complications such as otitis media in children; few studies have been conducted on more severe influenza-associated complications including febrile seizures (FS) and acute encephalopathy. Febrile seizures account for approximately 20\% of all hospitalized infants and young children with influenza.\textsuperscript{17} Numerous studies have shown a higher incidence of febrile seizure in children hospitalized with influenza than with other respiratory infections.\textsuperscript{18} Results from 2011 and 2012 studies conducted in Greece and Denmark indicated that 25.4\% and between 30-47\% of all FS cases could be attributed to influenza.\textsuperscript{19,20}

Acute encephalopathy is a less common yet more serious complication associated with influenza. The epidemiology of influenza-associated acute encephalopathy has been extensively studied in Japan, where there is a high prevalence of this complication, although cases have also been reported in North America, Europe and Taiwan.\textsuperscript{17} The Japanese Ministry of Health conducted a study where of the 217 identified cases of clinically diagnosed influenza-associated encephalopathy, 82.5\% were in children less than five years of age.\textsuperscript{17}

Recent studies have also demonstrated that the highest hospitalization rates attributed to influenza occur among children younger than two years of age.\textsuperscript{19} This confirms that the burden of influenza impacts children and their families, resulting in significant school absenteeism, antibiotic use, medical care visits and parental work loss, as noted in 2004. Several countries, including Argentina, Canada, Finland, Mexico, Singapore, and the United States have recently extended vaccination recommendations to include the younger age population.\textsuperscript{21} In response to the increasing concern of influenza burden on children, in 2007,
the European Centre for Disease Prevention and Control (ECDC) published a technical report on routine influenza vaccination in children, emphasizing the initial importance of determining specific national profiles of the disease burden. The report concluded that European data on paediatric disease burden was inadequate and would subsequently hinder government policy decisions regarding influenza vaccinations for children. As a result, the European Paediatric Influenza Analysis (EPIA) project was created in 2008 to collect and analyse data on the paediatric influenza burden in Europe. Although all European countries were invited to participate in the EPIA project, currently only seven countries are active participants: Denmark, England, Finland, Italy, The Netherlands, Scotland, and Spain. Initial findings from the EPIA project indicate considerable variability between countries regarding the burden of influenza-like illnesses. These findings underline the fundamental issue of the absence of a standardized protocol for national surveillance systems in Europe.

Box 6.2.2: Background of the EPIA Project

- In the 1980s, efforts were initiated to create a European surveillance project.
- In 1996, the project had evolved to the European Influenza Surveillance Scheme (EISS). EISS was later succeeded by the European Influenza Surveillance Network (EISN).
- The main objectives of the EISS were to aggregate and interpret epidemiological and virological surveillance data, to monitor influenza prevention and control policies in Europe and to contribute to European planning and response to pandemic influenza through surveillance, investigation and provision of information.
- EISS began with seven participating countries: Belgium, France, Germany, the Netherlands, Portugal, Spain and the United Kingdom.
- Initial funding came through the national governments with subsequent funding by the European Commission (DG SANCO) then grant funding through the European Centre for Disease Prevention and Control (ECDC).
- Since 2008, the responsibility for the former activities of the EISS has been transferred to the ECDC.
- The EPIA was formed around the EISS with its first modeling work focused on the influenza-like illness data and virological data collected by EISS from 1996–2008.
2.3.2 Pregnant women and perinatal outcomes

The World Health Organization considers pregnant women at higher risk for morbidity and mortality from influenza infection and therefore recommends that all pregnant women be immunized during the influenza season. However, individual countries have varying policies on the routine vaccination of pregnant women. As noted in the 2004 background paper, data on the burden of seasonal influenza in healthy pregnant women is limited and remains unchanged. Results from a few notable studies support the recommendation that all pregnant women will benefit from receiving an influenza vaccination. Furthermore, 2007 data confirms that pregnant women with comorbidities should also be vaccinated during the influenza seasons regardless of their stage in pregnancy. As pregnant women are a high-risk group for influenza infection, additional research is clearly needed to obtain concrete estimates of the influenza burden as well as the cost-effectiveness of implementing targeted influenza immunization programmes.

2.4 Tropical and developing countries

Few studies had been reported on the influenza burden in tropical and developing countries and this remains unchanged. Tropical and subtropical regions have mild winters that are subject to seasonal fluctuations in influenza incidence although the seasonal pattern is less evident than in temperate areas. In addition, there may be more than one period of viral activity making it difficult to elucidate the seasonality of influenza and measure its impacts. Several studies have observed higher disease burden in tropical and subtropical regions as compared to the United States. A recent 2012 study conducted in the subtropical region of Guangdong province in China concluded that a greater proportion of children less than five years of age had influenza infections compared to children in other age groups. Direct economic costs within the study period totaled approximately US$ 1 million. The importance of influenza surveillance and understanding the seasonality of influenza in individual regions cannot be underestimated. Lack of disease burden data can hinder a country’s ability to formulate a national vaccination policy, as is the case in Viet Nam. The ability to design effective control strategies and mitigate disease burden is ever more essential in the event of a pandemic.
3. **2009 Influenza A (H1N1) Pandemic Disease Burden**

3.1 **Emergence of a novel virus**

In early April 2009, a new influenza A (H1N1) virus emerged in Mexico and the United States. Confirmation that the viruses in Mexico and the United States were identical provided evidence that the new virus met the WHO criteria for a pandemic strain. However, by the time of its discovery, the virus had advanced beyond the possibility of successful containment. The virus quickly spread worldwide through human-to-human transmission and on 11 June 2009, the WHO elevated the influenza pandemic alert level to Phase 6, officially declaring a global pandemic, the first of the 21st century.

This 2009 H1N1 virus was found to be antigenically distinct from human seasonal influenza viruses although genetically related to viruses known to circulate in pigs, thus the virus is now referred to as ‘swine-origin influenza virus’ (S-OIV) A/H1N1. Molecular studies of the virus have since determined that it had been derived from several viruses including the North American H3N2 triple-assortment, the classical swine H1N1 lineage and the Eurasian ‘avian-like’ swine H1N1 virus. The pulmonary replication level of the 2009 H1N1 virus has been higher than that of seasonal influenza A (H1N1) viruses in experimentally infected animals; however the 2009 pandemic strain lacks the mutations that are associated with increased pathogenicity in other influenza viruses.

3.2 **Epidemiology**

The 2009 influenza A (H1N1) virus surfaced in a small village in Veracruz, Mexico; however it was overlooked as no illness resulted in hospitalization. The first two cases in the United States appeared in Southern California, in a ten-year-old boy and in a nine-year-old girl with febrile respiratory illnesses that required hospitalization. The virus propagated rapidly and by 18 April 2010, more than 214 laboratory-confirmed cases had been reported. Countries in the southern hemisphere reported more pandemic H1N1 cases in 2009 than any of the seasonal subtypes. Pandemic dissemination was more gradual in the northern hemisphere, occurring initially in the United States, Spain, Great Britain, Japan, and Germany before progressing to other countries. Infections rates also increased rapidly in Central and South America and Asia, and particularly in Thailand. However, very little epidemiological data is available regarding transmission of the virus in Africa. As of 2010, the number of influenza A (H1N1) cases worldwide remained unknown as a result of most cases being diagnosed clinically and not being laboratory-confirmed.

3.3 **Mode of transmission**

Initial transmission to humans is believed to have occurred at least several months prior to preliminary recognition of the first outbreak. The mode of transmission appeared to be similar to seasonal influenza viruses and involve close unprotected contact with respiratory droplets. Most outbreaks occurred in schools, day-care facilities, camps, and hospitals. Contrary to initial findings at the beginning of the pandemic, subsequent transmission studies in animal models demonstrated that the 2009 H1N1 pandemic virus transmits as efficiently as interpandemic influenza. Interestingly as of 2010, there had been no evidence that pigs played any role in the epidemiology or circulation of the virus in humans.
incubation period varied between approximately two to seven days which is comparable to interpandemic influenza.\textsuperscript{30}

### 3.4 Clinical presentation

Infection with the novel 2009 H1N1 pandemic virus caused mostly a mild, self-limiting upper respiratory illness characterized by fever, cough, sore throat, myalgia, chills, rhinorrhea, conjunctivitis, headache and shortness of breath.\textsuperscript{28} As of 2010, more than 50\% of patients presented with gastrointestinal symptoms including nausea, vomiting, and diarrhea.\textsuperscript{28} Young children also seemed to have marked irritability, severe lethargy, poor oral intake, dehydration resulting in shock, and seizure.\textsuperscript{30} Additional complications included invasive bacterial coinfections, encephalopathy, and diabetic ketoacidosis.\textsuperscript{30} Overall, the spectrum of clinical presentation varied from asymptomatic cases to primary viral pneumonia resulting in respiratory failure, acute respiratory distress, multi-organ failure, and death.\textsuperscript{28}

### 3.5 Influenza-associated morbidity and mortality

As stated in Section 3.1, quantifying the health burden of influenza is difficult as the illness can present a wide range of symptoms resulting in under-diagnosis, patients are not laboratory-confirmed as having influenza, diagnostics tests are not 100\% sensitive or specific and finally, influenza can also be masked by other comorbidities. Despite a substantial increase in laboratory testing during the pandemic, these recorded hospitalizations and deaths are a crude underestimation of the true pandemic burden.\textsuperscript{31} Nevertheless, a global estimate of the mortality associated with the 2009 H1N1 pandemic is necessary to document the effect of the pandemic in order assist in guiding allocation and delivery of prevention and treatment measures for future pandemics.\textsuperscript{32} However, by 2011 more than two years after the onset of the H1N1 pandemic, there still remained great controversy in regards to the morbidity and mortality burden of this pandemic relative to past influenza seasons.\textsuperscript{31}

A distinguishing feature of the 2009 H1N1 pandemic is that the virus disproportionately affected children and young adults as compared to the older age groups.\textsuperscript{28} In 2011, a national study, the first of its kind, was conducted in Mexico investigating the excess mortality and years of life lost (YLL) associated with the pandemic as compared to interpandemic influenza.\textsuperscript{31} Findings showed that Mexico experienced a higher excess mortality burden relative to that in the United States, Europe, or Australia including 11.1 excess all-cause deaths per 100 000 population and 445 000 YLL as a result of a series of three pandemic waves that occurred in the spring, summer and autumn of 2009.\textsuperscript{33,34} The two groups most severely affected by the pandemic were individuals aged 5-19 and 20-59 years.\textsuperscript{31} A separate study also conducted in Mexico corroborated the results of the national study with 14.9\%, 28\% and 22.9\% of hospitalizations in individuals aged 5-14, 15-29 and 30-44, respectively, compared to only 6.1\% in those over 60 years of age.\textsuperscript{35} Proportion of deaths demonstrated a similar trend with 21\%, 31.9\% and 27.1\% in individuals 15-29, 30-44, and 45-59, respectively, compared to only 8.9\% of deaths in those over 60 years of age.\textsuperscript{35}

Immediately following the outbreak, on 20 April 2009, the California Department of Public Health and 61 local health departments conducted a study to describe the epidemiological characteristics of the first 1 088 hospitalized and fatal cases reported due to the 2009 H1N1 pandemic virus.\textsuperscript{36} The median age, 27, for hospitalized individuals was discovered to be
younger than is typical for interpandemic influenza.\textsuperscript{36} Infants had the highest rate of hospitalization while the highest mortality rates were in those 50 years and older.\textsuperscript{36} A different study in the United States evaluating hospitalized patients with laboratory-confirmed influenza also determined that 45\% of the patients were children under 18 years of age and only 5\% were older than 65.\textsuperscript{37} Studies conducted in other countries further confirmed the initial morbidity and mortality patterns. Separate studies in England and Denmark reported a high incidence of infection in children with a disproportionately large impact on the age group 5-24 years.\textsuperscript{38,39} Studies in Australia and Argentina also reported the highest rates of hospitalization in children.\textsuperscript{28}

All studies mentioned have additionally demonstrated comparatively low morbidity in individuals older than 60 years of age. This deviation from the normal distribution of morbidity from interpandemic influenza suggests that the older population had acquired partial immunity to the 2009 H1N1 pandemic virus, presumably as a consequence of a prior exposure to an antigenically related influenza viruses resulting in the development of cross-protective antibodies.\textsuperscript{30,38} However, despite this partial immunity the highest case fatality rates were reported in the 50-60 year old population.\textsuperscript{28}

A modeling study published in 2012 developed a new approach to estimate global mortality and the number of YLL associated with the first year of circulation of the 2009 H1N1 pandemic virus in each country.\textsuperscript{32} The overall global distribution of deaths associated with the H1N1 pandemic in each country during the first year virus circulation is shown in Figure 6.2.1. Results from the study estimated that between 105 700 to 395 600 people died of associated respiratory illness and an additional 46 000 to 179 900 people died of associated cardiovascular complications.\textsuperscript{32} The overall global estimate from this study was more than 15 times higher than the number of laboratory-confirmed deaths reported to the WHO in the first 16 months of the pandemic.\textsuperscript{32} Furthermore, a disproportionate number of total cardiovascular and respiratory deaths, 51\%, occurred in the Africa and South-East Asian regions, as seen in Figure 6.2.2.\textsuperscript{32} Findings from this study illustrate the existing gap in the production and delivery of influenza vaccines to the Africa and South-East Asia regions. In order to improve global response to future influenza pandemic, concerted efforts must be made in addressing these disparities.
3.6 Economic burden

In addition to the health burden, attention should also be directed to the economic burden sustained during a pandemic. Assessing economic impact includes direct health care costs as well as the indirect costs of work absenteeism and loss of productivity; however, quantifying this impact can be difficult. A study conducted in 2010 stated that the global economic impact of the H1N1 pandemic remained unknown. A preliminary study from 2009...
estimated the economic impact of the pandemic in Mexico to more than $3.2 billion, which is approximately 3% of the gross national product. Subsequently, efforts were initiated to estimate the economic impact of the pandemic on the United Kingdom using a computable general equilibrium modeling experiment. The main outcome measures of this 2009 study included various scenarios with different pandemic severity, vaccination, school closure, and prophylactic absenteeism specified in terms of gross domestic product and output from different economic sectors. The findings of this study projected that depending on disease severity, of low to high fatality scenarios, the cost of a pandemic could result in between 0.5–4.3% reduction of gross domestic product (GDP). In the event of a mild pandemic, school closures and its related absenteeism would increase the economic impact; however for a more serious pandemic, the economic impact of school closures decreases while the advantages in mitigating the pandemic would increase. Furthermore, widespread behavioral change such as large scale prophylactic absence from work would also substantially increase costs with few health benefits. A pandemic influenza itself will not produce unprecedented economic impacts as even a high fatality rate with elevated levels of infection would only reduce GDP by less than 4.5%. However, balancing appropriate school closure policies and behavior change such as prophylactic absence from work with effective vaccination programs will be critical in determining the economic impact of an influenza pandemic.

3.7 Vulnerable populations

Complications from interpandemic influenza are often associated with underlying conditions, which were also cause for concern during the 2009 H1N1 pandemic. These risk factors include children under the age of five, pregnant women, individuals with chronic lung, renal and hepatic disorders, chronic cardiovascular conditions, metabolic disorders, neurologic conditions, hemoglobinopathy, long history of smoking, individuals over the age of 65, the morbidly obese and immunosuppressed patients. A study conducted in the United States in 2009 determined that out of 272 hospitalized patients with laboratory-confirmed H1N1 infection, 73% presented with at least one underlying medical condition including asthma, diabetes, heart, lung and neurologic diseases and pregnancy.

During pregnancy, numerous changes occur in the immune system to allow tolerance to paternally derived fetal antigens. These alterations on maternal immunity leave the mother susceptible to increased severe manifestations of certain infections, including influenza. Pregnant women, especially those in their second and third trimester or who were less than two weeks post-partum, appeared to be at higher risk for severe disease during the 2009 H1N1 pandemic. Following initial reports of infection in pregnant women, the U.S. Centers for Disease Control and Prevention (CDC) elevated surveillance of pregnant women. During the first months of the outbreak, between 15 April to 18 May, 2009, the CDC received reports of 34 confirmed or probably cases of pandemic H1N1 infection in pregnant women, of which 11 were admitted to the hospital. During the first month alone, the estimated rate of hospital admission in pregnant women was higher than that of the general population. Six deaths were also reported between 15 April and 16 June in which all the women had developed pneumonia and subsequent acute respiratory distress.

Severe obesity was also reported at higher rates, by a factor of five to 15, compared to the general population among patients with severe or fatal cases of 2009 H1N1 infection. Other disadvantaged groups including the indigenous populations of North America and the
Australasia-Pacific region reported increased rates of severe H1N1 infection by factors of five to seven.\(^{30}\) The WHO classified the 2009 H1N1 pandemic as moderately severe due to the residual immunity retained by the older population while the majority of cases presented with a mild and self-limiting illness.\(^{43}\) Although this new virus appeared less virulent than the 1918 H1N1 virus, the inability to predict which specific subtype will transmit to humans demonstrates the need of addressing the gaps in knowledge to effectively manage the next pandemic.\(^ {28}\) Future efforts should focus on increased virological surveillance of transmission and pathogenesis of disease and improved understanding of disease burden in low-resource settings and among disadvantaged populations.

4. EU Funded Pandemic and Avian Influenza Research Projects

European research on vaccine development for pandemic influenza has been financed since 2001 by the European Union. Early projects worked to develop an egg-free vaccine, which is faster and safer to produce, along with innovative application techniques. Research is now underway with the objectives of fighting the disease at the source (infected birds) and protecting human populations through pandemic influenza vaccines. Future EU research will improve vaccine efficiency by adding adjuvants, substances that enhance the body’s immune response to vaccine antigens. Additionally, research teams are currently focused on developing a universal flu vaccine that could provide a lifetime of protection from influenza.

The Framework Programme is the European Union’s primary funding mechanism for supporting collaborative, transnational research and development. Under the Fifth Framework Programme for Research (1998 to 2002, FP5) €6 million were spent on avian and pandemic influenza in 22 institutions and national reference laboratories across eight European countries.\(^ {44}\) For the Sixth Framework Programme (2002 to 2006, FP6), activities were extended and reinforced with a set of new projects launched in both the animal and human health sectors and with more than a three-fold increase in the EU contribution (€16 million plus a share in two large Networks of Excellence and an Integrated Project).\(^ {44}\) To date, a total of over 120 laboratories across 21 European countries have been funded for research on influenza within these Framework Programmes.\(^ {44}\) The European Commission has published a comprehensive report of all FP5 (1999 to 2002) and FP6 (2002 to 2006) funded projects that are either exclusively dedicated to research on any aspect of influenza (the majority of projects) or address a broader range of diseases, but with a significant part devoted to influenza which can be accessed in Appendix 6.2.1.

In 2007, the European Commission allocated an additional €20 million for research into avian and pandemic influenza. Relating to animal health, issues such as developing vaccines for avian species; improved diagnosis and early warning systems; the ecology and pathogenesis of avian influenza infections; migratory birds; avian influenza virus survival; reinforcement of community and national reference laboratories; and technology transfer to developing countries will be addressed. Relating to human health, issues such as clinical research on pandemic influenza vaccines, better understanding of the influenza virus and strengthening support to surveillance will be addressed. Several EU-funded projects including investigations of pandemic influenza vaccines, antiviral drugs, universal vaccines, and influenza in animals are also in progress. Examples include:
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- NOVAFLU - developing more effective strategies for the human vaccination against epidemic and pandemic influenza.
- AVIFLU - studying the pathogenesis of avian influenza, as well as improving diagnosis and control of avian infections.
- FLUAID - developing diagnostic tools and vaccines to be used in outbreak management and in the application of control measures based on vaccinations to combat avian influenza infection. Leading European institutes will cooperate with Asian laboratories as part of this research project.
- UNIVERSAL VACCINE - developing a powerful, new, safe, and easily-administered nasal vaccine for humans that provides lifelong protection against influenza. Website: http://www.universalvaccine.org
- VIZIER - identifying potential new drug targets against RNA viruses by providing a comprehensive structural characterization of the replicative machinery of a carefully selected and diverse set of viruses. Website: www.vizier-europe.org
- VIRGIL - the first European surveillance network capable of addressing current and emerging antiviral drugs resistance developments in the field of viral hepatitis and influenza. Website: www.virgil-net.org

The current Seventh Framework Programme (FP7) (2007 to 2013) will operate with an EU budget of €55 billion organized under four programmes corresponding to the four basic components of European research: cooperation, ideas, people, and capacities. Health research is one of ten high-level themes identified by FP7 which lies within the Cooperation Work Programme. The Cooperation Work Programme will operate with a budget of approximately €32.2 billion with €6 billion allocated to health research.

For the first time, research will be dedicated to emerging infectious diseases, including influenza. Primarily, the influenza projects of the health sector are related to pre-clinical and clinical development of new, innovative, safe and effective vaccines. Proposals will focus on universal influenza vaccines, providing longer-lasting and broader protection against multiple strains of influenza virus, with the ultimate aim of efficiently protecting the general population from seasonal and pandemic influenza. Various complementary scientific aspects such as basic virology, diagnostics, epidemiology, pathogenesis, surveillance, immune responses, animal viruses, novel drugs, clinical management of patients, behavioural aspects and optimized communication strategies are also covered by FP7 research. The first call for proposals is related to:

- Broadly protective vaccines, mechanisms of protection
- Standardization of immunological assays/surrogate markers for vaccine trials
- Point-of-care diagnostic tests: real-time polymerase chain reaction (PCR)
- Pandemic containment and mitigation strategies
- Surveys and novel mathematical models to evaluate effectiveness of containment measures
- International collaboration projects: pandemic preparedness/health system analysis in Viet Nam, Thailand, Indonesia, and Taiwan

A detailed description of proposed health research areas within the Cooperation Work Programme can be viewed in Appendix 6.2.2. A new framework programme, Horizon 2020, will be launched in 2014 with a €80 billion budget and will continue to support vaccine research and development for infectious diseases, including influenza. This section emphasizes the European Commission’s continued support for influenza research. In light of
the 2009 pandemic, the comprehensive report of influenza research projects initiated between 2001 to 2007 underscores the importance of periodic reviews of current research to identify the strengths and weaknesses of Europe’s funding and research portfolios.
5. Influenza Prevention and Control Strategies

5.1 Vaccination

Vaccination is considered the most effective mechanism to prevent the spread of influenza and also to mitigate the severity of illness and impact of disease. The sudden appearance and rapid global transmission of the 2009 influenza A (H1N1) pandemic resulted in a global prioritization to develop a vaccine. A primary concern was for the potential of the virus to gain additional virulence properties.

The 2009 interpandemic influenza vaccine was ineffective against the pandemic strain due to a lack of cross-protective immunity between the interpandemic and pandemic influenza strains and further emphasized the urgency for prompt vaccine development.

Due to the high mutation rate of influenza viruses, in order to achieve a complementary match between the circulating and vaccine viruses, the composition of interpandemic influenza vaccines must be reformulated every season based on recommendations by the WHO. Estimating influenza vaccine effectiveness (IVE) early in the influenza season assists in measuring the degree of match between the selected vaccine strains and the circulating strains. However, vaccine composition reformulation dictates that IVE estimates cannot be used to approximate IVE in subsequent years therefore IVE should be measured and monitored every year. For a pandemic situation, strain specific vaccines do not become available until four to six months after the beginning of vaccine development. Consequently, the pandemic virus is already in circulation as pandemic vaccines are being administered necessitating that IVE results be computed and delivered rapidly. In the context of a pandemic, vaccine effectiveness data should be provided by age group, by number of doses received, and by vaccine brand. The availability of annual IVE estimates at the beginning of each interpandemic season or pandemic is essential in order to:

- decide on recommendations for the use of the vaccine by specific age and risk groups,
- target complementary or alternative public health measures (e.g. antiviral agents) for population subgroups in which the vaccine is less effective,
- estimate more precisely the impact of current vaccination strategies on the burden of disease,
- provide quantification to the current virological system of comparing antigenic matches of vaccine and circulating viruses,
- encourage further investigations on the immunogenicity of various vaccine composition platforms,
- better manage and respond to reports of vaccine failures (especially during a pandemic),
- provide a basis for adequate risk management and cost-effectiveness analyses.

In 2007, the ECDC established the Influenza Monitoring Vaccine Effectiveness in Europe (MOVE) network with the aim of monitoring interpandemic and pandemic influenza vaccine effectiveness in the Member States of the European Union and European Economic Area (EU/EEA). The first step in the design of this network was to identify key methodological and practical issues in developing protocols for pilot studies. This was accomplished through a survey distributed among Member States, a literature review on IVE methods and consultations with influenza experts. Results from the survey and literature review
highlighted the variety of data sources used to estimate IVE and the difficulty with interpreting IVE data, which varies with age, risk group, outcome specificity, and virus-vaccine mismatch. Consultation with influenza experts yielded the following recommendations: measure IVE in the same population in various seasons; control for positive and negative confounding; and include laboratory-confirmation as an outcome measure in study designs.50

During the 2008 to 2009 influenza season pilot case-control studies were conducted in five countries, including Denmark, Hungary, Portugal, Romania, and Spain.48 In order to develop a sustainable system, the framework of existing general practitioner-based (GP) influenza sentinel surveillance systems was utilized and all participating countries are members of the EISN.48 The study population was restricted to community-dwelling elderly and IVE (influenza vaccine effectiveness) was measured against laboratory-confirmed influenza.48 To control for health seeking behavior, recent studies suggested comparing individuals consulting for ILI and are influenza positive to individuals consulting for ILI who test negative for influenza (negative controls).48 The feasibility of conducting a pooled analysis was additionally explored in order to increase the precision of estimates and to provide a summary IVE for the five studies. Country-specific and pooled IVE estimates indicated a protective effect of the 2008 to 2009 interpandemic vaccine in the elderly population in a year with a good match between the vaccine virus and the influenza A (H3) strain predominantly circulating in Europe.48 These results also suggested the feasibility in Europe of using test-negative controls to estimate interpandemic IVE against laboratory-confirmed influenza.48 Pooling of country-specific data was found to be necessary to have early interpandemic or pandemic IVE estimates and would also increase the precision of these estimates for subgroup analysis. A final observation indicated that future studies based on sentinel GPs to measure pandemic IVE will depend on the vaccination and control strategies of respective countries.48

During the 2009 to 2010 influenza season the I-MOVE network conducted case-control studies in seven countries (including France, Hungary, Ireland, Italy, Romania, Portugal, and Spain) based on sentinel GP surveillance networks.51 The objective of these studies was to estimate the effectiveness of 2009-2010 pandemic influenza vaccines against laboratory-confirmed pandemic influenza A (H1N1) (pH1N1).51 Data from all seven studies were also pooled to provide an overall adjusted estimate of IVE. Results demonstrated that one dose of a pandemic vaccine conferred adequate protection against laboratory-confirmed pH1N1.51 IVE was higher in individuals aged 65 years and older and also in those without any chronic disease conditions.51 Furthermore, point estimates suggested good IVE as early as eight days post-vaccination.51 Future studies should increase the sample size per country in order to allow for more precise stratified and pooled analyses.

A separate study conducted in Germany assessed the IVE of a monovalent AS03-adjuvanted vaccine, Pandemrix®, which was used almost exclusively during the 2009 pandemic in this country.52 One dose vaccination was recommended for all age groups. However as stated earlier, immunogenicity data was the only basis for the licensure of these pandemic vaccines therefore it is essential to estimate IVE in order to confirm that a one dose vaccination regimen induces sufficient protection across all age and risk groups.52 Preliminary results showed excellent IVE in individuals aged 14-59 years and moderately high IVE in those 60 years and older.52 The vaccine was also found to be effective in chronically ill persons.52
Future studies should further analyse IVE in the elderly and individuals with chronic conditions.

It is worth noting that following the H5N1 influenza outbreak, the amount of global attention, research and ultimately, funding directed towards influenza increased substantially. Many pharmaceutical companies have since invested in developing new vaccines therefore it is only practical and financially responsible that the effectiveness of these vaccines be monitored, both from the pharmaceutical industry and public health perspectives. This network was in the beginning stages of development when the 2009 H1N1 pandemic occurred. The basis for licensure of the pandemic vaccines that were produced relied on immunogenicity data available at the time; however, it is unknown how well they correlate with protection. As strong immunogenicity does not always result in robust vaccine effectiveness, the importance of estimating effectiveness of vaccines at the population level was further reiterated by the 2009 H1N1 influenza pandemic.

On 3-4 December 2012, the WHO and CDC convened the International Meeting on Influenza Vaccine Effectiveness with the aim to review the current landscape of IVE evaluation, to identify data pooling opportunities and to develop a consensus for best practices for IVE studies. The meeting identified key issues surrounding IVE evaluation including limited data available particularly in low- and middle-income countries (LMIC) and the need for standardization of methodology in measuring IVE to improve comparability between studies. International data pooling was also emphasized as an important strategy for generating regional and global IVE estimates. Final discussions focused on the critical need to communicate IVE findings appropriately and effectively as well as to develop a guidance document for best practices in IVE studies. With the potential to drive evidence-based public health decisions, IVE studies are essential for future influenza vaccine policy development.

5.1.1 Vaccine policies and coverage

A novel vaccine provision study

In 2003, the World Health Assembly (WHA) adopted a resolution on the “Prevention and control of influenza pandemics and annual epidemics.” In this resolution, the WHA recognized the substantial public health burden of influenza. Consequently, the WHO acknowledged the role of immunization in preventing and reducing this health burden by providing recommendations for the vaccination of high-risk population groups. This position is similarly reflected by many government public health policies, as more than 40% of countries worldwide include interpandemic influenza vaccination in their national immunization schedules. The 2003 WHA resolution also set a goal for countries with influenza vaccination policies, requesting for an increase in vaccine rates for all high-risk individuals. Despite this collective concern on the need to increase vaccination coverage, systematic worldwide data has not been available to assist public health authorities in assessing vaccine provision, uptake or the impact of immunization policies. Although the original background paper did provide data of vaccine provision in 56 countries from 1997 to 2003 conducted by the Macroepidemiology of Influenza Vaccination study group, no formal mechanism has been established to provide continuing information on a regional or global basis.
To address the lack of a formal monitoring system, the International Federation of Pharmaceutical Manufacturers and Associations Influenza Vaccine Supply task force (IFPMA IVS) developed a survey in 2008 to assess global influenza vaccine provision and reported the results of 141 countries from 2004 to 2007. In 2010, this database was updated and extended to include information from 157 countries from 2004 to 2009. A secondary objective included using a subgroup of 26 countries to collect data on immunization recommendations, reimbursement and communication policies to evaluate correlation with national vaccine provision data. A third and final study objective utilized United Nations (UN) data and a novel vaccine provision “hurdle” rate (set at 15.9% of the population, based on WHO immunization recommendations for the elderly) to compare vaccine provision with country development status.

Results from this study indicated a total worldwide distribution increase of 72% from 262 million doses in 2004 to 449 million doses in 2009 as depicted in Figure 6.2.3. On a WHO regional basis, distribution increased in all regions although growth was not uniform. The Americas and Europe consistently accounted for 75% to 80% of total vaccine provision each year.

Figure 6.2.3 Global interpandemic influenza vaccine dose distribution from 2004 to 2009 divided by WHO region


Note: AF- African; AM- Americas; EM-Eastern Mediterranean; EU- European; SEA-South East Asian; WP- Western Pacific

Over the six-year survey period, vaccine provision increased in more than 70% of the 157 study countries with notable rises in Europe (France, Germany, Italy, the Netherlands, Spain, and the United Kingdom), the Americas (Brazil, Colombia, Mexico, and the USA) and in China, Japan, and Thailand. However, growth was not consistent, as the United States’
distribution peaked in 2007 and subsequently decreased 23% in the following two years. A number of countries also experienced a decline of dose distribution, with a marked decrease in the Republic of Korea where provision deceased 27% over the study period. Overall, despite encouraging growth at the national, regional and global levels, no country distributed sufficient vaccines for half of its total population and only 20% of study countries achieved the study “hurdle” rate of 159 doses per 1 000 population, shown in Figure 6.2.4. Furthermore, in excess of two-thirds of countries did not provide adequate doses to encompass 10% of their populations while remarkably, one-third of countries did not distribute enough to protect even 1% of their populations. Figure 6.2.4, shown below, does demonstrate an improvement in most EU countries as compared to a similar figure on page 17 of the 2004 background paper.

On a per capita basis, vaccine supply did not correlate directly with national income. By UN designation, the study included 46 more developed and 108 less developed countries. Of the 31 countries with vaccine provision greater than 159 doses per 1 000 population, 29% (nine countries) were less developed. In the subgroup analysis of 26 countries, the presence of official vaccination recommendations did not demonstrate good correlation with higher vaccine provision. However, reimbursement and the use of extensive communication activities correlated 3.5-4.1 times more strongly with vaccine supply than the presence of an immunization policy alone.

The findings from this study reveal that despite the widely recognized benefits of influenza vaccination, national recommendations are not being fully implemented and immunization rates remain low. For example, in 2009 the United States distributed sufficient vaccine for 36% of its population although its Advisory Committee on Immunization Practices (ACIP) recommends that approximately 85% of the population be vaccinated. The strong correlation of reimbursement and communication activities with vaccine coverage reiterate previous research in Europe concluding that increasing vaccine rates require public education campaigns and funding for vaccinations in addition to healthcare workers proactively recommending immunization to at-risk individuals. The importance of continued efforts to increase vaccine coverage cannot be undermined as the use of interpandemic influenza vaccines not only protect against annual epidemics but also provides the foundation for pandemic preparedness. Annual interpandemic vaccine utilization sustains production capacity, which ultimately facilitates the global capability to respond during a pandemic.
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Figure 6.2.4 Global interpandemic influenza vaccine dose distribution per 1,000 population (2009)

2009 (H1N1) pandemic vaccination policies and coverage

Based on epidemiology of the population groups most affected during the initial phase of the pandemic, international organizations including the WHO Strategic Advisory Group of Experts (SAGE), the EU Health Security Committee (HSC), and the U.S.CDC issued evidence-based vaccination recommendations for target groups in order to assist in standardizing national policies. Although recommendations varied slightly across the organizations, health care workers (HCWs), pregnant women and individuals with underlying chronic conditions were uniformly included as priority groups. The WHO SAGE recommended that all countries prioritize immunizing HCWs first as a mitigation strategy to protect the essential health infrastructure and to vaccinate all other priority groups in the following order, as shown in Table 6.2.1. In addition, the WHO SAGE stated that initially as there will be an insufficient amount of pandemic vaccines available, a stepwise approach to vaccinating priority groups will need to be considered.

In August 2010, the ECDC requested the Vaccine European New Integrated Collaboration Effort (VENICE) consortium to conduct a survey collecting information on influenza A (H1N1) pdm09 vaccination policies and vaccination coverage in the EU, Norway and Iceland. Prior to the 2009 H1N1 pandemic, most EU/EEA countries had already included pandemic vaccines as a component of their national mitigation plans. All 29 EU/EEA countries participating in the VENICE project responded to the survey with 26 countries implementing pandemic vaccination programmes and one country provided vaccination recommendations but did not have a specific programme. Twenty-five countries also published official documentation in the form of a policy or guidelines on vaccination recommendations. Almost all countries with pandemic vaccination programmes had the same policy across the country with the exception of Sweden, who reported having different regional strategies.

Despite international recommendations set forth, results from the VENICE study indicate differing recommendations for target groups between countries. Vaccination of healthcare workers and pregnant women was recommended by all 27 countries with established vaccine recommendations. Variation in age group recommendations also existed with 12 countries recommending vaccination for all ages while six countries had recommendations for specific age groups in children and three countries had recommendations for specific adult age groups. All pandemic vaccine recommendations countries recommended vaccination for individuals with chronic respiratory, cardiovascular or renal disease; however, only 16 countries recommended vaccination for individuals with morbid obesity. Interestingly, although most countries identified similar target groups for vaccination, results demonstrate substantial variability in vaccination coverage. Reported vaccination coverage for the entire population ranged from 0.4% to 59% in 22 countries with the highest coverage reached in the Netherlands and the Nordic countries (30% to 59%). Vaccination coverage for HCWs ranged from 3% to 68% (13 countries); 0.0% to 58% for pregnant women (12 countries) and 0.2% to 74% for children (12 countries).

The notable variability in vaccination coverage between study countries even with similar vaccination recommendations is an important indicator of the improvement needed in effectively translating vaccine recommendations, whether at the national or international levels, into higher vaccination coverage. Individual countries should focus on strengthening or implementing vaccination coverage monitoring systems. Accordingly, international
organizations must create or utilize a standardized methodology in conducting annual population based surveys in order to strengthen vaccine coverage comparisons between countries.

Table 6.2.1: International organization recommendations for 2009 pandemic A (H1N1) vaccination

<table>
<thead>
<tr>
<th>Key Recommendations</th>
<th>WHO Strategic Group of Experts</th>
<th>EU Health Security Committee</th>
<th>U.S. Centers for Disease Control and Prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General considerations &amp; criteria for selecting priority and target groups</strong></td>
<td>‘Countries should determine their order of priority based on country-specific conditions.’</td>
<td>‘It is within the mandate and responsibility of Member States to develop a vaccination strategy for influenza A (H1N1) 2009.’ No priority order between categories below.</td>
<td>‘Vaccination efforts should focus initially on persons in five target groups, listed below.’ No priority order between categories below.</td>
</tr>
<tr>
<td><strong>Priority and Target Groups</strong></td>
<td>Healthcare workers • All countries should immunize HCWs as a first priority to protect health infrastructure</td>
<td>Healthcare workers</td>
<td>Healthcare workers and emergency medical services personnel • Persons who have direct contact with patients or infectious material</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>Increased risk for severe disease</td>
<td>Pregnant women</td>
<td>Pregnant women</td>
</tr>
<tr>
<td>Persons from age six months and up with chronic medical conditions</td>
<td>All persons from age six months and up with underlying chronic medical conditions • Increased risk for severe disease</td>
<td>Children and adolescents aged 5-18 years with medical conditions • Increased risk for influenza-related complications</td>
<td></td>
</tr>
<tr>
<td>Healthy young adults (aged 16-48 years)</td>
<td>To reduce morbidity and mortality</td>
<td>Persons who live with or provide care for infants ages less than months</td>
<td></td>
</tr>
<tr>
<td>Healthy children</td>
<td>To reduce transmission</td>
<td>Children aged six month to four years</td>
<td></td>
</tr>
<tr>
<td>Healthy adults (aged between 49 and 65 years) &amp; (aged above 65 years)</td>
<td>To reduce morbidity and mortality</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


5.1.2 Cost-effectiveness

The health burden of influenza is globally acknowledged as a threat to public health. The WHO estimates the global disease burden from influenza of up to one billion infections, three to five million cases of severe disease and between 300 000 and 500 000 deaths annually. Early estimates from the United States in February 2010 indicated 59 million illnesses, 265 000 hospitalizations, and 12 000 deaths from the 2009 H1N1 virus. Studies
have shown that the working population, known as healthy adults aged 15-64 years, constitutes the largest group affected by influenza. Although most people recover within one to two weeks, it does not attenuate the health and economic impact of the disease.

A 2009 study evaluated the effectiveness of influenza vaccination among working adults aged 50-64 years in reducing the rate of ILI and productivity losses. Findings from the study revealed that ILI occurred frequently with related morbidity among the study participants of working adults aged 50-64 years. Influenza-like illness was associated with 45% of days of illness due to all causes and 39% of work days lost due to all causes in the unvaccinated participants. Among the vaccinated participants, there was a substantial 45% reduction in the risk of ILI and more than 60% reduction in the number of days of illness and days of work lost. A previous systematic review of influenza vaccine for healthy adults aged 65 years and under demonstrated that vaccination correlated with a mean reduction in the number of days of illness of 0.48 days per person vaccinated and also with a mean reduction in the number of lost working days of 0.21 days per person vaccinated. Similar results from the 2009 study and prior analyses provide evidence that vaccinating working adults aged 50-64 years can offer benefits consistent with those previously seen in healthy working adults (<65 years) populations.

The outbreak of the 2009 H1N1 pandemic presented an opportunity to examine the cost-effectiveness of maternal influenza immunization against laboratory-confirmed influenza, which had not been previously studied. Initial data from the pandemic suggested that the 2009 H1N1 virus strain was generating higher morbidity and mortality among pregnant women, consistent with previous pandemics. Although the CDC ACIP committee recommends yearly influenza vaccination for all pregnant women, data shows a low 13% rate of maternal vaccination in the United States. This 2009 study used an analytic computer simulation model to simulate the decision of maternal immunization for an influenza epidemic and/or pandemic. Incremental cost-effectiveness ratios determined that when influenza prevalence reached ≥ 7.5% and influenza-attributable mortality is ≥ 1.05%, it is cost-effective to vaccinate pregnant women with either a single or two-dose regimen. With higher influenza prevalence, ≥ 30%, the single-dose strategy demonstrated cost-savings while the two-dose strategy remains highly cost-effective. These results provide evidence of the cost-effectiveness of maternal influenza vaccination at disease prevalence rates resembling both interpandemic seasons and pandemic outbreaks. Furthermore, the study showed that cost-effectiveness becomes increasingly established as prevalence and severity of influenza increases within the population. However, a different study published in the same year by the same author reported reticence among pregnant women in accepting vaccination using a pandemic avian influenza vaccine that had been rapidly developed. Even so, the demonstrated safety of interpandemic vaccines during pregnancy, the ethical obligations that exist for protecting vulnerable populations and favorable cost-effectiveness justify strong and continued support for maternal influenza vaccinations.

Historically, the target groups for national vaccination recommendations have included nursing home residents, the elderly, and individuals with underlying medical conditions. Recent evidence, however, indicates substantial health and economic consequences associated with influenza among children as well. Studies describe children as having the highest rates of illness from influenza infections resulting in increased healthcare
utilization. Hospitalization rates have also been reported to be similar to those observed among the elderly. Additional concerns include indirect costs such as productivity losses for parents and the transmission of influenza within households and communities. Yet despite the availability of effective vaccines to prevent influenza in children and the increasing documentation of the health and economic costs of influenza in children, broad variation exists within international vaccination recommendations for children. In 2011, a systematic review was conducted yielding 20 different studies that had assessed the cost-effectiveness of influenza vaccination in children. Most studies showed that vaccination of healthy children would be cost-saving or cost-effective. Two studies indicated that vaccination of the highest risk children resulted in the greatest cost-savings. A major limitation of most of these studies was that few incorporated the potential benefits of vaccinating school children in regards to reducing transmission within households or communities. This omission may have resulted in the underestimation of the benefits of vaccinating school children. The decision by policy-makers, clinicians, and patients to include children in vaccination programmes is an important task with tangible consequences. Future research dictates an opportunity that requires the consideration and understanding of the health and economic consequences of illness and also the cost-effectiveness of vaccination.

5.1.3 Global production capacity

Although vaccination is one of the most effective methods to mitigating the impact of an influenza pandemic, a successful vaccination response hinges upon a timely and adequate vaccine supply. Recognizing the threat of pandemic influenza and the need to substantially strength global preparedness and response activities, the 2005 World Health Assembly (WHA) requested that the WHO collaborate with its international and national partners in order to reduce the global shortage of influenza vaccines. In May 2006, the WHO convened a consultation to develop a plan for identifying and implementing the best methods to reduce the anticipated gap between influenza vaccine demand and supply during a pandemic. It was realized at that time that if a pandemic were to occur, there would be a shortage of the sufficient amount of vaccine needed, in the range of several billion doses, in order to protect the world’s population. An additional observation was the marked variation between countries in their respective priorities, resources and capacities for establishing national influenza vaccination policies and programmes. A third and equally important observation from this meeting was that all major influenza vaccine manufacturers were located almost exclusively in Australia, North America, Europe, and to a limited extent, Asia. This realization provided concrete evidence that many resource-constrained countries did not have the means to access interpandemic influenza vaccines and therefore would be the most severely affected during a pandemic.

To address these prominent gaps in vaccine supply, three mutually reinforcing strategies were identified:

1) increase the use of interpandemic influenza vaccine;
2) increase influenza vaccine production capacity; and
3) promote influenza vaccine research and development.

These strategies consequently became the foundation for a global pandemic influenza action plan to increase vaccine supply, which was thereafter known as the Global Action Plan for Influenza Vaccines (GAP).
The second activity for increasing influenza vaccine production capacity encompassed both short-term and medium- to long-term objectives. The short-term objective was to facilitate sufficient vaccine production to immunize two billion people within six months following the availability of a pandemic virus vaccine candidate. The medium- to long-term objective was to produce enough vaccine to immunize the world’s population of 6.7 billion people.

A principal achievement of the GAP plan is its prominent role as the catalyst for the significant expansion in global influenza vaccine manufacturing capacity. Interpandemic vaccine production increased from 350 million doses in 2006 to approximately 900 million doses by June 2009. In 2010, the WHO conducted a survey of vaccine manufacturers in order to quantify the increase in global influenza vaccine production capacity since the inception of GAP and actual production in response to the 2009 H1N1 pandemic. The survey was distributed to 33 current or potential influenza vaccine manufacturers, listed in Table 6.2.2, with projected production capacity by the second quarter of 2010. The questionnaire requested data on actual production (in millions of doses) of monovalent influenza A (H1N1) pandemic vaccine by formulation as of 1 December 2009 and forecasted production of any formulation by 1 March 2010 and 1 June 2010.

Table 6.2.2 Influenza vaccine manufacturers with expected production capacity by 2010

<table>
<thead>
<tr>
<th>ADImmune Corporation</th>
<th>Denka Seiken</th>
<th>Novartis Vaccines &amp; Diagnostics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baxter</td>
<td>GlaxoSmithKline Biologicals</td>
<td>Omnivest</td>
</tr>
<tr>
<td>Berna-Crucell</td>
<td>GPO Thailand</td>
<td>Panacea Biotech</td>
</tr>
<tr>
<td>Bharat Biotech</td>
<td>Green Cross Corporation</td>
<td>Sanofi Pasteur</td>
</tr>
<tr>
<td>Biken</td>
<td>Henan Hualan Biological Engineering Inc.</td>
<td>Serum Institute of India</td>
</tr>
<tr>
<td>Changchun Changsheng Life Sciences Limited</td>
<td>Institute of Virology</td>
<td>Shenzhen Neptunus Bioengineering Co.</td>
</tr>
<tr>
<td>Chemo-Sero-Therapeutic Research Institute</td>
<td>Vaccines and Sera Torlak</td>
<td>Sinopharm</td>
</tr>
<tr>
<td>Bio Farma</td>
<td>IVAC</td>
<td>Sinovac Biotech</td>
</tr>
<tr>
<td>Cantacuzino Institute</td>
<td>MedImmune</td>
<td>Solvay Pharmaceuticals</td>
</tr>
<tr>
<td>CSL Biotherapies</td>
<td>Microgen</td>
<td>Vabiotech</td>
</tr>
<tr>
<td>Dalian Aleph Biomedical Co., Ltd</td>
<td></td>
<td>ShangHai Tianyuan Bio-Pharmaceuticals Co., Ltd</td>
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Results from the survey revealed that the number of monovalent pandemic H1N1 vaccines produced by 1 December 2009 was 534 million doses. Forecasted production by 1 March 2010 and 1 June 2010 was 1 303 million doses and 1 367 million doses, respectively. Of the 1 367 million doses to be produced by June 2010, 46% (636 million doses) were projected to originate from the WHO Europe (EUR) geographic Region, 30% (410 million doses) from the Americas (AMR) Region, and 21% (293 million doses) from the Western Pacific (WPR) Region. This distribution of vaccine production aligns with the distribution of the number of global vaccine production facilities. At the time of survey administration, there were 41 current and potential influenza vaccine production facilities spread across 25 countries. Nine of these countries also had recently acquired the capability to manufacture influenza
vaccines (Figure 6.2.5). Sixteen (39%) of the 41 facilities are located in the WPR and 12 facilities (26%) are located in the EUR. Seven manufacturers in the Americas Region (AMR, n=2), the Eastern Mediterranean Region (EMR, n=2), the South-East Asia Region (SEAR, n=2), and the WPR (n=1) are expected to begin vaccine production over the next five years. A notable observation from the survey was the lack of current and potential manufacturers in the sub-Saharan Africa (AFR) Region. Even with the emergence of new vaccine manufacturers globally, more than 80% of interpandemic influenza vaccine doses produced in the 2009-2010 season will have come from the seven large manufacturers located in the United States, Canada, Australia, western Europe, Russia, China, and Japan.

Figure 6.2.5 Countries with influenza vaccine production capacity in 2006 and 2010

![Map showing countries with influenza vaccine production capacity in 2006 and 2010.](image)


Finally, the survey demonstrated that regardless of extensive efforts by all stakeholders during the 2009 pandemic, the number of available pandemic vaccine doses for use was well below the WHO’s GAP targets. A WHO survey previously conducted in May 2009 estimated an annual global production of 4.9 billion doses; however, forecasted pandemic vaccine production 12 months after the availability of vaccine virus was only 28%, 1.37 billion doses, of the initial estimate. Furthermore, as the short term goal of GAP was to be able to provide enough vaccine to immunize two billion people, the actual production by December 2009 was only 534 million doses of monovalent pandemic vaccine.

Expanding the global production capacity is not sufficient enough, however, to ensure universal access to influenza vaccine during a pandemic. Moreover, it is not realistic or possible to establish vaccine production in every country. For these reasons, the WHO funded grants to manufacturers are contingent upon an agreement to sell 10% of their vaccine production at an affordable price to United Nations agencies for distribution to countries without production capacity. The ability to expand to almost 900 million doses...
was achieved mainly by the considerable investment by multinational manufacturers in new and enlarged production plants.\textsuperscript{62} Despite substantial growth in global production capacity, the 2009 H1N1 pandemic underlined remaining gaps in the availability of vaccine, especially in developing countries. A sizeable portion of the projected pandemic vaccine production was already reserved prior to the onset of the pandemic through advanced-purchase agreements by high-income country governments. This resulted in the substantial delay of pandemic H1N1 vaccine to most developing countries until January 2010, more than eight months following the declaration of a pandemic by the WHO.\textsuperscript{62} The historic adoption of the Pandemic Influenza Preparedness (PIP) Framework at the 64th WHA in May 2011 was the culmination of five years of protracted negotiations.\textsuperscript{61} The PIP Framework provides comprehensive political and technical guidance on ensuring an efficient, effective, equitable, fair, and transparent mechanism for sharing influenza viruses and access to vaccines and other benefits.\textsuperscript{61} The complete document can be accessed in Appendix 6.2.3.\textsuperscript{63}

In 2011, the WHO convened the second WHO GAP consultation in order to review progress made from the first five years and lessons learned from the 2009 H1N1 pandemic.\textsuperscript{61} This second meeting assembled representatives from United Nations agencies, national governments, funders, regulatory authorities, manufacturers, nongovernmental organizations, and the research community. Proposed actions for increasing influenza vaccine production capacity include \textsuperscript{61}:

- Continued evaluation of new methods and approaches for production optimization;
- Investigating the feasibility of multipurpose facilities;
- Reduction of the vaccine production timeline;
- Strengthening national regulatory agencies in order to efficiently assess and approve influenza vaccines;
- Ensuring stringent post-marketing surveillance and
- Facilitating increased safety and risk communication between governments.

Annual interpandemic vaccine utilization sustains production capacity (See Section 5.1.1); however production capacity alone also does not automatically advance equitable access to vaccines. Therefore, pandemic preparedness is a monumental task that requires diligence and the commitment and cooperation at the national, bilateral and international levels including public and private sector partnerships, in order to build adequate capacity to respond to the next influenza pandemic.

\textbf{5.1.4 WHO technology transfer initiative}

In accordance with GAP’s vaccine production capacity objective, the WHO influenza vaccine technology transfer initiative was introduced in 2007, seeking to create regionally based, independent and sustainable influenza vaccine production capacity in developing countries.\textsuperscript{64} Financial support has been provided by the Public Health Agency of Canada, the Ministry of Foreign Affairs of Japan, the United Kingdom Department for International Development, the United States Department of Health and Human Services, and the Asian Development Bank.\textsuperscript{61} To date, approximately US$ 28 million of seed funding has been granted to 11 developing country manufacturers (Brazil, Egypt, India, Indonesia, the Islamic Republic of Iran, Mexico, the Republic of Korea, Romania, Serbia, Thailand, and Viet Nam).\textsuperscript{61} Funding has also enabled the establishment of a centre for excellence for training and transfer of influenza vaccine production technologies to new manufacturers.\textsuperscript{64}
To facilitate the technology transfer process, the WHO also created an influenza vaccine technology ‘hub’ – a novel concept to pooling resources for vaccine manufacturing capacity-building. The Netherlands Vaccine Institute (NVI), which over the past decade has implemented numerous technology transfer projects to developing country manufacturers for various vaccines, was selected to conduct all training and technology transfer. The technology ‘hub’ model encompasses a complete manufacturing process that is void of intellectual property restrictions and other barriers resulting in simultaneous accessibility by multiple recipients. By establishing partnerships with technology proprietors, WHO has been able to negotiate a non-exclusive royalty-free license to develop, manufacture and sell to the public sector both interpandemic and pandemic egg-derived live-attenuated influenza vaccines (LAIV). WHO will then provide sub-licenses to manufacturers in developing countries. In the first two years of operation, a transferable pilot process for egg-based inactivated whole virus influenza A vaccine production was established as well as a course curriculum on production and quality control. Future expansion of the curriculum include cell-culture based technology for viral vaccine production, split virion influenza production, and generic adjuvant formulation. Technology transfer facilitated by the ‘hub’ model has thus far succeeded in building production capacity in developing countries.

To measure interim results of the technology transfer initiative, a survey was administered in 2010 to all 11 developing country manufacturers receiving grants from the WHO. Three manufacturers (27%) responded as having already produced and distributed interpandemic influenza vaccine in their countries. The other eight countries indicated projected commencement of commercial-scale vaccine production between 2010 and 2012. Additionally, five countries (India, Indonesia, the Republic of Korea, Romania and Thailand) produced licensed pandemic influenza vaccines between 2009 and 2011. Finally, although two countries do not plan to introduce interpandemic influenza vaccination in their national programmes by this date, the remaining nine manufacturers (82%) will be able to meet the demand for interpandemic influenza vaccine in their country by 2015.

Technology transfer is a complicated process that requires the creation of a solid partnership the technology provider and the country recipient. The technology provider must be committed and also willing to transfer a complete production process. The recipient must also have established experience in vaccine production and the ability to conduct research into new technologies. The Instituto Butantan-Sanofi Pasteur partnership can be viewed as a model for successful technology transfer which has led to the technological independence of the institute in serving as a strategic public health tool. The avian influenza outbreak in 2003 was a powerful indicator for Brazil to increase its influenza pandemic preparedness. At the time, the country did not have the influenza production capacity therefore Brazil pursued a technology transfer partnership to construct a dedicated influenza vaccine production facility. In the interim, the plan was to formulate and finish monovalent bulk vaccines supplied by an international vaccine manufacturer, who would become the technology provider. Brazil selected Sanofi Pasteur as its technology transfer partner due to the company’s extensive experience in large-scale influenza vaccine production and also the established relationship of the company with Brazil. The technology transfer would be for an egg-based inactivated split interpandemic influenza vaccine as well as a whole virion adjuvanted H5N1 vaccine. With funding from the Ministry of Health and the State of Sao Paolo Office of Health and final validation from Sanofi Pasteur, the construction of a new influenza production plant was completed and ready for production by September 2010. Beginning in 2011, the new facility plans to produce 20-25 million doses of trivalent southern
hemisphere interpandemic vaccine every year. Following receipt of a financial grant from the WHO technology transfer initiative, a pilot plant was constructed to allow the development of basic technology to produce small vaccine lots for evaluation in animal models and under good manufacturing practices (GMP) rules, for a Phase I clinical trial to evaluate safety and immunogenicity. From 2007 to 2009, the pilot plant produced six lots of H3N2, 10 lots of H5N1 (split), 17 lots of H5N1 (whole virion), and 1 lot of H1N1 (split).

Given limited to no production capacity in many countries, technology transfer and utilization of the ‘hub’ model is cost-effective. However this novel technology transfer platform is a considerable endeavor that will necessitate financial and technical support and commitment from governments and the private sector. Consideration for local and regional demands along with selection of vaccine production technologies appropriate to the local setting must be also ensured during this process. It is only through continued collaborative efforts that a sustainable production capacity will be achieved.

5.1.5 WHO international H5N1 vaccine stockpile

One of GAP’s priorities is to promote equitable, timely, and sufficient access to influenza vaccines during a pandemic, with a specific focus on countries with no influenza vaccine production capacity. In order to achieve this objective, the WHO was called upon to seek international support for a H5N1 influenza vaccine stockpile that would benefit developing countries. A previous WHO meeting held in early October 2007 had discussed policy options for the use of H5 vaccines, including potential use during the interpandemic period and also the potential use of a stockpile in the event of a pandemic. Scientific evidence presented at this meeting demonstrated no significant safety concerns with the H5 vaccines reviewed. The primary outcome of this meeting included two proposed policy options for use of a WHO H5N1 vaccine stockpile: i) for rapid containment in response to a pandemic signal and ii) to provide assistance to countries with no vaccine production capacity by vaccinating essential groups of the country population considered to be critical to maintain functionality of the country.

In late October 2007, the WHO convened an informal consultation on the technical specifications for an WHO international H5N1 influenza vaccine stockpile. The objective of the meeting was to generate recommendations for the establishment, operation and sustainability of the proposed vaccine stockpile. Technical specifications discussed included quality, safety, efficacy, regulatory pathways, logistic parameters and guiding principles for access to the stockpile. The perspectives of key stakeholders, including industry, developing country recipients, regulatory agencies, and donors were also taken into consideration.

Key lessons from the management of other WHO vaccine stockpiles (e.g. yellow fever and meningitis) were presented prior to further discussion of technical specifications of the proposed stockpile. Vaccine stockpiles can assume different characteristics depending on the disease, the use of the vaccine, and principles such as equitable access. The creation of an international vaccine stockpile is also a complex process which in addition to the stockpile itself; includes ancillary equipment, shipping, vaccination campaigns, waste management, and surveillance elements. Funding and maintenance of production capacity were also noted as important factors to ensure vaccine supply continuity. Finally, a distinguishing factor of the H5N1 vaccine stockpile from current vaccine stockpiles is that the proposed use of the H5N1 stockpile is intended for outbreak control rather than a mass vaccination
therefore only a small proportion of the vaccine is expected to be released to a given population.\textsuperscript{68}

Results from the previous meeting on policy options for the use of H5 vaccines were utilized in accordance with this meeting in order to generate recommendations for the WHO Department of Immunization, Vaccines, and Biologicals (IVB) SAGE group for decision-making. Box 6.2.4 outlines a summary of recommendations on the technical specifications for a WHO international H5N1 vaccine stockpile. The comprehensive meeting report can be accessed in Appendix 6.2.4.\textsuperscript{68}

Box 6.2.4: Summary recommendations for a WHO international H5N1 vaccine stockpile

- In the event of human-to-human transmission of H5N1 virus, stockpiled vaccines would be used for rapid containment of a pandemic and equitable distribution to low- and middle-income countries (LMIC) to immunize essential populations as defined by the Member State.
- Although clinical and non-clinical requirements differ for pandemic versus interpandemic vaccines, the WHO guidelines on clinical and non-clinical evaluation of vaccines are considered applicable for an H5N1 vaccine stockpile.
- Strain selection and the continued appropriateness of the H5N1 strain to induce immunity against drift variants should be based on WHO recommendations.
- Vaccines should be licensed by a functional national regulatory authority (NRA) and submitted for WHO prequalification.
- Clear selection criteria for acceptance of vaccines should be developed. Based on current evidence, only inactivated influenza vaccines (IIV) should be considered.
- Data requirements for regulatory approval of an H5N1 stockpile vaccine are additional to those for interpandemic vaccines.
- Written criteria should define what needs to be done, by whom and when.
- The WHO should update the draft target specifications to assess continued potency of stockpiled vaccine.
- The WHO should facilitate data exchange among laboratories studying the stability of stockpiled vaccine.
- Country pandemic preparedness plans should include acceptance of vaccines from the stockpile.


During the 2009 H1N1 pandemic, the WHO EURO was active in facilitating various vaccine procurement activities.\textsuperscript{43} These activities included vaccine development and procurement, negotiating with vaccine manufacturers, prequalification of pandemic H1N1 vaccines, and stockpiling to ensure provision of vaccines at a reduced price to lower income countries of the WHO European Region.\textsuperscript{43} In September 2009, the EC also provided technical assistance with developing public tender notices to EU Member States that had not yet procured pandemic H1N1 vaccines.\textsuperscript{43}
5.2 Antiviral agents

Although vaccination plays a prominent role in the prevention and control of influenza, its utility, if not adequately available, is insufficient during a pandemic. This is due to the time required to approve, register, and manufacture a new vaccine. Therefore in the interim, antiviral therapy is an effective and critical tool to mitigating the effects of an influenza pandemic. Current antiviral agents can be classified as either neuraminidase inhibitors (NAIs) or M2 inhibitors. Commercially-available NAIs include oseltamivir and zanamivir; M2 inhibitors include amantadine and rimantadine. NAIs are the preferred treatment option due to the continued high prevalence of influenza A (H1N1) and influenza A (H3N2) resistance to the M2 inhibitors. The high resistance to one of the two classes of antiviral agents underscores the need for the development and approval of new NAIs other than oseltamivir and zanamivir. In 2010, two new NAIs; laninamivir and peramivir, were approved for clinical use for the treatment of influenza A infection in Japan. A 2012 study was conducted to evaluate the clinical effectiveness of all four NAIs, oseltamivir, zanamivir, laninamivir, and peramivir on influenza A (H1N1) and (H3N2) infected patients during the 2010-2011 season. Duration of fever was used as the indicator of clinical effectiveness. For influenza A (H3N2) infected patients, the peramivir treatment group had the fastest time of fever alleviation compared to the other NAIs. No significant difference in the time to alleviation was observed for the other antivirals. Only oseltamivir and zanamivir were compared in the influenza (H1N1) infected patients and no significant difference was observed in the time to fever alleviation. Currently available NAIs are effective but the potential for drug resistance justifies further analysis of the effectiveness of the newly licensed NAIs to treat influenza infection.

5.2.1 Cost-effectiveness

During the 2009 influenza A (H1N1) pandemic, oseltamivir and zanamivir were used to treat infection; however, the virus was most susceptible to these drugs during the first 48 hours of infection. Early antiviral treatment with NAIs was recommended for H1N1 infected patients with severe symptoms or underlying conditions associated with a high risk of developing interpandemic influenza complications in all high-income countries except for the United Kingdom. These recommendations were based on existing knowledge and understanding of antiviral treatment for interpandemic influenza. However, initial data following the onset of the H1N1 pandemic indicated that unlike interpandemic influenza, a high proportion of severe and fatal influenza complications were occurring in previously healthy young individuals. Given these data and the decreased efficacy of NAIs more than 48 hours after the onset of symptoms, a re-evaluation of antiviral treatment recommendations for whether to treat all patients with antiviral therapy or only those at high risk for complications was needed. In late 2009, a decision model study was conducted using available data in order to estimate the clinical and economic outcomes associated with early initiation of NAIs in all symptomatic patients versus only those at high risk for influenza complications. Study results confirmed that systematic treatment of ILI during an influenza A (H1N1) epidemic wave was both effective and cost-effective. Regardless of risk status, antiviral treatment with NAIs should have been initiated for all patients who present to care with ILI during the influenza A (H1N1) pandemic wave. However, during the interpandemic influenza season when probability of influenza is low, the administration of NAIs for treatment of influenza infection is less effective and less cost-effective.
5.2.2 Stockpiling

Stockpiling antiviral agents is a functional strategy to mitigating the impact of future influenza pandemics; however, limited data exists in regards to the optimal long-term size of a stockpile under the different capabilities of countries around the world. A 2011 study used an epidemic economic model to evaluate the costs of antiviral stockpile sizes and their effects on total mortality.\textsuperscript{72} Study countries included Brazil, China, Guatemala, India, Indonesia, New Zealand, Singapore, the United Kingdom, the United States, and Zimbabwe.\textsuperscript{72} This study demonstrated that stockpiling antivirals considerably reduced mortality.\textsuperscript{70} Stockpiling in more developed countries showed greater potential to avoid expected costs therefore for perfect allocation, covering 15\% of the country population is needed.\textsuperscript{72} For misallocation, 25\% to 30\% coverage is necessary to minimize deaths and reduce economic costs.\textsuperscript{72} Stockpiling in less developed countries stockpiling could also assist in avoiding substantial fatalities.\textsuperscript{72} For all countries, antivirals should not be the preferred treatment of susceptible individuals but rather be reserved for treatment of influenza infected individuals, where its use would be more successful.\textsuperscript{72} Furthermore, under current antiviral pricing, results also indicated that stockpiling is not cost-effective for more than two-thirds of the world’s population.\textsuperscript{72} Interestingly, oseltamivir and zanamivir are expected to go off-patent in the next five years (2016 and 2013, respectively).\textsuperscript{72} The use of generic antivirals would enable stockpiling to be more cost-effective for China, Indonesia, and India.\textsuperscript{72} However, for resource-limited countries, generic antivirals would still not be cost-effective underlining the need for international collaboration to ensure equitable access to antiviral treatment.

Assuring an international commitment to antiviral stockpiling the PIP Framework, discussed in Section 5.1.3, includes antiviral stockpiling as part of the pandemic influenza preparedness benefit sharing system.\textsuperscript{63}

Antiviral therapy has been proven effective to treat influenza infection; however escalating antiviral resistance to current drugs provides the research opportunity to develop novel therapeutics with reduced drug resistance potential. Additional analysis is also needed to verify the global use of antivirals in order to determine its cost-effectiveness during the 2009 H1N1 pandemic. This information will be critical in the global preparation for future pandemics.

5.3 Rapid influenza diagnostic tests

Rapid and accurate laboratory diagnosis of viral infection is paramount to reducing the morbidity and mortality burden of influenza and its associated social and economic consequences. Studies have demonstrated improved viral clearance in infected persons who began treatment within the first four days of illness, emphasizing the need for rapid and accurate laboratory diagnosis in both inpatient and outpatient settings.\textsuperscript{73}

Rapid influenza diagnostic tests (RIDTs) are rapid, simple-to-use, point-of-care antigen tests that can generate results in 10-30 minutes.\textsuperscript{74} Previous studies on interpandemic influenza have demonstrated high specificities of RIDTS but varying sensitivity levels.\textsuperscript{74, 75, 76} Comparisons of rapid tests evaluated in different studies are difficult to make due to variability across study designs regarding sample sizes, patient age, specimen type, and comparators. Different populations have also been reported to yield different sensitivities, with higher sensitivities in young children as compared to adults.\textsuperscript{75} This may be due to
higher levels and longer duration of viral shedding in children.\textsuperscript{75} In addition, most current RIDTs do not distinguish different influenza A virus subtypes. While influenza can be ruled in using RIDTs, influenza cannot be ruled out with negative results, thus nucleic acid testing or viral culture must be employed for further confirmation.\textsuperscript{74}

During the 2009 H1N1 outbreak, commercially-available RIDTs had not been developed specifically to detect influenza A (H1N1) therefore their performance in detecting this new virus was unknown.\textsuperscript{77} Multiple studies have since investigated the diagnostic accuracy of current RIDTs to detect H1N1 infection. Results are inconclusive as some studies reported lower sensitivity while other reported similar sensitivity as compared to interpandemic influenza.\textsuperscript{77,78,79} As an influenza virus testing method, RIDTs fill the void as a first-line test. More importantly it has utility in patient and outbreak management, enabling clinicians to initiate prompt infection-control measures as well as begin antiviral treatment in high-risk populations earlier. However, it is equally imperative that clinicians understand its limitations, that a negative test should be confirmed using RT-PCR or cell culture.

5.3.1 Cost-effectiveness

As stated above, early treatment within 48 hours of onset has been associated with lower risks for disease progression therefore a rapid clinical decision to treat hospitalized patients is imperative. Recent studies have reported inconclusive results on the diagnostic accuracy of ‘point-of-care’ antigen tests and although PCR tests are highly sensitive, they are expensive and have longer turnaround times (TAT). A 2012 study evaluated the potential costs and outcomes of diagnostic test-guided and empirical antiviral treatment approaches in hospitalized patients with severe respiratory infection in Hong Kong.\textsuperscript{80} A decision tree was designed to simulate the outcomes of four management strategies, including: immunofluorescence assay (IFA)-guided treatment, PCR-guided treatment, empirical treatment with PCR and empirical treatment alone.\textsuperscript{80} Total direct medical cost, survival rate from influenza infection, and quality-adjusted life years (QALYs) were used as key performance indicators.\textsuperscript{80} Results from this study suggest that when interpandemic virus strains were predominant during an influenza season, empirical antiviral treatment alone is a cost-effective option when influenza prevalence levels exceed 2.5%.\textsuperscript{80} When prevalence is less than 2.5% PCR-guided treatment is the most cost-effective approach.\textsuperscript{80} In contrast, when the 2009 H1N1 virus strain was predominant, empirical treatment alone was would be the more cost-effective option for a wider range of prevalence levels, from 0.4% to over 25%.\textsuperscript{80}

Many RIDTs have been developed since the 2009 H1N1 epidemic; however, comprehensive studies on their diagnostic accuracy and cost-effectiveness are absent. A future research priority should be to focus on the potential role of RIDTs for the next influenza pandemic.

6. Vaccination Strategies

Influenza A infection induces an initial innate immune response followed by an adaptive immune response with T cell infiltrates in the lungs.\textsuperscript{81} This robust response is also usually characterized by a significant amount of immunopathology. \textsuperscript{81} The combined immune response and accompanying pathology leaves the host susceptible to secondary bacterial pneumonia, known to be a major cause of death during influenza pandemics.\textsuperscript{81}
Vaccination remains the most effective measure in the prevention and control of influenza and the WHO has urged countries to broaden influenza vaccination programs in order to achieve high vaccination coverage. However, limitations of current vaccination strategies have resulted in the development of novel technologies in vaccine platforms, production methodology, and delivery mechanisms.

6.1 Inactivated versus live attenuated vaccines

Inactivated and live attenuated vaccines are both effective in the prevention of influenza; however, the protection conferred by each varies widely depending on the antigenic match between the viruses in the vaccine and the viruses that are circulating at the time. Because of the antigenic variation between virus strains, the WHO convenes twice annually to recommend the viruses for inclusion in influenza vaccines for the Northern and Southern Hemispheres.

Inactivated influenza vaccines have been used for nearly 70 years with reported 75-90% protection rates. The basis of protective immunity is the induction of strain-specific neutralizing antibodies, which means that the vaccine only provides protection against viruses that are closely antigenically aligned with those in the vaccine. Consequently, inactivated vaccines confer less protection against antigenic drift variants within a subtype of the influenza virus and also do not provide protection against viruses from different subtypes. Influenza vaccines are a sterile, aqueous suspension of a strain or strains of influenza virus. There are four types of available inactivated influenza vaccines:

1) A suspension of whole virus particle inactivated by a suitable method (whole virion vaccine);
2) A suspension treated so that the virus particles have been partially or completely disrupted by biochemical means (split vaccine);
3) A suspension treated so that the preparation consists predominantly of hemagglutinin and neuraminidase antigens (subunit vaccine);
4) A suspension of inactivated influenza virus particles, split or subunit components formulated with an adjuvant.

Since 1967, the WHO Expert Committee on Biological Standardization has provided recommendations for the production and quality control of inactivated influenza vaccines. The most recent revision in 2005 takes into consideration new development methods on influenza vaccine production including: mammalian cell culture production, the use of adjuvants, the development of reverse genetics for the generation of vaccine viruses, and increased levels of pandemic planning (see Appendix 6.2.5). The 1997 (H5N1 virus), 1999 (H9N2 virus) and the 2003 (H5N1 and H7N7 viruses) outbreaks of avian influenza prompted serious concern of a possible pandemic outbreak. These events illustrated that different strategies for the production and use of vaccines are necessary in response to a pandemic. Reducing the time between the emergence of a human influenza pandemic virus and the availability of safe and effective pandemic influenza vaccines has been recognized as a high priority in global health security. To promote coordination between national regulatory authorities, the 58th report of the WHO Expert Committee on Biological Standardization released guidelines on regulatory preparedness for pandemic influenza vaccines, which can be viewed in Appendix 6.2.6.
Live attenuated influenza vaccines (LAIV) are composed of attenuated viruses that contain the same HA and NA antigens as in inactivated vaccines, as required by the World Health Organization and national regulatory authorities. LAIV vaccines have been shown to induce neutralizing serum antibodies, mucosal antibodies, and cellular immunity. Cross-reactive T-cell responses elicited by LAIV can provide heterosubtypic immunity, which can limit viral infection and replication, and reduce disease severity. Given that the influenza virus replicates in nasopharyngeal epithelial cells, LAIV is administered by intranasal drops or spray, an easy route of administration. One of the potential disadvantages to the use of live, attenuated vaccines is that the possibility exists that the attenuated microbe in the vaccine could revert to a virulent form and become pathogenic. However, LAIV has been shown in clinical studies to be genetically stable with no loss of attenuation. Additionally, LAIV cannot be administered to individuals with compromised immune systems. Despite these obstacles, the WHO states that LAIV may be more appropriate for the production of pandemic vaccines because it requires less complex downstream processing than what is needed for inactivated vaccines.

In 1979, the WHO drafted recommendations for the production and quality control of live attenuated influenza vaccines, to take into account the increased interest in immunization using live attenuated viruses. These recommendations, which apply to seasonal and pandemic vaccines, were subsequently revised in 2009 to provide national regulatory authorities and vaccine manufacturers with guidance in developing processes to assure the quality, safety, and efficacy of human live attenuate influenza vaccines for intranasal administration. As the technical report has not been published yet, a preliminary draft of these recommendations can be viewed in Appendix 6.2.7.

### 6.2 Vaccine production methodology

Vaccines have typically been produced from viruses propagated in hen eggs. However, the supply of eggs is limited and would be even more so in the event of a zoonotic outbreak of avian influenza or other diseases affecting chicken flocks. Egg-based production necessitates advanced planning, which is ultimately not feasible in the case of sudden increased demand such as a pandemic and is susceptible to microbial contamination. A new virus strain may also grow poorly in eggs or yield low levels of HA protein, resulting in the need for egg-adaptation through serial passage. Interestingly, although the inactivated vaccines produced lower-than-expected yields of HA protein, the live attenuated 2009 H1N1 viruses reached very high titres in eggs, allowing this vaccine to be distributed first and in a single dose.

In light of these constraints, the WHO has recommended using established mammalian cell lines as an alternative culture system. The use of a cell culture production system has several advantages: assured availability of substrate for virus growth that would allow for increased flexibility to meet fluctuations in demand, avoids the generation of egg-adaptive mutations in the HA protein, provides better manufacturing control through a closed-system fermentation process and is safer for individuals who are sensitive to egg proteins. Three cell lines, Madin Darby canine kidney (MDCK), Vero and PER.C6., have demonstrated effectiveness in vaccine production. A clinical trial conducted in healthy adults in the USA, Finland and Poland during the 2007-08 influenza season, evaluated the clinical efficacy of a cell culture-derived influenza vaccine compared to an egg-derived trivalent inactivated subunit influenza vaccine. Results concluded that the cell culture-derived and the egg-
derived vaccines were effective in preventing influenza, were well-tolerated and presented good safety profiles.\textsuperscript{88} Of the three available cell lines, the only cell line that has universal regulatory acceptance is Vero cells. Moreover, pandemic influenza vaccines derived from this cell line have been well-tolerated and immunogenic.\textsuperscript{89}

However, cell culture production is not without its limits. For inactivated vaccines, the process would require the production of high-yield re-assortments with sufficient HA protein.\textsuperscript{56} Multiple passage through tissue culture may introduce cell-line-specific mutations that can lead to the selection of variants with antigenic and structural changes in the HA protein, resulting in decreased efficacy of vaccines.\textsuperscript{84} Regulatory issues surrounding cell culture include the presence of potential extraneous agents in mammalian cells and the unknown side effects that may occur as a result of residual host cell and media proteins in combination with new adjuvants.\textsuperscript{84}

6.3 Adjuvants

The use of adjuvants to modulate vaccine immunogenicity has been in practice for more than 80 years.\textsuperscript{90} Adjuvants are compounds that enhance the ability of a vaccine to elicit strong and robust immune responses.\textsuperscript{91} In this conventional role, adjuvants are presently used to: 1) increase the response to a vaccine in the general population; 2) increase seroconversion rates in populations with reduced responsiveness due to age or disease; 3) facilitate the use of smaller doses of antigen and 4) also allow for vaccination with fewer injections.\textsuperscript{91} Adjuvants behave by prolonging the antigen exposure time to the immune system, enhancing the delivery of antigen to antigen-presenting cells or by providing immunostimulatory signals that potentiate the immune response.\textsuperscript{92} An ideal adjuvant is able to increase a vaccine’s immunogenicity without adversely affecting the safety of the immunogen.\textsuperscript{92} While some adjuvants have substantially improved immune responses, they have also been associated with intolerable toxicities.\textsuperscript{92} Known adverse events following immunization of these adjuvanted influenza vaccines include the formation of sterile abscesses and cysts at the injection site, systemic febrile reactions and the excess occurrence of Bell’s Palsy.\textsuperscript{92} When the avian influenza vaccines were in development, the WHO encouraged the use of adjuvants in the case of a pandemic given the limitations in vaccine supply worldwide and the susceptibility of influenza viruses to mutate.

The function and safety of adjuvants have mostly been derived empirically without a strong understanding of their cellular and molecular mechanisms of action.\textsuperscript{91} Innate and adaptive immunity, both involved in the protection against invasive pathogens, were previously understood as functioning independently of each other. However, recent data suggests the emergence of a second role for adjuvants: engaging components of the innate immune system to produce the most effective forms of immunity by modulating the adaptive immune response.\textsuperscript{91} The use of adjuvants to influence the balance of induced-antibody and cell-mediated immunity have been investigated in preclinical and clinical studies to: 1) provide functionally appropriate types of immune response; 2) increase the generation of memory cells; 3) increase the speed of initial response, which is critical in a pandemic outbreak; and 4) alter the breadth, specificity or affinity of the immune response.\textsuperscript{91}
6.3.1 Aluminum salts

Historically, aluminum compounds have been the most widely used adjuvants for more than 80 years. There are numerous aluminum compositions; however, aluminum hydroxide (AlOH), aluminum phosphate and alum remain the most commonly utilized adjuvants in vaccines for humans. The immuno-modulating and immuno-stimulating effects of aluminum salts occur through several potential mechanisms of action. Aluminum compounds can function as an antigen depot by slowly releasing the antigen over time, can induce local inflammation by attracting antigen presenting cells (APCs) to the injection site and also improve uptake by APCs, as the antigen adsorbed to aluminum salts appears to the immune system as a particulate antigen as opposed to a soluble antigen. Although aluminum compounds have demonstrated safety, reported adverse events include sterile abscesses, eosinophilia, myofasciitis and granuloma formation.

While some initial studies failed to demonstrate improved immune responses in primed individuals who had received an aluminum-adjuvanted vaccine, other studies demonstrated a modest improvement in antibody response, especially in unprimed individuals. When candidate H5N1 vaccines were able to achieve antibody responses only through high dosage levels, studies were initiated to investigate whether aluminum salts could further enhance the immunogenicity of subvirion H5N1 vaccines. Results from a 2008 Phase I-II clinical trial reported that a meaningful beneficial effect of AlOH adjuvant was not observed after evaluating varying doses of HA with or without 600 µg of AlOH in healthy adults. These findings confirm conclusions from previous studies using subvirion H5N1 vaccines. Studies have also been conducted using aluminum-adjuvanted whole-virus vaccines; however, results remain inconclusive due to the exclusion of a comparable non-adjuvanted control group in some studies and demonstrated poor immune responses with the adjuvanted vaccine in other studies.

Despite a lack of evidence supporting a biologically meaningful effect, currently aluminum salts are the only licensed adjuvants in the USA. During the 2009 H1N1 pandemic, out of the eight vaccines utilized in Europe, only one included an aluminum adjuvant (Fluval P, Omnivest).

6.3.2 Oil-in-water emulsions

Oil-in-water emulsions are another group of compounds commonly used for vaccine adjuvants. MF59 and AS03 have emerged as potential adjuvants for influenza vaccines. MF59 is licensed in Europe for use with a seasonal vaccine for the elderly and with more than 27 million doses distributed, post-marketing surveillance studies have yet to identify any safety concerns related to this vaccine. Early studies evaluating MF59 with the potential pandemic vaccine strains, H5N3 and H9N2, in healthy young adults showed significantly improved antibody responses in the adjuvanted vaccine groups compared to the non-adjuvanted vaccine group. Subsequently a 2008 study evaluated the MF59 and alum adjuvants with a candidate H5N1 vaccine in healthy adults and also found significantly higher antibody responses in the MF59 vaccine group as compared to the alum and non-adjuvanted vaccine groups. In 2011, a study demonstrated additional efficacy of MF59 with a trivalent inactivated vaccine in infants and young children. Another study conducted in 2011 further elucidated the effects of MF59 on the quantity, diversity, specificity and affinity maturation of antibody responses to an H1N1 pandemic vaccine in different age groups.
determined that MF59 increased the diversity and volume of neutralizing antibody responses to the vaccine while also increasing the strength with which the antibodies were binding to the influenza virus.\textsuperscript{6} During the 2009 H1N1 pandemic, out of the eight vaccines utilized in Europe, two included a MF59 adjuvant.\textsuperscript{94} AS03 is another emulsion currently being investigated as an adjuvant for influenza vaccines. A 2007 study evaluating an AS03-adjuvanted H5N1 vaccine in healthy adults demonstrated significantly improved antibody responses in the adjuvanted vaccine group compared to the non-adjuvanted vaccine group.\textsuperscript{92} A recent study conducted in 2011 further demonstrated the immunogenicity of a single dose AS03-adjuvanted H1N1 2009 vaccine in individuals 18-64 years of age and also in individuals older than 64 years of age.\textsuperscript{97} This single dose vaccination was also able to induce long-term persistence of the immune response until at least six months after the initial dose.\textsuperscript{97} Out of the eight pandemic vaccines used during the 2009 H1N1 pandemic, only one, Pandemrix\textsuperscript{™} (GSK) included the AS03 adjuvant.\textsuperscript{94}

Although both MF59 and AS03 have been shown to induce more local or systemic reactions within three days of vaccination compared to non-adjuvanted vaccines, there have been no serious adverse events reported.\textsuperscript{49} Following the 2009 H1N1 pandemic, a 2011 study concluded that the MF59-adjuvanted H1N1 vaccine, Focetria\textsuperscript{™}, was generally well tolerated with transient adverse events and mild to moderate in intensity.\textsuperscript{98} Overall, MF59 and AS03 stimulate stronger antibody responses that also have the potential to be cross-protective against other virus strains.\textsuperscript{92} As a result, these oil-in-water adjuvants allow for antigen dose sparing and fewer doses.\textsuperscript{91}

In 2009, the WHO held a virtual consultation on the safety of adjuvanted influenza vaccines.\textsuperscript{99} The purpose of the consultation served to review known and theoretical safety concerns associated with adjuvants in influenza vaccines and to discuss methods to prospectively evaluate vaccine safety.\textsuperscript{99} A summary of the report can be accessed in Appendix 6.2.8.\textsuperscript{99} Although adjuvants have demonstrated their potential to substantially improve immune responses to influenza vaccines, a research priority in future studies should be to evaluate the safety and immunogenicity of adjuvants in vulnerable populations such as the young, the elderly, pregnant women, and in immunocompromised individuals.\textsuperscript{92} Adjuvants may not have been necessary to augment the immune response to the 2009 H1N1 pandemic vaccines; however, their significance cannot be undermined in the ability to respond to future influenza pandemics.

6.4 Alternative vaccine platforms

6.4.1 Reverse genetics

The development of antigenically relevant vaccine viruses is an important component to vaccine production. The viruses must be safe for inclusion into a vaccine and also carry efficient manufacturing properties. Absence of a suitable virus can severely impede vaccine production, a circumstance not favorable in the event of a pandemic. As described on page 25 of the 2004 background paper, the disadvantages of the genetic re-assortment technique for creating vaccine reference strains has led to the use of reverse genetics technology. The conventional genetic re-assortment technique is not able to be used with highly pathogenic avian viruses because the resulting re-assortments are highly pathogenic for embryonated eggs and may be capable of human infection. However, using reverse genetics technology, a safe H5N1 candidate vaccine virus was created.\textsuperscript{100} Results from ferret studies demonstrated
that this candidate vaccine virus, NIBRG-14, was safe and appropriate for pandemic influenza vaccine manufacture. Some European countries have also used this virus to gain regulatory approval of an H5N1 vaccine as part of the core dossier regulatory approach developed by the EMA as a ‘fast track’ procedure for pandemic vaccine approval. Following the pandemic threat of H5N1, more than 17 candidate vaccine viruses have been developed using reverse genetics technology. Utilizing lessons learned from the H5N1 vaccine development, vaccine viruses were quickly developed for the 2009 H1N1 pandemic. As of October 2009, 16 H1N1 2009 vaccine viruses have been established. The WHO has provided guidelines on the development of influenza vaccine reference viruses using reverse genetics, which can be viewed in Appendix 6.2.9.

6.4.2 Recombinant DNA technologies

The constraints of conventional production strategies have led to the development of recombinant DNA techniques as new production platforms. Upon selection of the influenza vaccine virus strains, the genetic sequence of the HA proteins can be used to generate HA and NA antigens in cell culture. The purified antigens will then serve as the active ingredients for the candidate vaccine. This novel approach would eliminate the need to handle pathogenic viruses and also to adapt the viruses to grow in eggs or cells. The use of recombinant proteins, virus-like particles, viral vectors, and DNA plasmids are technologies currently being investigated and although most are in the early stages of development, they have the potential to substantially reduce production timelines.

6.4.3 Universal vaccines

The ideal influenza vaccine is one that is safe, provides long-term and cross-strain protection and can also be manufactured rapidly. Investigative targets in the search for a universal vaccine have been the highly conserved external domain of the influenza matrix 2 (M2) protein and the conserved epitopes from the influenza NP, matrix 1 (M1), and HA proteins. Results from preclinical studies have demonstrated that candidate vaccines targeting the aforementioned conserved components of the influenza virus has stimulated broad cross-reactive antibody response either when administered alone or in combination with adjuvants. A 2012 Phase IIa clinical trial conducted in healthy adult volunteers evaluated a novel influenza vaccine in a vaccination and influenza challenge study. The vaccine demonstrated safety and immunogenicity. This study was able to provide preliminary evidence of clinical efficacy of a T-cell based influenza vaccine, with a 60% reduction of laboratory-confirmed influenza in vaccinated individuals. This study provides evidence that this novel approach could be successful; however, additional studies are needed to characterize safety and efficacy in larger populations and to assess vaccine immunogenicity in the elderly and in younger age groups. Future studies in larger populations and in vulnerable populations remain a research priority.

The following table summarizes the distribution of current and new approaches that address the challenging areas of influenza vaccine production, including egg versus cell-based production and novel platforms.
Table 6.2.3 Current and new approaches to influenza-vaccine production

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Stage of Development</th>
<th>Licensed or approved</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Preclinical development</td>
<td>Phase I and II</td>
</tr>
<tr>
<td>Inactivated vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg-based</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell-based</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>With adjuvant</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Live-attenuated vaccines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg-based</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Cell-based</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Alternative platforms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recombinant proteins</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Virus-like particles</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Viral vectors</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>DNA-based vaccines</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Universal vaccines</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>


6.5 Vaccine delivery mechanisms

Despite the safety and effectiveness of vaccines, many individuals go unvaccinated each influenza season. Issues of concern include vaccine acceptance and cost. Novel vaccine delivery mechanisms that elicit stronger immune responses as well as increase influenza vaccination rates are currently being investigated.

6.5.1 Traditional needle-based vaccination

Influenza vaccines have typically been administered by intramuscular injection. This method stimulates the production of serum antibodies which protect the lower respiratory tract against influenza infection. While the lower respiratory tract is protected, it leaves the upper respiratory tract susceptible to initial infection because of an absence of antibody induction in the nasal mucosa. Additional disadvantages include safety issues surrounding the use of needles, low acceptance among patients due to needle-phobia and logistical challenges in mass vaccination programmes.

6.5.2 Needle-free vaccination

The disadvantages encountered with the traditional needle-based intramuscular vaccines can be circumvented through the use of needle-free vaccination systems. Current methods in development are evaluating both mucosal tissue and skin immunization systems. Mucosal immunization includes the nasal, pulmonary, oral cavity, or gastrointestinal tissues while skin immunization includes intradermal or transcutaneous delivery.

Needle-free vaccinations do not require trained health-care personnel to administer the vaccination to patients, thus reducing costs. As the vaccination is pain-free, individuals with needle-phobia are more likely to accept needle-free vaccination than injection-based
vaccination. A study conducted in Switzerland found that 97% of study participants would choose an intranasal vaccine spray compared to an injection, when offered the choice. Vaccine delivery through the respiratory tract, alimentary tract, or skin may also elicit mucosal immune responses at the site of virus entry and improve cellular immunity. Enhancing vaccine effectiveness may also improve vaccine acceptance among the public population. In an event where a mass vaccination campaign may be necessary, such as during a pandemic, the logistical barriers associated with the supply and disposal of syringes and needles would be substantially reduced. Furthermore, the potential use of dry vaccine formulations would eliminate the need for a cold chain for storage and distribution. Collectively, these advantages would ultimately increase the speed of vaccinations, critical in a pandemic environment.

However, one of the major weaknesses of needle-free vaccines is their limited effectiveness. Mucosal vaccinations, unless formulated as a live attenuated vaccine, requires large amounts of antigen and usually in several doses in order to elicit a strong immune response. In a pandemic situation, mucosal vaccination with inactivated vaccines is consequently impractical due to the financial and logistical measures involved. In contrast, dermal vaccination with doses similar to parenteral vaccination may be feasible with the use of proper delivery methods or appropriate adjuvants. Additionally, studies have demonstrated the adjuvants alum, MF59 and influenza virosomes ineffective for intranasal vaccinations. Although there has previously been little evaluation of possible adjuvants for transcutaneous vaccination as compared to intranasal vaccination, currently there are numerous pre-clinical assessments underway evaluating both vaccination systems.

**Mucosal immunization**

Mucosal tissues are large in size and exhibit immunological competence, making them attractive target sites for vaccination. Moreover, mucosal vaccinations are easy to administer and can induce both strong systemic and local immune responses, which can protect at the point of virus entry. Intranasal administration is the most widely-studied form of mucosal immunization and is the only approach that has been approved for commercial use. For increased effectiveness, presently all intranasal influenza vaccines commercially available are LAIV vaccines. Safety concerns of the higher risk for wheezing and hospitalization of young children who receive LAIV have prompted studies evaluating the use of inactivated vaccines. However, inactivated vaccines have produced adverse events as well, namely the occurrence of facial palsy following administration of a heat-labile enterotoxin (LT)-adjuvanted vaccine. The toxic properties of the LT adjuvant has stimulated the evaluation of a detoxified LT adjuvant, though these studies have only been in animals thus far. These adverse events stemming from both activated and inactivated intranasal vaccines have occurred at either the late-stages of pre-licensure development or after licensure, with a relatively low incidence. Powder formulations developed for nasal delivery have also demonstrated promising results, remaining in the nasal cavity longer than the liquid formulation. This may suggest higher bioavailability and immune responses; however, these assessments have only been conducted in animal studies.

**Dermal immunization**

The skin is also an appealing target site for vaccination as it is easily accessible and a highly immunocompetent organ. The skin is divided into the stratum corneum, the epidermis, and
the dermis, with the latter two rich in antigen-presenting cells (APC).\textsuperscript{82} Although the intact stratum corneum prevents the penetration of foreign molecules; once it has been penetrated, antigens are capable of reaching the abundance of APCs in the epidermis and dermis.\textsuperscript{82} It is this pathway that intradermal vaccination has the theoretical potential to allow dose sparing delivery, essential in the event of a pandemic.\textsuperscript{103} Intradermal delivery using traditional microneedles has been studied in various clinical trials.\textsuperscript{82} These trials concluded that a low-dose 0.1 mL intradermal vaccine (typically one-fifth of the standard volume of adult intramuscular influenza vaccines) induced antibody titers comparable to or higher than the conventional full dose intramuscular vaccine.\textsuperscript{103} However, local inflammatory reactions such as erythema occurred significantly more frequently following intradermal as compared to intramuscular vaccination.\textsuperscript{103} Furthermore, the procedure for intradermal delivery using traditional needles is technically challenging and therefore not suitable for routine vaccinations.\textsuperscript{82} However, intradermal vaccination can also be administered with specially designed needles that allow for controlled depth of skin penetration.\textsuperscript{82} The BD Soluvia (BD Medical Pharmaceutical Systems) device has shown favorable results in Phase II and Phase III clinical trials and the EMA has approved an intradermal influenza vaccine utilizing this device.\textsuperscript{82}

An additional approach to intradermal vaccine delivery is the use of arrays of pointed microneedles, which can also penetrate the stratum corneum.\textsuperscript{82} The advantage to this delivery is that the microneedles are designed to target cells in the epidermis without touching the nerves in the underlying tissue therefore eliciting little sensation and no pain.\textsuperscript{82} This mechanism is also an easy technique to administer the vaccine, requiring no specially trained medical personnel.\textsuperscript{82} A 2009 clinical trial demonstrated that individuals who received doses of 3 µg or 6 µg hemagglutinin per influenza strain via the MicronJet device (NanoPass Technologies, Ltd.) produced similar immune response compared to those who received 15 µg by intramuscular injection.\textsuperscript{82}

Jet injectors are also an alternative option to delivering vaccine to the epidermal, subcutaneous or intramuscular tissues.\textsuperscript{82} Suitable for mass vaccination campaigns, this needle-free mechanism offers improved safety and avoids the risk of cross-contamination by using a disposable syringe.\textsuperscript{104} A 2011 study investigated the safety, tolerability, and immunogenicity of an inactivated trivalent seasonal influenza vaccine administered with the needle-free disposable-syringe jet injector, LectraJet M3 RA.\textsuperscript{104} There were no related serious adverse events (SAEs) and adverse events that did occur (erythema and induration) were transient and well tolerated.\textsuperscript{104} Overall, the jet injector proved to be well-tolerated and immunogenic as compared the traditional needle-syringe method.\textsuperscript{104}

Vaccines can also be delivered through the skin by the transcutaneous approach of using patches. The vaccine can be formulated on a patch with a Escherichia coli LT adjuvant or alternatively, the patch can contain only LT and is applied on the skin at the site of vaccine injection.\textsuperscript{103} A 2005 study conducted in the elderly concluded that subjects who had received both the vaccine and the patch had greater antibody responses compared to those who received the vaccine alone.\textsuperscript{103}

Although these novel vaccine delivery mechanisms seem promising, a future research priority is clinical research evaluating their immunogenicity, especially among different populations, and in conjunction with adjuvants.
7. Current Product Pipeline

7.1 Vaccines

The EU has instituted procedures, managed by the EMA, in order to expedite the authorization and availability of vaccines in the event of an influenza pandemic. As stated in the 2004 background paper, in 2004 the EMA published guidelines on the development and registration of pandemic influenza vaccines based on a ‘mock-up vaccine’ strategy. This ‘mock-up’ strategy allows a vaccine to be developed and authorized in advance of a pandemic, based on information generated with a virus strain that could potentially cause a pandemic. The official document provides guidance on the dossier structure and content for pandemic influenza vaccine marketing authorization and addresses the quality requirements, non-clinical safety requirements, and clinical requirements for the mock-up vaccine. A pandemic will not allow time for clinical trials to be conducted therefore it is recommended that immunogenic and safety data be obtained for ‘mock-up vaccines’ which are developed and tested during the interpandemic period. During a pandemic, once the virus strain causing the pandemic is identified, the manufacturer can include this strain in the mock-up vaccine and apply for it to be used as the actual pandemic vaccine. Under the assumption that the actual pandemic vaccine is similar to and is produced in the same manner as the ‘mock-up vaccines’, clinical data from the core pandemic dossier can be extrapolated to the actual pandemic vaccine resulting in rapid approval and registration for immediate use. This critical document ultimately provides the basis for a fast track authorization procedure for pandemic influenza vaccines. In 2008, the EMA published a revised edition of these guidelines, which can be accessed in Appendix 6.2.10.

The emergence of the swine-origin (S-OIV) A/H1N1 influenza virus in 2009 elicited a rapid global response in the development and production of pandemic influenza vaccines. Interpandemic influenza immunization presents unique challenges including the requirement of annual immunizations, multiple co-circulating virus strains, antigenic change of the influenza virus, and a broad age spectrum of disease. The development of pandemic influenza vaccines include the additional obstacles of the need to induce a broad spectrum and long-lasting immune response, a much more rapid manufacturing time, and a large enough production capacity to reach everyone in the world who is at risk. These challenges continue to stimulate the development of new technologies in the production of pandemic influenza vaccines.

Vaccine development has evolved to a number of diverse platforms including inactivated whole virus vaccines, split vaccines, subunit vaccines, live attenuated vaccines, adjuvanted vaccines, egg-produced vaccines, cell-cultured produced vaccines, vaccines utilizing different delivery mechanisms as well as combinations of the various vaccines mentioned above. For the 2009 influenza A (H1N1) pandemic, different vaccine types were utilized in the United States and Australia as compared to Europe. The United States and Australia, and on a limited scale in Europe, used non-adjuvanted monovalent vaccines. The United States did not have a fast-track system established for adjuvanted influenza vaccines to be registered and approved therefore no adjuvanted influenza vaccine has ever been licensed.

In contrast, within the EU, adjuvanted pandemic vaccines were more widely used. The Celvapan® (Baxter), Focetria® (Novartis) and Pandemrix® (GSK) vaccines were authorized
through the central procedure under the EMA although the use of Pandemrix® was more common. The EMA reported that as of August 2010, 30.5 million people had been vaccinated with Pandemrix® compared to 6.5 million with Focetria®. In addition to Pandemrix® and Focetrix®, by December 2009, six other influenza A (H1N1) pdm09 vaccines were available in the European Union (EU)/European Economic Area (EEA). Table 6.2.4 provides an overview of the composition of all centrally licensed vaccines available in the EU during the 2009 H1N1 pandemic.

Currently authorized pandemic vaccines in the United States and Europe are shown in Annex 6.2.1.

Table 6.2.4: Overview of available influenza A (H1N1) pandemic vaccines in the European Union in December 2009

<table>
<thead>
<tr>
<th>Name, producer</th>
<th>Product description</th>
<th>Culture medium</th>
<th>Haemagglutinin content</th>
<th>Adjuvant emulsion</th>
<th>Number of doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellvapan, Baxter</td>
<td>Whole virion, wild-type A/California/7/2009 (HxN1), inactivated</td>
<td>Vero cell-derived</td>
<td>7.5 µg</td>
<td>None</td>
<td>All &gt; 6 months 2 x 0.5 mL</td>
</tr>
<tr>
<td>Pandemrix, GSK</td>
<td>Split-virion, reassortant A/California/7/2009 (HxN1)-like strain, inactivated, adjuvanted</td>
<td>Egg-derived</td>
<td>3.75 µg (per full dose)</td>
<td>AS03</td>
<td>Adults, adolescents and children &gt; 10 years 1 x 0.5 mL, Children 6 months – 9 years 2 x 0.25 mL</td>
</tr>
<tr>
<td>Focetrix, Novartis</td>
<td>Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (HxN1)-like strain, inactivated, adjuvanted</td>
<td>Egg-derived</td>
<td>2.5 µg</td>
<td>MF59.C1</td>
<td>Adults, adolescents and children &gt; 9 years 1 x 0.5 mL, Children 6 months – 8 years 2 x 0.5 mL</td>
</tr>
<tr>
<td>Fluval P. Omnivest</td>
<td>Whole virion, reassortant A/California/7/2009 (HxN1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>6 µg (per full dose)</td>
<td>Aluminium phosphate</td>
<td>Adults and adolescents &gt; 12 years 1 x 0.5 mL, Children 12 months – 12 years 1 x 0.25 mL</td>
</tr>
<tr>
<td>Panenza, Sanofi Pasteur</td>
<td>Split-virion, reassortant A/California/7/2009 (HxN1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>15 µg (per full dose)</td>
<td>None</td>
<td>Adults, adolescents and children &gt; 8 years 1 x 0.5 mL, Elderly ≥ 60 years and children 3 – 8 years 2 x 0.25 mL, Children 6 – 35 months 2 x 0.25 mL</td>
</tr>
<tr>
<td>Cervel, Novartis</td>
<td>Surface-antigens (haemagglutinin and neuraminidase), reassortant, A/California/7/2009 (HxN1)-like strain, inactivated</td>
<td>MOCK cell-derived</td>
<td>3.75 µg (per full dose)</td>
<td>MF59.C1</td>
<td>Adults 18 – 40 years, children 3 – 17 years 1 x 0.35 mL, Adults &gt; 40 years 2 x 0.25 mL</td>
</tr>
<tr>
<td>PanvaxH1N1, CSL</td>
<td>Split-virion, reassortant A/California/7/2009 (HxN1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>15 µg</td>
<td>None</td>
<td>Adults, adolescents and children &gt; 9 years 1 x 0.5 mL</td>
</tr>
<tr>
<td>CANTGRIP, Cantacuzino</td>
<td>Split-virion, reassortant A/California/7/2009 (HxN1)-like strain, inactivated</td>
<td>Egg-derived</td>
<td>15 µg</td>
<td>None</td>
<td>Adults ≥ 18 years 1 x 0.5 mL</td>
</tr>
</tbody>
</table>


7.1.1 Pandemic vaccine safety

Available data in 2010 demonstrated that pandemic influenza vaccines were well tolerated and performed similarly to the corresponding interpandemic vaccines in relation to vaccine safety and lack of serious adverse events. These data support the validity of a ‘mock-up’
strategy for rapid development of a safe vaccine during an influenza pandemic. Clinical trials evaluating pandemic H1N1 vaccines produced by European manufacturers also indicated good tolerability with only minor side effects in health children, adults and the elderly. During the 2009 pandemic, monitoring of adverse events following immunization (AEFI) depended on existing national pharmacovigilance systems, such as notification by health professionals and the public to national drug agencies and, when existing, surveillance networks for rare disorders. Concurrently, vaccine authorization obligations required manufacturers to undergo the same rigorous manufacturing oversight, product quality testing and lot release procedures as interpandemic vaccines. Manufacturers were also obligated to conduct systematic post-marketing surveillance and send monthly periodic safety update reports (PSURs) to the EMA. To be vigilant in investigating vaccine safety, national authorities conducted additional pharmacovigilance activities including clinical trials, additional registries, active specific vigilance, follow up of vaccinated cohorts and multi-centre studies in children and pregnant women. Preliminary safety data as of March 2010 reported that out of 867,556 vaccines registered in Italy, 1,246 (0.14%) spontaneous reports of AEFI had been received. In The Netherlands, a prospective cohort study following 3,780 individuals vaccinated with Focetria® found that 28% of the 94% respondents reported a mild AEFI. Individuals vaccinated with Pandemrix® stated pyrexia as the most frequently reported AEFI.

The detection of rare safety signals require examining large population numbers, which is most feasibly facilitated by combining data across countries, and careful post-marketing surveillance. Following the onset of the 2009 H1N1 pandemic, the WHO and the ECDC initiated the Paniflow and Vaccine Adverse Events Surveillance and Communication (VAESCO) projects, respectively, to monitor vaccine safety. Paniflow is a web-based reporting tool whereas VAESCO links large computerized clinical databases and immunization registries. Additional details on these projects are outlined in the table below.
Guillain-Barré Syndrome

As reported on page 30 of the 2004 background paper, a swine-origin influenza A (H1N1) subtype A/NJ/76 vaccine had been developed and distributed in 1976 in anticipation of an influenza pandemic. However, the vaccine was found to be associated with a sevenfold increased risk of Guillain-Barré syndrome (GBS) and vaccination was immediately discontinued. Subsequent prospective surveillance studies on seasonal vaccines used in the 1978, 1979, 1980, 1992, 1992 seasons have demonstrated no or modest increases in the risk of Guillain-Barré syndrome although the exact causal mechanism of this phenomenon has never been elucidated. Despite corroborating data from multiple studies of little to no risk, the ECDC requested VAESCO to investigate a possible association between the pandemic vaccines used in Europe during the 2009/2010 winter season and GBS. Similar studies were conducted around the world including, the United States, Canada, Australia, Japan, Taiwan, and Singapore. A multi-country case-control study conducted by VAESCO in 2011 concluded that there was no increased risk of GBS following the administration of adjuvanted vaccines, Pandemrix® and Focetria®, and that this data was consistent across all countries in the study. Interestingly, while there has been no evidence of association...
between GBS and influenza vaccines, there has been a documented association of GBS with influenza infection itself.\textsuperscript{49}

**Narcolepsy**

Narcolepsy is a rare chronic neurological sleep disorder caused by the brain's inability to regulate sleep-wake cycles normally.\textsuperscript{94,108} Although its etiology is unknown, narcolepsy is considered to be an auto-immune disease that includes a strong genetic predisposition with the HLA DQB1*0602 allele having been associated with most cases.\textsuperscript{109} Narcolepsy is a disorder of excessive daytime sleepiness that may occur both at rest and during periods of activity, such as talking and eating.\textsuperscript{94} The most severe cases also experience cataplexy, which is a sudden loss of muscle tone causing collapse in response to an emotional stimulus.\textsuperscript{94} Onset of disease before the age of 10 is rare; the peak age of narcolepsy is late adolescence into early adulthood.\textsuperscript{109} Though symptoms generally begin in adolescence the condition is not often suspected by clinicians, leaving some cases undiagnosed until adulthood. Patients have also been misdiagnosed with depression or having attention deficit disorder (ADD).\textsuperscript{94}

On 12 October 2009, Finland began a national vaccination campaign using the AS03-adjuvanted vaccine Pandemrix®.\textsuperscript{108} The first case of narcolepsy in a child that had been vaccinated with Pandemrix® was reported in February of 2010.\textsuperscript{109} By August, there were 14 cases of confirmed narcolepsy in Pandemrix®-vaccinated children prompting concern of an association between the vaccine and narcolepsy in children.\textsuperscript{109} Similarly in Sweden, the first cases of narcolepsy in children were reported to the Medical Products Agency (MPA) in the spring of 2010 with increasing number of cases by late summer.\textsuperscript{110} Following these reports, the Finnish health authorities decided to terminate the use of Pandemrix®. A recent 2012 study in Finland conducted a systematic analysis of the incidence of narcolepsy in children 17 years and younger between 2002-2010.\textsuperscript{109} Findings show a 17-fold increase in the incidence of childhood narcolepsy in 2010 as compared to 2002-2009.\textsuperscript{109} Of the 54 diagnosed childhood narcoleptic patients, 50 children had received the Pandemrix® vaccine within eight months before onset of symptoms.\textsuperscript{109} Additionally, there was a moderate (three-fold) increase of narcolepsy in adolescents with no increase seen in adults over the age of 20.\textsuperscript{109} A retrospective cohort study also conducted in Finland in 2012 evaluated the possible association between Pandemrix® and incidence of narcolepsy in children and adolescents. Findings from this study show a 12.7-fold risk of narcolepsy in 4-19 year olds within eight months after receiving a Pandemrix® vaccination as compared to those unvaccinated in the same age group.\textsuperscript{108} A similar study of children and adolescents conducted by the MPA in Sweden also found a seven-fold higher incidence of narcolepsy in those vaccinated with Pandemrix® compared to those who were not vaccinated.\textsuperscript{110} Preliminary passive reporting data from France, Norway and Ireland also described an increase in the number of narcolepsy cases in Pandemrix®-vaccinated children and adolescents.\textsuperscript{108}

Following these initial studies, the ECDC and VAESCO conducted two multi-country epidemiological studies in order to investigate a possible association between the increase of narcolepsy cases following the administration of influenza A\textit{(H1N1)pdm09} vaccines.\textsuperscript{94} These studies occurred in eight countries including: Finland and Sweden, known as the signaling countries as they originally reported the safety signal; and Denmark, Italy, France, the Netherlands, Norway and the United Kingdom, known as the non-signaling countries in these studies. The case-control study was able to confirm the association between vaccination with Pandemrix® and increased risk of narcolepsy in children and adolescents (aged 5-19
years) in the signaling countries of Finland and Sweden. No association was found in adults, corroborating the results from initial Finnish and Swedish studies. Primary analysis, which is designed to avoid biases such as media attention and diagnostic awareness, resulted with no significant risk to children and adolescents in the non-signaling countries. In contrast, sensitivity analyses, which assess the robustness of results from the primary analysis, demonstrated the importance of time-related factors that can affect the strength of association between exposure and outcome. When analysis identified disease onset as the date when excessive daytime sleepiness began and only considered cases with an onset prior to media attention, results produced an increased risk for narcolepsy for children and adolescents following of influenza A(H1N1)pdm09 vaccination in both signaling and non-signaling countries. Interestingly, a similar sensitivity analysis also showed an association in adults in the non-signaling countries prior to the onset of media attention.

The 2009 influenza A (H1N1) pandemic was the first event to reveal a possible association between vaccination and narcolepsy. As stated previously, Pandemrix® was the most frequently utilized vaccine during the pandemic. Four countries, Denmark, Finland, Norway, and Sweden, offered only Pandemrix®. Other countries offered a variety of combinations of available pandemic vaccines. Variability in vaccine recommendation guidelines also existed across countries. Some countries recommended vaccinations to their entire population while other countries recommended it only to selected risk groups. Of the countries that did offer Pandemrix®, Canada and the United Kingdom did not report the safety signal even though both countries have the same genetic susceptibility to narcolepsy as the Nordic countries. Interestingly, the HLA DQB1*0602 allele is almost twice as common in northern than in southern Europe. Although the initial Finnish and Swedish studies were able to demonstrate a strong safety signal between Pandemrix® and narcolepsy in children, it must also be noted that they also achieved 75% vaccine coverage in children and adolescents and 67% vaccine coverage in children, respectively, due to the administration of vaccines through the school health systems. This is in contrast to France and Italy where they achieved 10% and 0.3% vaccine coverage rates, respectively. A recent Chinese study demonstrated a three-fold increased incidence of narcolepsy following the onset of the 2009 H1N1 pandemic season; however these results were independent of vaccination. Following review of the ECDC and VAESCO studies, in 2011, the EMA recommended restricting use of Pandemrix® to individuals under 20 years of age and only in the absence of an available interpandemic trivalent influenza vaccine and if immunization against H1N1 is still required.

The collective observations and results from the described studies suggest a multifactorial nature to this new phenomenon. A technical report summarizing the studies conducted by the ECDC and VAESCO recommends the following recommendations for future studies:

- Increase the number of cases collected from the period prior to increased public awareness of narcolepsy association.
- Collect national data from countries that were not included in the initial report, especially those with high national vaccine coverage rates in other population groups also not studied in this initial report.
- Expand the investigation to countries outside of Europe, such as Canada and Brazil, that used the AS03-adjuvanted vaccine yet did not have as much media attention regarding the possible narcolepsy association.
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- Conduct additional epidemiological studies to determine the role of different environmental factors and the use of adjuvants in the possible association to narcolepsy.

In 2012, the EMA conducted a review of the results from the Finnish National Institute of Health and Welfare (THL) investigating differences in immunological response triggered by various pandemic influenza vaccines as a potential risk factor for the development of narcolepsy. The EMA concluded that the results were insufficient to draw any conclusions and did not lead to new concerns regarding Pandemrix® or other influenza vaccines. Based on current evidence, the role between the Pandemrix® vaccine specifically its antigen and adjuvant; and narcolepsy remains unknown. Although Pandemrix® is authorized for use in the EU, it is currently unavailable. The EMA will continue to review further analysis of the association between Pandemrix® and narcolepsy as it becomes available.

7.2 Antiviral agents

Compared to 2004, current antiviral therapy remains unchanged with four commercially licensed products including: neuraminidase inhibitors (NAIs) oseltamivir and zanamivir, and the adamantanes, amantadine and rimantadine, which are M2 ion-channel inhibitors. Only one of these products, oseltamivir, was included in the WHO Model List of Essential Medicines for selected high-risk patients. In the initial stages of the 2009 H1N1 pandemic, NAIs were invaluable in controlling the spread of influenza. However, increased use of these antiviral agents led to the emergence of drug-resistant variants of the virus ultimately resulting in reduced drug efficacy. Additional limitations to these anti-influenza drugs lie in several critical areas: high prevalence of M2 inhibitor resistance among H3N2; H5N1 and H1N1 isolates during therapeutic use; limited antiviral efficacy among certain populations and in severe cases of influenza; and a lack of parenteral agents for seriously-ill patients. These are the principal factors that continue to drive the need for the development of new antiviral agents, particularly in regards to broad reactivity against all virus strains and subtypes, drug resistance, pandemic preparedness, and the consideration of combination therapy.

Although the existing NAIs and M2-ion channel inhibitors differ substantially in their mechanisms of action and tolerability profiles, they both utilize a pathogen-targeted approach to controlling influenza infection. In addition to this approach, candidates presently in development are investigating the use of host-targeted approaches, immunomodulators and combination therapy in inhibiting influenza viral replication and infection. There has also been increasing interest in development strategies focusing on modulating influenza-induced influenza inflammation. The cyclo-oxygenase (COX) pathway and peroxisome proliferator-activated receptor agonists (PPARs) are known key regulators of inflammation and have been identified as potential therapeutic targets.

Current and investigational antiviral agents have proven to be effective when administered as a single drug regimen; however, combination therapy is also being evaluated for the potential to elicit additive or synergistic effects in inhibiting influenza viral replication. A 2011 study demonstrated that the combination oral oseltamivir and intravenous (IV) zanamivir administered in healthy Thai adults was well tolerated and elicited no significant pharmacokinetic interactions between the two drugs. A 2012 study evaluated the RNA polymerase inhibitor favipiravir in combination with peramivir, a NAI, against pandemic
influenza A 2009 H1N1 virus infections in mice. Results also demonstrated that the combination therapy performed better than suboptimal doses of each individual compound. Another study conducted in 2012 investigated a triple combination antiviral drug (TCAD) regimen consisting of amantadine, oseltamivir, and ribavirin against amantadine-resistant 2009 influenza A H1N1 virus infections in mice. Findings demonstrated in vivo efficacy of TCAD therapy against resistant influenza strains.

It is likely that influenza virus strains will confer resistance to monotherapy; therefore future antiviral agents for the treatment management of influenza will need to have broad spectrum activity and improved pharmacological profiles. This includes greater potency that restricts viral replication, fewer dose regimens, reduced risk of antiviral resistance, and the further exploration of combination therapy to target different viral proteins or factors of viral pathogenicity. A comprehensive overview of antiviral agents in the preclinical or clinical stages is shown in Table 6.2.6.

Table 6.2.6: Antiviral agents in development

<table>
<thead>
<tr>
<th>Antiviral agent</th>
<th>Manufacturer</th>
<th>Administration route</th>
<th>Development phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pathogen-targeted approaches</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laninamivir (CS-8958)</td>
<td>Biota Holdings &amp; Daiichi Sankyo Co., Ltd.</td>
<td>Inhaled</td>
<td>Currently licensed in Japan as Inavir and seeking regulatory approval worldwide.</td>
</tr>
<tr>
<td>Peramivir</td>
<td>BioCryst Pharmaceuticals</td>
<td>Intravenous</td>
<td>Phase III</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Currently licensed in Japan</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>GlaxoSmithKline</td>
<td>Intravenous</td>
<td>Phase II-III</td>
</tr>
<tr>
<td>Favipiravir (T-705)</td>
<td>Toyama Chemical Co., Ltd.</td>
<td>Oral</td>
<td>Phase II-III</td>
</tr>
<tr>
<td><strong>Host-targeted approaches</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DAS-181 (Fludase)</td>
<td>NexBio, Inc.</td>
<td>Inhaled</td>
<td>Phase I</td>
</tr>
</tbody>
</table>

Source: manufacturers’ websites

### 7.3 Rapid diagnostic tests

Viral culture has been the long-standing gold standard for influenza diagnosis; however, the lengthy turnaround time (TAT) for results has reduced its functionality for optimal patient management. Results from direct antibody staining (DFA) may be available in hours but this method requires specialized equipment and training to interpret results. More recently, RT-PCR has superseded this method as the gold standard due to its high detection rate and result output in hours instead of days. However, this test is the most expensive and not widely available because of the specialized equipment and expertise require. The limitations of these traditional methods have been evident in the recent development of more highly
accurate and rapid molecular assays. The 2009 influenza A H1N1 virus pandemic underlined the importance of precise assays with brief TAT and the ability to differentiate influenza strains in order to accurately monitor the spread of an outbreak and ensure effective clinical management of patients. Traditional and more recent methods of influenza virus detection are highlighted in the following table. Annexes 6.2.2 and 6.2.3 show commercially-available rapid influenza diagnostic tests and molecular diagnostic tests with longer time until results are produced.

### Table 6.2.7 Influenza virus testing methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Virus strains detected</th>
<th>Test time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral cell culture</td>
<td>A &amp; B</td>
<td>3-10 days</td>
</tr>
<tr>
<td>Direct (DFA) or Indirect (IFA) antibody staining</td>
<td>A &amp; B</td>
<td>1-4 hours</td>
</tr>
<tr>
<td>Reverse transcriptase polymerase chain reaction (RT-PCR)</td>
<td>A &amp; B</td>
<td>1-6 hours</td>
</tr>
<tr>
<td>Rapid influenza diagnostic test (RIDT)</td>
<td>A &amp; B</td>
<td>&lt; 30 minutes</td>
</tr>
</tbody>
</table>

Source: adapted from [http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm](http://www.cdc.gov/flu/professionals/diagnosis/rapidlab.htm)

Future research priorities should focus on developing specific and sensitive RDTs to ensure accurate case management and epidemiological surveillance.

### 8. Future research opportunities

Following the initial outbreak of avian influenza in 1997, the threat of a potential influenza pandemic was recognized by key stakeholders. A substantial amount of financial support and research has since been allocated to increasing pandemic influenza preparedness at the international level. The subsequent unexpected emergence of the 2009 H1N1 influenza pandemic challenged these efforts in every aspect of pandemic preparedness. Fortunately, the new virus appeared less virulent than anticipated.

The EU has recognized the public health impact of influenza through the establishment of extensive influenza-related surveillance networks, consortiums, and research projects. The necessary information collected will inform future policy development and decisions. However, the prevention and control of influenza requires immense efforts and strong partnerships during both the interpandemic and pandemic periods. Cooperation and collaboration between all key stakeholders will facilitate a rapid and effective response in the event of a future pandemic.

Future influenza research should be prioritized in the following areas:
- The virology and pathogenicity of influenza viruses in order to predict and prepare for the next pandemic.
- Improved quantification methods to more accurately assess the economic burden of influenza.
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- Improved global and country surveillance systems in order to accurately estimate morbidity and mortality, particularly in developing countries.
- Understanding barriers to immunization uptake combined with evaluation of interventions.
- Expansion of global vaccine production capacity particularly in low and middle income countries.
- Global and country-level vaccine coverage information and monitoring systems.
- Rapid scale up of vaccine production in case the next pandemic is caused by a subtype that is less antigenic and requires two doses of vaccine.
- Standardization of methodology in measuring vaccine effectiveness.
- Vaccine platforms that produce safe and effective vaccines with cross-strain and long-lasting protection against influenza.
- Additional studies on the cost-effectiveness of vaccination.
- Development of new antiviral agents with broad reactivity against all virus strains and subtypes.
- Development of RIDTs to accurately detect and distinguish between different influenza virus subtypes.

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## Annexes

### Annex 6.2.1: Current FDA and EMA approved pandemic vaccines

<table>
<thead>
<tr>
<th>Vaccines</th>
<th>Manufacturer</th>
<th>Administration route</th>
<th>Indications and dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FDA Approved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>CSL Limited</td>
<td>Intramuscular injection</td>
<td>6 months – 35 months 2 x 0.25 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 months – 9 years 2 x 0.5 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>ID Biomedical Corporation of Quebec (IDB)</td>
<td>Intramuscular injection</td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>Novartis Vaccines and Diagnostics Ltd.</td>
<td>Intramuscular injection</td>
<td>4 - 9 years of age 2 x 0.5 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 – 17 years of age Single 0.5 mL dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>Sanofi Pasteur, Inc.</td>
<td>Intramuscular injection</td>
<td>6 months – 35 month 2 x 0.25 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>36 months – 9 years 2 x 0.5 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 years and older Single 0.5 mL dose</td>
</tr>
<tr>
<td>Influenza A (H1N1) 2009 Monovalent Vaccine</td>
<td>MedImmune, LLC.</td>
<td>Intranasal spray</td>
<td>2 -9 years of age 2 x 0.2 mL approximately four weeks apart</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10 – 49 years of age Single 0.2 mL dose</td>
</tr>
<tr>
<td><strong>EMA Approved</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daronrix</td>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 – 60 years of age 2 doses, three weeks apart</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Manufacturer</th>
<th>Type</th>
<th>Age Range</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Foclia</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Novartis Vaccines and Diagnostics S.r.l.</td>
<td>Intramuscular injection</td>
<td>18 – 60 years of age</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
<tr>
<td><strong>Pandemic influenza (H5N1) (split-virion, inactivated, adjuvanted)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
<tr>
<td><strong>Pandemic Influenza Vaccine H5N1</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Baxter AG</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
<tr>
<td><strong>Pumarix</strong></td>
<td>GlaxoSmithKline Biologicals S.A.</td>
<td>Intramuscular injection</td>
<td>18 years and older</td>
<td>2 x 0.5 mL at least three weeks apart</td>
</tr>
</tbody>
</table>

<sup>a</sup> Vaccines do not have trade names.

<sup>b</sup> Vaccines have been authorised under “exceptional circumstances” which occurs when the applicant shows that they are unable to provide comprehensive data on the efficacy and safety of the medicine for which authorisation is being sought, due to the rarity of the condition it is intended for, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of such data.

<sup>c</sup> Dosage not specified in the European Public Assessment Report for this vaccine.
## Annex 6.2.2: Rapid influenza diagnostics tests

<table>
<thead>
<tr>
<th>Rapid diagnostic test</th>
<th>Manufacturer</th>
<th>Viral strain detection/differentiation</th>
<th>Viral subtype differentiation</th>
<th>Specimen type</th>
<th>Time to result</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Film Array</strong></td>
<td>Biofire Diagnostics, Inc.</td>
<td>A, B</td>
<td>H1, 2009 H1N1, H3</td>
<td>NP</td>
<td>1 hour</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td><strong>Liat Influenza A/B</strong></td>
<td>iQuum, Inc.</td>
<td>A, B</td>
<td></td>
<td>NP</td>
<td>20 minutes</td>
<td>US-IVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24 patients in 8 hrs.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Liat Influenza A/2009 H1N1</strong></td>
<td>iQuum, Inc.</td>
<td>A only</td>
<td>2009 H1N1</td>
<td>NP</td>
<td>26 min.</td>
<td>EUO, RUO</td>
</tr>
<tr>
<td><strong>QuickVue Influenza A + B</strong></td>
<td>Quidel Corp.</td>
<td>A, B</td>
<td></td>
<td>NP</td>
<td>10 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td><strong>Sofia Influenza A+B FIA</strong></td>
<td>Quidel Fluorescence</td>
<td>A, B</td>
<td></td>
<td>Nasal swab, NP*</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NP aspirate/wash</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BinaxNOW Influenza A &amp; B</strong></td>
<td>Alere, Inc.</td>
<td>A, B</td>
<td></td>
<td>Nasal swab, NA/W, NP</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td><strong>Clearview Exact Influenza A&amp;B</strong></td>
<td>Alere, Inc.</td>
<td>A, B</td>
<td></td>
<td>Nasal swab</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td><strong>Directigen EZ Flu A + B</strong></td>
<td>Becton Dickinson</td>
<td>A, B</td>
<td></td>
<td>NA/W, NP, throat swab</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td><strong>BD Veritor System for Rapid Detection of Flu A+B</strong></td>
<td>Becton Dickinson</td>
<td>A, B</td>
<td></td>
<td>Nasal swab</td>
<td>10 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td><strong>Denka Seiken Quick ExFlu</strong></td>
<td>Denka Seiken CO., Ltd.</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Quick Navi</strong></td>
<td>Denka Seiken CO., Ltd.</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Nasal swab, NA/W, throat swab</td>
<td>8 min.</td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Espline Influenza A&amp;B-N</strong></td>
<td>Fujirebio, Inc.</td>
<td>A,B</td>
<td>Not disclosed</td>
<td>Nasal swab, NA, NP</td>
<td></td>
<td>Japan</td>
</tr>
<tr>
<td><strong>Rockeby Influenza A Antigen</strong></td>
<td>Rockeby Biomed</td>
<td>A only</td>
<td>H3N2, H5N1</td>
<td>Nasal swab, NA/W, NP, throat swab</td>
<td>10 min.</td>
<td>IVD</td>
</tr>
<tr>
<td><strong>TRU FLU</strong></td>
<td>Meridien Biosciences</td>
<td>A, B</td>
<td></td>
<td>Nasal swab/wash, NP swab/aspirate</td>
<td>15 min.</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td><strong>Formosa One Sure Flu A/B Rapid</strong></td>
<td>Formosa Biomedical Technology Corp.</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td>Not disclosed</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>artus Influenza A/B RG RT-PCR kit</strong></td>
<td>Qiagen</td>
<td>A, B</td>
<td></td>
<td>NP</td>
<td></td>
<td>US-IVD</td>
</tr>
<tr>
<td><strong>Infinity RVP Plus</strong></td>
<td>AutoGenomics</td>
<td>A, B</td>
<td>2009 H1N1</td>
<td>Not specified</td>
<td></td>
<td>RUO</td>
</tr>
<tr>
<td><strong>3M Rapid Detection Flu</strong></td>
<td>3M</td>
<td>A, B</td>
<td></td>
<td>Nasal swab, NA, NP</td>
<td>15 min.</td>
<td>US-IVD</td>
</tr>
</tbody>
</table>
## Update on 2004 Background Paper, BP 6.2 Pandemic Influenza

<table>
<thead>
<tr>
<th>A+B</th>
<th>Manufacturer</th>
<th>Test Type</th>
<th>CLIA-Waived</th>
<th>Specimens</th>
<th>Time</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSOM Influenza A&amp;B</td>
<td>Sekisui Diagnostics, LLC.</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab</td>
<td>10 min</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Xpect Flu A&amp;B</td>
<td>Thermo Fisher Scientific</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, nasal wash, throat</td>
<td>15 min.</td>
<td>US-IVD, CE-IVD</td>
</tr>
</tbody>
</table>

* Only nasal swab and NP specimens are CLIA-waived.

Product status unknown: MultiCode-PLx (EraGen Biosciences acquired by Luminex in June 2011)
## Annex 6.2.3: Molecular diagnostics tests with longer time to result

<table>
<thead>
<tr>
<th>Molecular diagnostic test</th>
<th>Manufacturer</th>
<th>Viral strain detection/differentiation</th>
<th>Viral subtype differentiation</th>
<th>Specimen type</th>
<th>Time to result</th>
<th>Regulatory approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xpert Flu Assay</td>
<td>Cepheid</td>
<td>A, B</td>
<td>2009 H1N1</td>
<td>Nasal aspirate/wash (NA/W) or nasopharyngeal swab (NP)</td>
<td>75 min.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>xTAG Respiratory Viral Panel (RVP) v1</td>
<td>Luminex Corp.</td>
<td>A, B</td>
<td>H1, H3, H5</td>
<td>NP</td>
<td>96 patients in 8 hrs. (5min/pt)</td>
<td>US–IVD, Health Canada IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>xTAG RVP FAST</td>
<td>Luminex Corp.</td>
<td>A, B</td>
<td>H1, H3</td>
<td>NP</td>
<td>&lt; 4 hrs.</td>
<td>US–IVD, Health Canada IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Prodesse ProFlu+</td>
<td>Hologic Gen-Probe, Inc.</td>
<td>A, B</td>
<td></td>
<td>NP</td>
<td>&lt; 4 hrs.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>ResPlex II Plus Panel PRE</td>
<td>Qiagen</td>
<td>A, B</td>
<td>2009 H1N1</td>
<td>Not specified</td>
<td>&lt; 6 hrs.</td>
<td>RUO</td>
</tr>
<tr>
<td>Prodesse ProFAST+</td>
<td>Hologic Gen-Probe, Inc.</td>
<td>A only</td>
<td>H1, H3, 2009 H1N1</td>
<td>NP</td>
<td>&lt; 4 hrs.</td>
<td>US-IVD, CE-IVD Europe</td>
</tr>
<tr>
<td>Verigene RV+</td>
<td>Nanosphere</td>
<td>A, B</td>
<td>H1, H3, 2009 H1N1</td>
<td>NP</td>
<td>&lt; 2.5 hrs.</td>
<td>US-IVD</td>
</tr>
<tr>
<td>Verigene Respiratory Virus XP</td>
<td>Nanosphere</td>
<td>A, B</td>
<td>H1, H3, 2009 H1N1</td>
<td>Not specified</td>
<td>&lt; 1.5 hrs.</td>
<td>RUO</td>
</tr>
<tr>
<td>Seeplex Influenza A/B One Step Typing</td>
<td>Seegene</td>
<td>A, B</td>
<td>H1, H3, 2009 H1N1</td>
<td>NP aspirate/swab, bronchoalveolar lavage</td>
<td>&lt; 5 hrs. (?)</td>
<td>Health Canada IVD</td>
</tr>
<tr>
<td>RespiFinder 15 and 19</td>
<td>Patho Finder</td>
<td>A, B</td>
<td>H5N1</td>
<td>Nasal swab, NP aspirate/lavage, bronchoalveolar, sputa</td>
<td>&lt; 6 hrs.</td>
<td>CE-IVD</td>
</tr>
<tr>
<td>RespiFinder 22 and SMART 22</td>
<td>Patho Finder</td>
<td>A, B</td>
<td>H1N1</td>
<td>Nasal swab, NP aspirate/lavage, bronchoalveolar, sputa</td>
<td>&lt; 6 hrs.</td>
<td>CE-IVD</td>
</tr>
<tr>
<td>RealAccurate Respiratory RT PCR v2.0</td>
<td>Patho Finder</td>
<td>A, B</td>
<td>No</td>
<td>Nasal swab, NP aspirate/lavage, bronchoalveolar</td>
<td>2 hrs.</td>
<td>CE mark</td>
</tr>
<tr>
<td>Simplexa Flu A/B/RSV Direct</td>
<td>Focus Diagnostics</td>
<td>A, B</td>
<td>No</td>
<td>NP</td>
<td>&lt; 1 hr.</td>
<td>US-IVD</td>
</tr>
</tbody>
</table>
### Simplexa Influenza A/H1N1 (2009)

- **Focus Diagnostics**: A only
- **2009 H1N1**: Nasal swabs, NP aspirate/swab
- **Time**: < 1 hr.
- **Approval**: US-IVD, CE mark

### Quidel Molecular Influenza A + B

- **Quidel Molecular**: A, B
- **2009 H1N1**: No
- **Time**: < 75 min.
- **Approval**: US-IVD

*Only approved by CE-IVD Europe*
Appendices

Appendix 6.2.1  Influenza Research: EU Funded Projects 2001 – 2007
Appendix 6.2.2  European Commission FP7 Cooperation Work Programme
Appendix 6.2.3  WHO Pandemic Influenza Preparedness Framework
Appendix 6.2.4  Informal Consultation on Technical Specifications for a WHO International H5N1 Vaccine Stockpile
Appendix 6.2.5  WHO Expert Committee on Biological Standardization: 54th report
Appendix 6.2.6  WHO Expert Committee on Biological Standardization: 58th report
Appendix 6.2.7  WHO Expert Committee on Biological Standardization: 60th report
Appendix 6.2.8  WHO Virtual Consultation on the Safety of Adjuvanted Influenza Vaccines
Appendix 6.2.9  WHO Guidance on Development of Influenza Vaccine Reference Viruses by Reverse Genetics
Appendix 6.2.10 EMA Guideline on Dossier Structure and Content for Pandemic Influenza Vaccine Marketing Authorisation Application