ECDC RISK ASSESSMENT

2009 influenza A(H1N1) pandemic

Version 7 – 17 December 2009

Table of contents

Stockholm, December 2009

What's new or different in this update?

This update is informed by the experience this autumn in Europe and North America as well as further analyses from the Southern Hemisphere's temperate countries during their winter season.

It includes:

- The first 'synthesis' from a European country looking at the epidemiological findings from the experience of the UK from April to September 2009.
- An analysis of a number of studies which on balance conclude there is little or no effect of seasonal influenza immunisation on the risk of infection or disease from the 2009 pandemic A(H1N1) virus.
- A table comparing and contrasting the recent experience of seasonal influenza and 2009 pandemic influenza A(H1N1).
- An initial report of the D222G mutation in the haemagglutinin gene though noting that these spontaneous mutations have been observed since the start of pandemic.
- The first reports of transmission of oseltamivir-resistant viruses in Europe in a special setting (a ward with immunocompromised patients).
- The first published report of deaths from the pandemic virus in the EU including an indication of the percentage of these that occurred among people who are and are not in a risk group.
- One report from the United States of increased invasive pneumococcal disease associated with the pandemic infection.
- Discussion of the fact that although infection rates are declining in the countries first affected in the EU (western and northern countries), infection rates are still high and rising in some eastern European countries where access to pharmaceutical countermeasures is likely to be more difficult.
- Note of the risks for the holiday period (Christmas and New Year) when people travelling may be at heightened risk of acquiring infection and also some primary care services may be reduced, thereby putting more pressure on hospital services.

Executive summary

This update of the ECDC pandemic risk assessment for Europe is based on data and analyses available in early December 2009. It draws on the experience in European countries, North America and the Southern Hemisphere's temperate countries, which have already passed through a winter with the new virus. This description deals with the infection and the disease. Specifically, it does not include comments on the pharmaceutical countermeasures, nor their likely effectiveness and safety. These are dealt with separately in dedicated ECDC documents.

After transmitting heterogeneously but at low levels over the summer in European countries, epidemics of the pandemic virus infection have now affected all EU countries. Indeed some of the countries first affected are now experiencing declines in transmission. At this stage, it cannot be predicted exactly how intense the peaks of transmission will be. However, ECDC has agreed with Member States' and WHO's reasonable worse case planning assumptions (see Table 2) that will assist those Member States that were not significantly affected by the first wave over the summer with their final preparations. Nevertheless, it is important not to regard these assumptions as predictions of what will happen.

This pandemic is proving a significant health event for European countries and is putting particular stress on some health services, especially hospitals and their intensive care capacity. However, the experience also shows that well prepared healthcare services are able to cope and there should be no special strain on the essential services outside the health sector if they have undertaken robust business continuity planning.

To date, important features of the 2009 influenza A(H1N1) pandemic include the following:

- Europeans are being affected by transmission waves earlier in the season than is common with seasonal influenza.
- The large majority of those infected experience a mild, self-limiting illness or an asymptomatic infection.
- There are a minority of people who will experience more severe disease, and some of these will die despite medical care. About 30% of these are not in any risk group.
- While there is much that is similar between the 2009 influenza A(H1N1) pandemic and the seasonal influenza that affects Europe each year, there are also important differences:
  - when the pandemic waves are taking place they are resulting in more cases at once;
  - there is an underrepresentation of older people affected by the pandemic relative to seasonal influenza since many, but not all, have some immunity against the pandemic virus; though older people who are infected are experiencing the highest rates of severe disease and death of any age group;
  - the spectrum of severe disease includes cases of primary viral pneumonia causing severe acute respiratory distress syndrome (ARDS); these cases are especially difficult to manage
  - secondary bacterial infection are occurring;
  - deaths among adults are occurring at a considerably younger age than normally seen with seasonal influenza;
  - in some cases, even in healthy individuals, onset and progression of disease is rapid;
  - there are many asymptomatic or very mild infections.
- Because of the large number of cases occurring at once, it is important that they are dealt with at home or in primary care if hospitals are not to be overwhelmed.
- If only a small proportion of cases result in severe illness that will still be enough to stress some hospital healthcare systems, especially intensive care units. A number of Member States have expanded their intensive care services accordingly.
- There are no reports of unusual transmission routes for this influenza compared with normal seasonal influenza viruses and there is no indication of risk of infection through food.
- Though there have been some reported outbreaks of the pandemic virus infection in domestic animals this does not seem to be an important route of transmission to humans now. The predominant route of infection is from human to human.
- Clinical attack rates are highest in children and, following that, young adults.
- Of all age groups, that with highest mortality rate is older persons (60 years and older).
- The groups experiencing severe disease and requiring hospitalisation the most—those in the risk groups—are people with chronic underlying medical conditions, pregnant women (although the individual risk of a pregnant woman experiencing severe disease is low) and young children (younger than two years of age).
- From Southern Hemisphere and American data it is estimated that the risk of an infected person requiring intensive care rises if they have a series of well recognised risk factors: pregnancy (tenfold rise), asthma or other chronic respiratory disease (threefold), massive obesity (sixfold). (In all these cases, the comparison is with a person without any risk factors.)

- Most young children going into hospital experience short illnesses and spend little time in hospital. In contrast, hospitalised adults spend much longer periods there.
- The underlying conditions putting people at risk are different for adults and children but similar to those for seasonal influenza. In adults, the major risk groups—apart from pregnant women—include those with chronic respiratory or metabolic disorders. Children most at risk are those with chronic neurological or developmental conditions.
- There are adults and children who experience severe disease or even death without any obvious underlying condition. These comprise between 20 and 30% of the deaths attributed to influenza.
- The mortality due to this pandemic in Europe has yet to be estimated. Though it may be similar in numbers to what is seen in some ordinary influenza seasons, it will seem different because of the higher number of younger people and people without underlying conditions.
- The number and proportions of infected people with symptoms will be especially difficult to estimate as there will be many people with mild disease and it will not be possible to estimate all those infected until serological studies are completed.
- Almost all the isolates of the pandemic viruses analysed have been sensitive to the neuraminidase inhibitors (oseltamivir and zanamivir), but they are resistant to the adamantanes (amantidine and rimantidine).
- There have been a few pandemic virus isolates that have been resistant to oseltamivir (though sensitive to zanamivir).
- As with seasonal influenza viruses many of these resistant mutations are appearing in immunocompromised patients with persistent infections and taking antivirals. There have been at least two outbreaks and transmission of these viruses among immunocompromised persons in a hospital setting and one probable incident of community transmission. One of the hospital outbreaks is in Europe.
- It has become clear that some spontaneous mutations of the pandemic virus have appeared, notably one known as D222G in the haemagglutinin gene. These have been observed since the start of the pandemic including in EU countries.
- Although the current seasonal influenza vaccine contains a component effective against another A(H1N1) virus, it is not effective against the 2009 pandemic influenza A(H1N1) virus.
- It is difficult to predict what the mix of pandemic and seasonal influenza viruses will be this season. The experience in the Southern Hemisphere is that the 2009 pandemic influenza A(H1N1) has, on the whole, reduced the proportion of other influenza A and B viruses and entirely replaced the seasonal A(H1N1). There are only very few other influenza A viruses circulating, notably A(H3N2) at present. Though there remains a possibility of influenza A(H3N2) and B epidemics early in 2010 when the pandemic waves have passed.

There remain a number of important areas of uncertainty, topics where initial trends need a degree of quantification or information is simply lacking. These include:

- **The extent of asymptomatic infections and the levels of infection and immunity in the population, following the initial wave or waves. Sufficient post-pandemic wave serological data are still lacking.**
- **The possible pattern of infection from January 2010 onwards – will there be continuing transmission, further waves or only very little further transmission?**
- **Will the seasonal influenzas appear?**
- **The absolute level of risk of severe outcome in healthy people and in those in most of the risk groups.**
- **The attributable mortality due to this pandemic overall and by age group.**
- **The reason why some individuals experience severe illness but most do not and the pathological process of the underlying severe disease.**
- **The significance of the mutant viruses observed to date.**
- **The exact degree of effectiveness of pharmaceutical countermeasures such as antivirals (please note that this will feature in other ECDC publications rather than this risk assessment).**

Some of these are research questions and feature in the public health research agenda being developed by the World Health Organization (WHO), to which ECDC has contributed. http://www.who.int/csr/disease/influenza/research_agenda/en/index.html

ECDC will work with Member States, other European Agencies, notably the European Medicines Agency and European Food Safety Authority, the European Commission, WHO and its other international partners to gather more information to update this risk assessment at intervals.

Pandemic viruses are unpredictable and can change their characteristics as they evolve and perhaps reassort with other influenza viruses, though there is no evidence that this has happened yet. It

therefore remains possible that the pandemic virus could acquire resistance to neuraminidase inhibitors or even become more pathogenic.

Comments on the risk assessment and details of further relevant data and analyses are most welcome and should be sent to PHE-incoming@ecdc.europa.eu preferably marked *ECDC Pandemic Risk Assessment 2009*

Source, date and type of request

ECDC internal decision, 18 May 2009. Intervening revisions have responded to questions and suggestions from a variety of sources including the European Commission, Member States and WHO as well as from ECDC staff. Last revision, 6 November 2009.

Specific question

Health implications for Europe regarding the 2009 influenza A(H1N1) pandemic.

Consulted experts

Internal ECDC experts. ECDC Advisory Forum

Evidence assessment

The evidence underlying this risk assessment comes from published data, studies, routine reports and other technical documents from public health organisations and agencies including the World Health Organization (WHO), the United States Centers for Disease Control and Prevention (CDC), and official sources in a number of other affected countries. Increasingly these have come from Europe. Unpublished data and analyses are noted but not referenced.

The current evidence comes mostly from observations of the pandemic and reported cases in Europe and the US over the summer, autumn and winter as well as the analyses of the pandemic waves in countries in the Southern Hemisphere during their winter. A particular difficulty arises from the mild nature of the disease, which means that many infections are undetected and unreported while more severe disease and deaths are likely to be captured in surveillance systems. This means that observed rates or ratio percentages (numbers of hospitalisations or deaths per 100 reported cases or population denominators) are likely to be biased upwards. They are correct observations, but can be misleading for planning purposes.

Topics of prime public health importance are dealt with in Section 2 and areas of particular uncertainty are listed in Section 3.

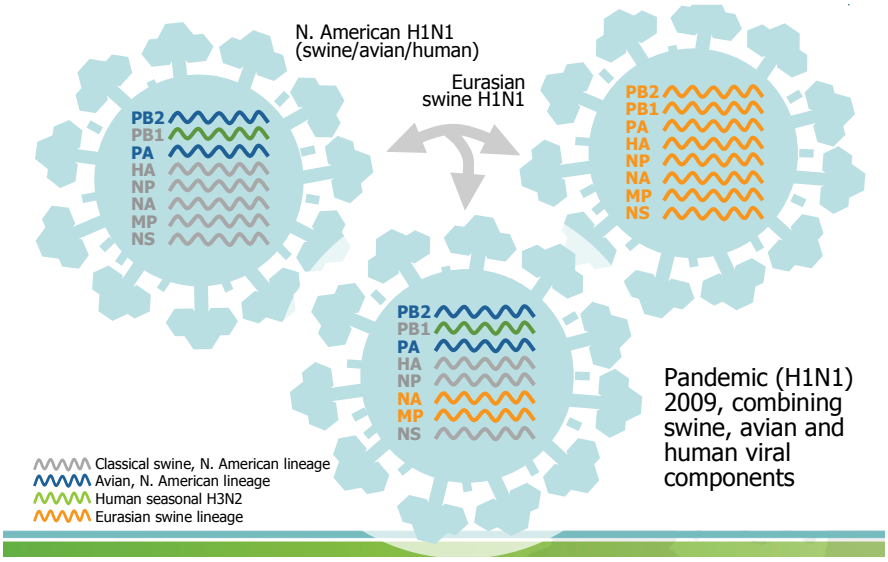
Risk assessment

1 Background

A new influenza A virus was identified by the United States CDC in April this year in samples from two cases and retrospectively in cases in Mexico [1-3].

The basic genetic structure of the virus has been described and this information is available through publicly accessible websites [4-6]. The virus has a number of genetic elements from two different types of swine influenza, but also elements originally from avian and human influenzas that were incorporated into other swine influenza viruses (Figure 1) [5,7,8].

Figure 1: Genetic origins of the 2009 pandemic influenza A(H1N1) virus combining swine, avian and human



It is unclear whether the specific reassortment leading to the new virus took place in pigs or humans. In recent years, occasional swine influenza infections in humans have been detected through surveillance of humans, especially in North America. Swine influenza viruses with genes from avian, human and swine influenzas have previously been circulating in pigs in the US, and have occasionally been transmitted to humans [7, 8]. However, those infections have not transmitted efficiently from human to human. In contrast, this new virus is transmitting efficiently from human to human*. Because the disease spread widely to all continents it met WHO's predetermined criteria for a pandemic influenza strain and is a human influenza†[9]. The infection has been global for some time [10].

WHO and other international agencies are now calling the disease 'pandemic H1N1 2009'. The term 'swine flu' is inaccurate and confusing.

There are several recent examples of influenza viruses of animal origin that have transmitted to humans. Some have also transmitted occasionally from human to human. The most obvious example being the avian A(H5N1) influenza 'bird flu', which has been circulating in East and Southeast Asia for more than a decade, and which has caused severe infections and deaths in the region. However, human-to-human transmissions of A(H5N1) and other avian influenzas have been very limited [11]. The 2009 pandemic influenza A(H1N1) is the first animal influenza for some years to have adapted sufficiently to be referred to as a human influenza.

2 Important features

Each pandemic is different and there are always a series of unknowns when a new influenza virus emerges and causes a pandemic. ECDC refers to the most important of these as the 'known unknowns' [12, 13] (Figure 2). Some of these remain unknown or at least unclear but for several of the unknowns, data are becoming available from many affected countries; notably from North America [14], the Southern Hemisphere[15] and European countries [16].

* The virus is not genetically related to the single human swine flu infection recently detected in a human in Europe [http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19120, Personal communication to ECDC A Hay WHO Influenza Collaborating Centre, May 2009]

† Information on the spread of the pandemic is being updated regularly on WHO websites (http://www.who.int/csr/disease/swineflu/en/index.html) and information on the spread in the European Union/EEA countries can be found on the ECDC website (http://ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx).

Figure 2: For any pandemic virus, what can and cannot initially be assumed?

What probably can be assumed:

Known knowns

- Modes of transmission (droplet, direct and indirect contact).
- Broad incubation period and serial interval.
- At what stage a person is infectious.
- Broad clinical presentation and case definition (what influenza looks like).
- The general effectiveness of personal hygiene measures (frequent hand washing, using tissues properly, staying at home when you get ill).
- That in temperate zones transmission will be lower in the spring and summer than in the autumn and winter.

What cannot be assumed:

Known unknowns

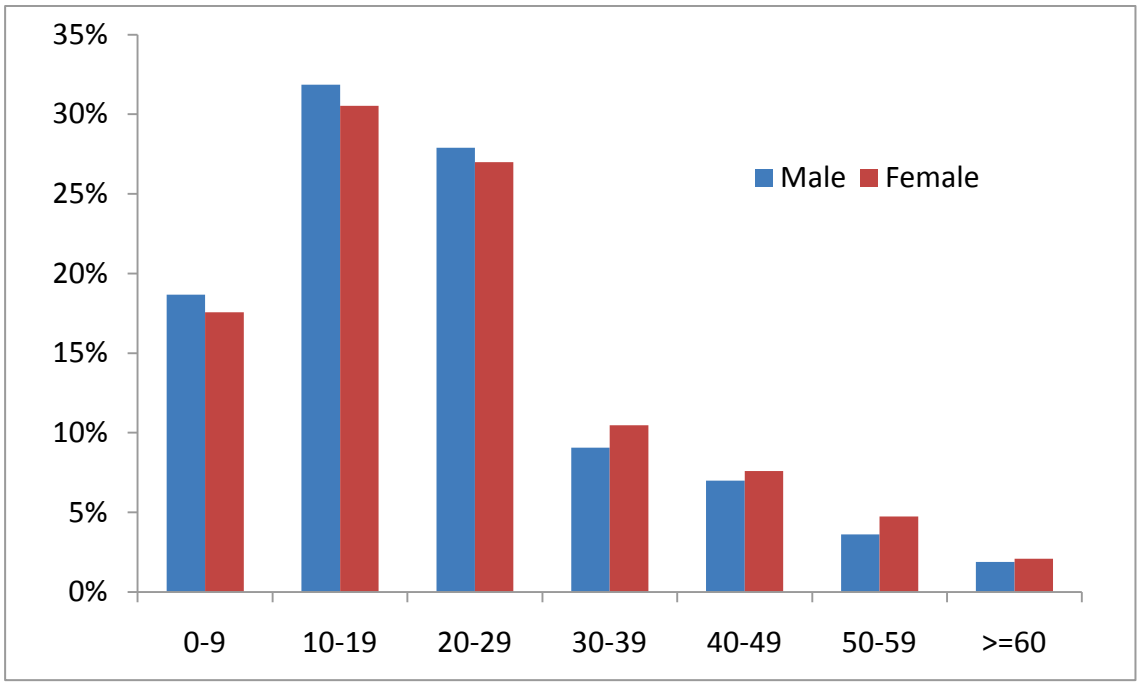
- Antigenic type and phenotype.
- Prior immunity in population.
- Resistance to antivirals.
- Age-groups and clinical groups most affected.
- Age-groups with most transmission.
- Clinical attack rates.
- Pathogenicity (case-fatality rates).
- 'Severity' of the pandemic.
- Precise parameters needed for modelling and forecasting (serial interval, R_o).
- Precise clinical case definition.
- The duration, shape, number and tempo of the waves of infection.
- Will new virus dominate over seasonal type A influenza?
- Complicating conditions (super-infections).
- The effectiveness of interventions and counter-measures including pharmaceuticals.
- Exactly how safe are pharmaceutical interventions?

2.1 Basic epidemiology and basic parameters

2.1.1 Age and sex

Among reported cases, the observed age distribution is unusual and different from seasonal influenza, being skewed towards younger age groups [17]. There is a marked underrepresentation of infections in people over 65 years of age, who made up only 2% of the initial reported cases. In Europe, the reported cases tend to be young: median age being 25 years in those who acquired the infection during travel, and 13 years in those domestically infected. Nearly 80% of all cases are individuals under 30 years of age [17-20] (Figure 3).

Figure 3: Distribution by age and gender of individual case reports of 2009 pandemic influenza A(H1N1) infection, 28 EU/EEA countries, 19 April–22 September 2009 (n = 9 813)



2.1.2 Prior immunity

Broadly speaking, males and females are equally affected (Figure 3) [21]. However, the distribution by age group varies widely [18]. There are consistent serological laboratory results indicating that older people are less affected due to some enduring immunological memory of an earlier influenza A(H1N1) infection with a similar phenotype [22],[16].

In Finland, a retrospective seroprevalence analysis of more than 1000 serum specimens collected in 2005 has been carried out to determine the presence and level of cross-reactive antibodies against 2009 pandemic influenza A(H1N1) virus. Haemagglutination inhibition (HI) analysis revealed that 15–20% of individuals born 1930–1944 have detectable antibodies against the 2009 pandemic influenza A(H1N1) virus. The prevalence of antibodies is higher in older generations and individuals born 1920–1929 and 1909–1919 show 57% and 96% seroprevalence, respectively. It is noteworthy that in the oldest generations (born 1909–1929), approximately 50% of the seropositive individuals have relatively high cross-reactive antibody levels (HI titre ≥ 40). These data indicate that infections caused by the Spanish flu and its descendant viruses are likely to have given immunity against the current pandemic virus. This is supported by the epidemiological findings in Europe (Figure 3) and elsewhere around the world that individuals presently older than 65 years of age are underrepresented among those who have contracted the pandemic 2009 virus*.

A serological study conducted in the US found that only 4% of persons (4 of 107) born after 1980 had pre-existing cross-reactive antibody titres of 40 or more against 2009 pandemic influenza A(H1N1), 34% of persons (39 of 115) born before 1950 had antibody titres of 80 or more, and 11 out of 11 who were born between 1910 and 1929 had antibody titres of 80 or more.

Aside from the evidence from serological studies three observational studies (two in the USA [23, 24], one in Australia [25]) indicated no significant effect of the seasonal vaccine against 2009 pandemic influenza A(H1N1) infection and only one Mexican study showed a protective vaccine effect [26, 27].

The relatively low attack rates overall for a pandemic and the distinctive age distribution (see Figure 3) are consistent with significant background levels of immunity in the adult population that increases with age. Hence clinical attack rates are twice as high in people under 16 years than in older people. This is also consistent with serological information from Australia and the United States as well as the studies in Finland. The limited immunity in younger adults is considered to arise from earlier exposure to the seasonal A(H1N1) virus while the higher levels in older adults is due to exposure to the pre-1957 seasonal A(H1N1) virus (which was replaced by the 1957 pandemic virus).

2.1.3 Basic parameters†

Incubation period (the period from exposure to symptoms appearing): The indications are that the incubation period is little different from other human influenza though the distribution may have a longer tail than is usually observed; the results to date are a median of 1.5 to 2 days with a range of 1–7 days [30].

Generation time – serial interval (the interval between successive generations of infection): Between 2.5 and 3 days.

Reproduction number (R_o) (the average number of secondary infections caused by an index case): There have been a number of estimates for this ranging from 1.1 to 1.8 but with higher values observed in groups with close proximity, notably in school settings [31].

At the early stages of the pandemic during high susceptibility rates in populations, the basic reproduction number ranged from 1.4–1.6 in Mexico [32] and 1.2–1.7 in Peru [33] to 1.80–2.15 in New Zealand [31]. Higher values have been observed in countries where transmission is intense [14,23,26], with even higher figures in some closed communities, such as schools [13]. Lower values of what is then called the 'Effective Reproduction Number' are observed in populations which have prior immunity, have already experienced significant waves of the pandemic or after effective vaccination uptake. The derived reproduction number also depends on the modelling approach used; for example, analysis based on confirmed cases in Australia during the period of exponential growth of the pandemic (i.e. the second half of May 2009) indicated a reproduction number of 2.4 (95% CI: 2.1-2.6), but when undetected transmission was also taken into account, this estimate was reduced to 1.6 (95% CI: 1.5-1.8) [34].

* For further information: Professor Ilkka Julkunen at National Institute for Health and Welfare (THL), Finland (ilkka.julkunen@thl.fi).

† This section especially draws on a review undertaken by and for the World Health Organization [28] WHO. Considerations for assessing the severity of an influenza pandemic. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations. 2009 May 29;84(22):197-202, [29] WHO, Weekly Epidemiological Report, Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus, 13 November 2009, available at: http://www.who.int/wer/2009/wer8447.pdf.

Secondary attack rates (the percentage of people showing clinical disease among close contacts in home and other enclosed settings): These have ranged from 7 to 13%, though it must be noted that because of mild and asymptomatic infections true secondary infection rates may be considerably higher.

Proportions of symptomatic and asymptomatic infections: For reasons mentioned above and in section 2.2.2 (Asymptomatic and mild cases), this may be especially difficult to determine for this pandemic.

Period of infectivity: This has yet to be determined. There are anecdotal reports of detection of expressed virus through polymerase chain reaction (PCR) beyond symptomatic periods, but detection of virus by such sensitive tests does not necessarily imply infectiousness. With a mild infectious disease, decisions on exclusion periods need therefore to be taken with a degree of pragmatism and exercise of judgment [35].

2.2 Disease characteristics

2.2.1. Modes of transmission

There is no evidence to date suggesting that the virus spreads in any different way from other human influenza, i.e. other than by droplets from coughing and sneezing and direct and indirect contact with respiratory secretions from infected persons [36]. There is no evidence suggesting unusual transmission routes for influenza and no reason to suggest transmission through food [37].

2.2.2 Spectrum of disease

Asymptomatic and mild cases

The finding of test-positive cases without symptoms in contacts of known cases—during field epidemiology studies and from serological findings—have demonstrated that there are numerous asymptomatic cases in this pandemic[16]. This is seen for seasonal influenza and all pandemics. However, a notable feature of this pandemic is the numbers of mild cases that do not fit classical case definitions of influenza-like illness (ILI) or even acute respiratory infections (ARI). This is also suggested by baseline data from clinical trials in Australia [38]. Hence the precise proportion of asymptomatic cases among all infections is going to be more difficult to determine than usual (Figure 4). Equally, clinical attack rates and therefore case fatality ratios will be exceptionally difficult to determine and highly sensitive to the case definition used.

Uncomplicated mild disease—clinical features

Among the cases reported early on, the only notable clinical feature that differs to date from seasonal influenza is seen in some reports of more gastro-enteric symptoms than are common for seasonal influenza [39]. But these gastrointestinal symptoms have almost always been accompanied by other more usual signs of influenza. The distribution of symptoms in Europe is similar to that described in the USA, with the proportion of patients reporting gastrointestinal symptoms being around 14% [18].

Severe disease—clinical features

A considerable amount of data have now become available on the clinical characteristics of the severe cases of 2009 pandemic influenza A(H1N1) [19, 40-43] and was reviewed at a global consultation organised by WHO. One notable feature mentioned at that meeting and in other case reports was of some individuals who became very sick very quickly. This included some people without any underlying conditions [44].

The median interval between symptoms' onset and hospital admission varied between six days in Mexico and four days in Canada [41, 45]. Delay in seeking care and especially in the late use of antivirals—or not using antivirals at all—was associated with a poor outcome [44, 46]. Almost half of 722 reported cases requiring intensive care unit (ICU) admission in New Zealand and Australia had a viral pneumonitis and a distinct acute respiratory distress syndrome (ARDS) that are unusual for and much rare than in seasonal influenza. Pathological investigation indicates diffuse alveolar damage, haemorrhagic interstitial pneumonitis with lymphocyte proliferation and few neutrophils, which are consistent with viral pneumonitis and ARDS. The precise mechanism of the development of ARDS is unclear but hypoxia plays an important role [44, 46].

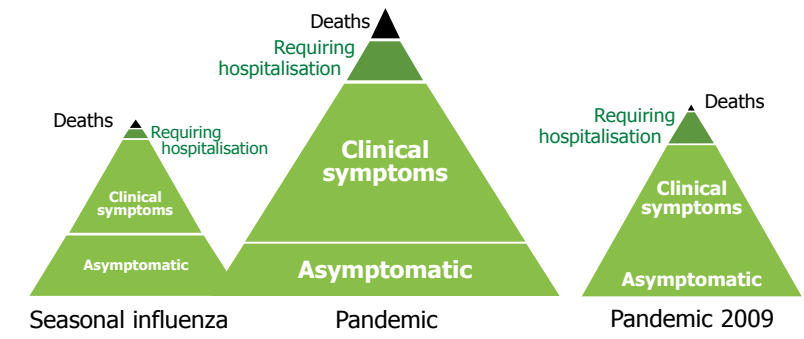
Co-infection (secondary infection) with bacteria and bacterial pneumonias has been seen but is less common than with seasonal influenza. The WHO review meeting reported that co-infection with bacteria has been documented in post-mortems in the USA and Canada. In New Zealand and Australia, 20% of cases admitted to ICU had secondary bacterial pneumonia. This is very similar to the data reported from Canada, where 24% of ICU cases had evidence of bacterial pneumonia. The most frequently isolated pathogens were *Staphylococcus aureus* and *Streptococcus pneumoniae*. Healthcare-associated infections, such as ventilator-associated pneumonia, have been identified in critically ill cases with a prolonged hospital stay. Multiple pulmonary emboli have been observed in several very severe cases in patients in the USA admitted to ICUs with refractory ARDS.

These viral pneumonias and ARDS are difficult to manage and ventilate and can require highly specialised care. The most common cause of death in these cases is progressive organ failure [47]. In children, severe disease is less common, with most hospitalisations being short. However, as with seasonal infection, there are cases of bacterial supra-infection [48].

A preliminary study from the USA indicates that 2009 pandemic influenza A(H1N1) hospitalisations seem to be associated with an increase in invasive pneumococcal disease (IPD). One study from the Denver Metro area (Colorado) found an increase in invasive pneumococcal cases reported in a pre-existing Active Bacterial Core surveillance system (ABCs) that coincided with an October peak of the pandemic influenza hospitalisations. This finding needs further investigation [49]. It was noted that similar increases in cases of pneumococcal disease were seen in other ABCs sites and in previous pandemics though this finding has not yet been reported from European countries.

In various countries, extracorporeal membrane oxygenation (ECMO) has been used to treat patients with ARDS not responding to mechanical ventilation. The largest published experience comes from Australia and New Zealand [50]. The use of ECMO very much depends on its availability. In Australia and New Zealand, it was used at a rate of 2.6 cases per million population. A similar incidence of ECMO use in Europe would mean a rough estimate of 1300 cases during the 2009/10 winter. The median age of patients treated with ECMO in Australia and New Zealand was 34.4 years. Among the 68 cases observed, many had pre-existing conditions of which the most common were obesity (BMI > 30) present in 50% of cases, followed by asthma (28%) and diabetes (15%). A secondary bacterial infection was identified in 28% of cases. The majority of the patients receiving ECMO survived (mortality rate was 21%). This is lower than the mortality rate observed for patients receiving ECMO for other reasons. Data on the effectiveness of ECMO treatment are difficult to obtain as it would be unethical to study a control group of patients with similar clinical severity not receiving ECMO. However, the positive outcome of the majority of patients requiring ECMO suggests that the treatment is likely to have reduced mortality.

Figure 4: Seasonal influenza compared with pandemic — proportions of types of cases



*2.2.3 Clinical attack rate**

Clinical attack rates for the current pandemic are especially difficult to estimate because of the many mild cases. During previous pandemics it was unusual to observe population clinical attack rates of less than 20%, while for seasonal influenza, rates are usually between 5 and 10% [51]. However, this pandemic is unusual because of the prior immunity, especially in older people. Because of the mild nature of many cases clinical attack rates are hard

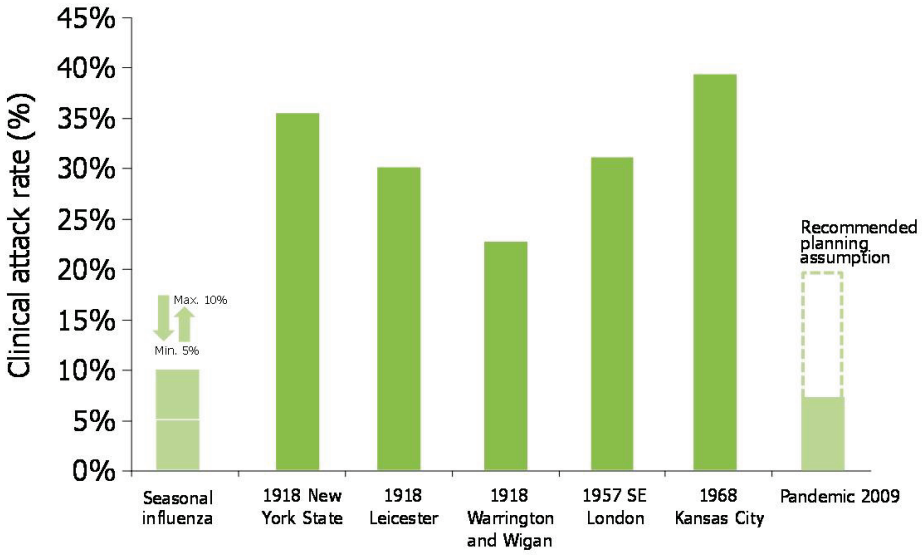
* Technically, the three 'rates' (clinical attack, hospitalisation and case fatality rates) should be called 'ratios' as they are proportions and do not have a time component as all rates should. The 'clinical attack rate' is the proportion of the population that is infected and has symptoms (i.e. asymptomatic infections are excluded). When considered for a pandemic, it can extend over the whole first wave period and mean the 'cumulative attack rate'. The 'case hospitalisation rate' is the proportion of those affected (with symptoms) that are ill enough to go to hospital, while the 'case fatality rate' is the proportion of those affected who die as a direct or indirect consequence of their infection.

to determine and vary from study to study. One using ILI as a criterion will result in a low rate, while one including more mild disease will result in higher figures. Experience from the Southern Hemisphere, where there were stringent criteria, resulted in low rates of 10% or less [40]. In a study conducted in Mexico, a figure of 30% was observed in one community [13]. While lower figures have been observed in North America—notably in New York City where a telephone survey in May gave a figure of 7% [52]—this transmission took place in the Northern Hemisphere's spring, when the United States in particular was still in the 'initiation' phase of its pandemic wave. Given the time of year, this probably does not represent the final cumulative clinical attack rate, which is always higher for pandemic than seasonal viruses (see Figure 5). An estimate of the attack rate of clinical infections in New Zealand was 8% for the 2009 season which rises to 11% if assumptions are made for asymptomatic infections [36]. This is little different from a normal influenza season [40, 51, 53, 54]. In an American investigation based on its Emerging Infection Programme, between 34 million and 67 million cases of 2009 pandemic influenza A(H1N1) occurred between April and 14 November 2009 [55]. While an estimate for England, made in order to provide a denominator for death data, was about 1% of England's population (estimated range 0.5–2.2%) [56].

In Europe, higher clinical attack rates were observed in focal outbreaks in closed communities. In school outbreaks in the UK and France, figures of around 30 and 50% have been reported [16] [57, 58]. As is the case with other human influenza infections, there will probably be many mild and asymptomatic cases [18, 51]. Certainly in New York most of those affected did not consult a doctor [59].

This notwithstanding, for planning purposes it is safest to assume population attack rates of up to 20% in the first year of the pandemic (planning assumptions represent reasonable worst-case scenarios). Attack rates will naturally be considerably lower during second waves in European areas that have already experienced significant first waves over the summer.

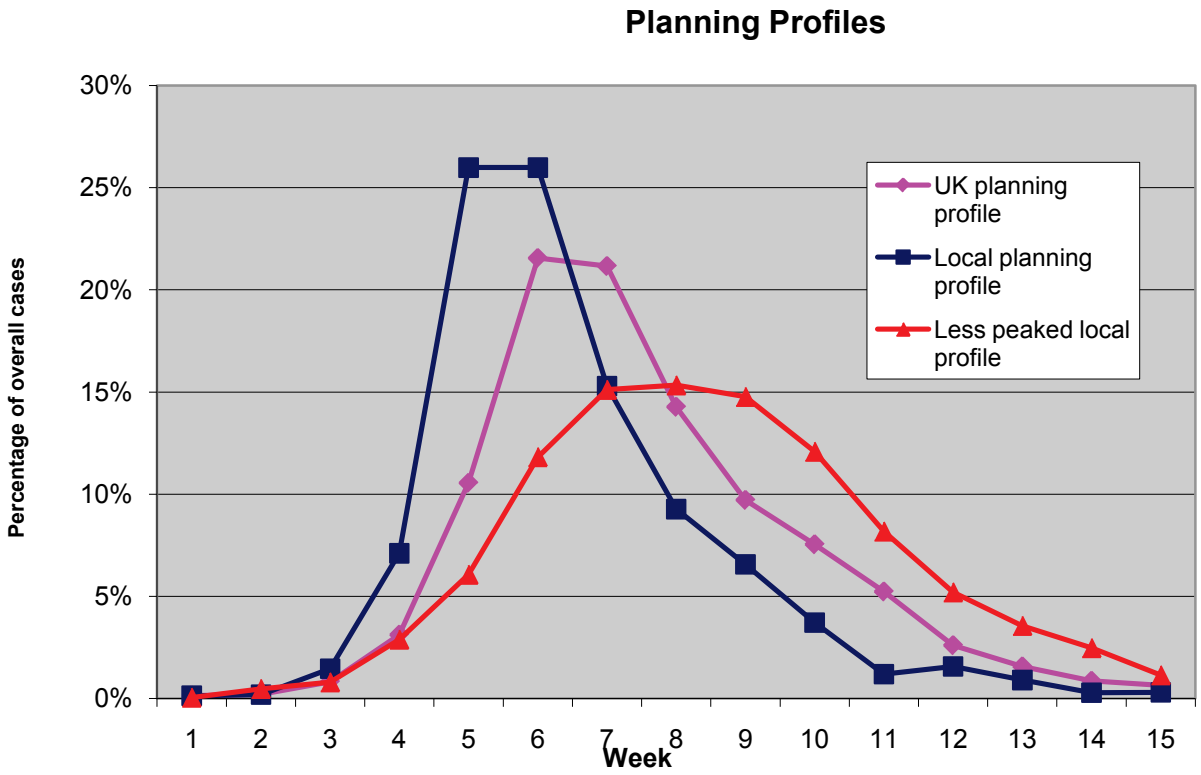
Figure 5: Numbers affected during seasonal influenza epidemics and pandemics (overall clinical attack rate in previous pandemics)



2.2.4 The pattern of epidemics

There is no reason to expect that the epidemic curve for this pandemic will be any different from others. Reasonable national and local planning curves are shown in Figure 6. It is important to note that again the height of the curve is *not* a prediction: It is a reasonable worse case scenario. Further, different considerations and lower peaks will apply for European populations who experienced a significant numbers of infections over the summer.

Figure 6: National and local planning profiles (UK), proportion of local population becoming ill per week



Source: ECDC revised pandemic 2009 planning assumptions for Europe. Available at: http://www.ecdc.europa.eu/en/healthtopics/Documents/091111_Pandemic_(H1N1)_2009_Planning_Assumptions_for_EU_EEA_countries.pdf

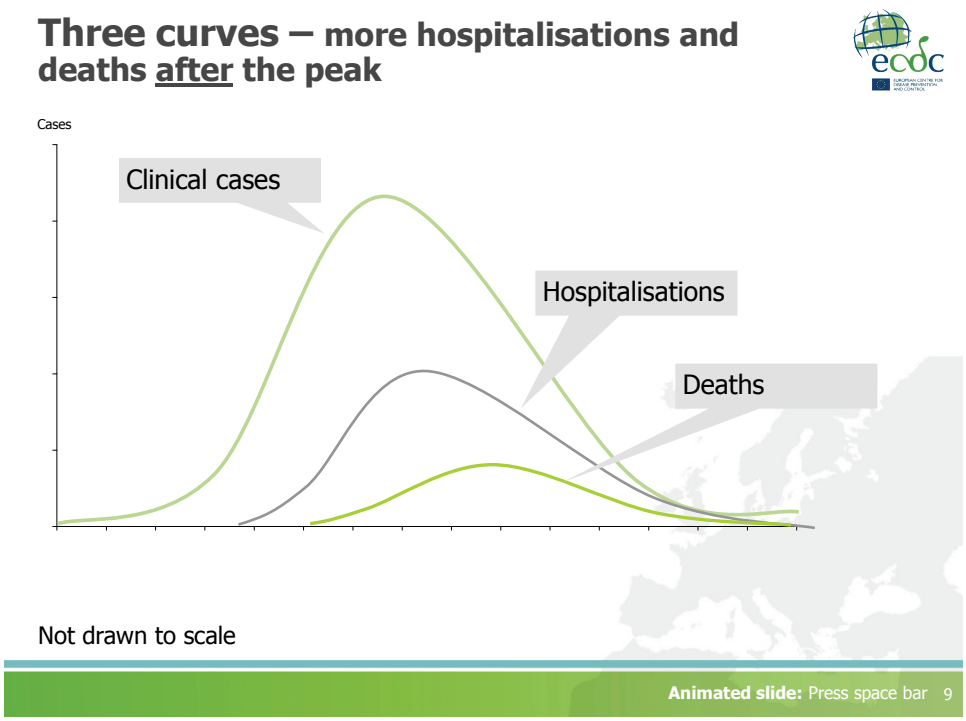
No pandemic has ever behaved in so neat a way as shown here. It is especially important to note the difference between national and local curves. The local curves are narrower and with a higher central peak, i.e. local pandemic spread is shorter and sharper but also highly variable. Different European countries and different parts of countries experience waves at different times. The duration of a winter wave is usually 16 weeks in all though it may be longer for large countries and those with scattered populations. At times of low transmission, such as in the summer, the pattern of the waves has been especially sensitive to school closures.

For planning purposes, there are four components of a pandemic wave: initiation, acceleration, peak and decline. After the decline, influenza can be expected to settle back down to its seasonal pattern again. The seasonal flu may be worse than the years before the pandemic because it is invigorated with new genetic material. The same four phases actually apply to epidemics as well. This particular wave had an erratic initiation phase in Europe with small outbreaks in the summer and early autumn and a major wave in one or two countries [16]. Most of the European countries experienced their main initiation and acceleration phases between mid-October and the end of November 2009. At the time this document has been updated (December 2009) many of the EU countries are experiencing their declining phase though incidence and transmission remain high, especially in the eastern countries of the EU.

A particular feature observed in countries that were affected by the pandemic in the summer is that waves this autumn have been more muted than expected because of the extensive infections that had already taken place. Thus the summer waves experienced by countries such as Spain and the UK might have contributed to reducing the burden on health services in the autumn [16, 60].

It is important to note that there is a time lag between cases occurring in the community and hospitalisations and, even later, deaths so that even after the peak of a pandemic wave the numbers of hospitalised cases and deaths keep rising for some time. So that while transmission is declining in many EU countries the numbers of deaths reported by MS are increasing.

Figure 7: Idealised epidemic curves showing clinical cases, hospitalisations and deaths during an influenza pandemic



Though infection rates are declining in the countries first affected in the EU (western and northern countries) infection rates are still high and rising in some eastern European countries where access to pharmaceutical countermeasures is likely to be more limited [61].

2.2.6 Hospitalisation rates

Descriptions of hospitalisation rates at the national or European level are unusual because of the paucity of hospital surveillance systems. The data from the United Kingdom up to early July (with an observed hospitalisation rate of 1–2%) are useful because patients at that time had generally not been hospitalised for infection control purposes. The denominator is also likely to be more complete than is often the case, as it is derived from vigorous case finding and contact tracing [21] [16]. However, more recent estimates of case hospitalisation rates have limited value at the moment given the influence of various numerator and denominator biases that are likely to occur. Therefore only a selected number of suspected cases are currently laboratory tested and they mainly represent those hospitalised. However, for reasons previously stated, the overall number of clinical cases is unknown [20]. It is therefore best to rely on population estimates of hospitalisation rates. In the southern hemisphere, rates ranged from 9 to 25 per 100 000 population [29]. Except for the UK figures above, data on hospitalisation rates are not yet available for Europe. Eventually the rates will be sensitive to the capacity of European hospital services and primary care, and traditions of populations to bypass primary care and go directly to hospital emergency departments. For these reasons, recommended planning assumptions will tend to be generous and higher than have been observed in the southern hemisphere (see section 2.2.8).

Particular stress may arise in the coming holiday season (Christmas and New Year) if primary care services move over to holiday working schedules and patients who would normally be cared for in the community go to emergency rooms and hospitals.

In addition as travel increases in Europe for the holiday period some infection risks will rise as will the likelihood that people will become unwell away from their usual medical services.

Age differences in hospitalisation

Some estimates are available from the United States where a population-based surveillance system network (the Emerging Infections Program (EIP)) is in place. In 16 EIP sites from 1 September 2009 to 28 November 2009 EIP cumulative rates (including influenza A, influenza B, and 2009 pandemic influenza A(H1N1) for children aged 0–4 years and 5–17 years were 9.0 and 3.5 per 10 000 population, respectively. For adults aged 18–49 years, 50–64 years, and ≥ 65 years the rates were 1.7, 1.7 and 1.5 per 10 000 population, respectively. These cumulative rates

come from September to November when influenza activity was very high in the US. However, the age differential pattern is an important one for planning of hospital services [14].

Hospitalisation rates reported in countries in the southern hemisphere vary considerably and are difficult to compare given the different criteria used for hospital admission which, in turn, may reflect differences in the availability of services. In Australia (New South Wales), a total of 1 214 confirmed cases were admitted to hospital which gives an incidence of 17.2 per 100 000 population [62].

In Brazil, using a case definition of severe acute respiratory infection (SARI), the overall incidence of SARI was 3 per 100 000 inhabitants with two peaks: one in the group up to five years old (3.8 per 100 000) and one in the group of 20–29 year-olds (4.6 per 100 000) [63].

Epidemiological reports from North America indicate a significant burden on hospitals though a relatively moderate number of morbidities. In the United States, among 13 217 reported cases of 2009 pandemic influenza A(H1N1) there were 1 082 (8.2%) hospitalisations [19], while in Canada, among 7 107 reported cases there were 1 441 (20.3%) hospitalisations [41].

In England the overall rate of hospitalisation during the first wave (summer) of the pandemic ranged from 1.3% to 2.5%, depending on the methodology used to estimate the total number of cases of pandemic influenza (HPA, unpublished data). Case hospitalisation ratios were considerably higher for infants < 1 year and adults > 65 years, compared with all other age groups. Using data reported by primary care trusts to the Department of Health in England, the highest rates of hospitalisation for people with suspected pandemic influenza were observed in those aged less than five years. Hospitalisation rates declined in August, increased again in late September but now have begun to decline again [16, 64].

Use of intensive care services

A crucial parameter for planning includes the requirements for critical or intensive care. Some information comes from the southern hemisphere (Australia and New Zealand). Based on the analysis of all (722) confirmed 2009 pandemic influenza A(H1N1) 2009 cases requiring ICU admission over a period of three months (June – August 2009), the estimated incidence of ICU admission was 2.9 (95% CI 2.65–3.1) per 100 000 population [43]. For planning purposes, another approach is to consider that 15% of hospital admissions will require intensive care. However, because patients going into intensive care will stay in hospital longer, in prevalence surveys up to 25% of cases hospitalised for influenza may be found occupying intensive care beds on any given day [65, 66]. There are important age differences for this, with younger children rarely going into intensive care.

2.2.7 Case fatality rates (CFR)

Estimated rates are coming down and most estimates for industrialised countries are less than 0.02%, sometimes considerably lower [55, 56, 67]. Earlier published estimates are highly variable and reflect the various factors that can influence its measurement and its actual value including, among others, social and healthcare-related factors [28]. An overall CFR of 0.6% was calculated based on deaths reported worldwide and analysed by an epidemic intelligence team. However, the range of CFR varied from 0.1 to 5.1% depending on the country [68]. In Mexico, case ascertainment favoured detecting patients with more severe illness, hence a report of a CFR of just over 1% (119 deaths among 10 962 cases) gives a probably misleadingly high case fatality rate [69]. An indirect method gave a value of 0.4% [69] while initial estimates for the United States gave a figure ranging from 0.5 to 1% [70]. This is somewhat above what is considered normal for seasonal influenza. In Europe, the initial figure was also around 1%, but again that was certainly an overestimate [21]. In the first affected country in Europe (the United Kingdom) the observed rate, with data as of 15 July 2009, was 0.3% (28 deaths in 10 649 confirmed cases) [71]. This is not that different from what has been observed in modelling studies [72]. More recently, based on national reports of deaths from England, a figure of 26 (range 11 – 66) per 100 000 cases has been estimated for the UK which uses an estimated total of 540 000 cases [55, 56]. Using another approach that employs the same method for cases, hospitalisation and deaths, the US CDC has derived estimates with confidence limits. This gives estimates 18.8 per 100 000 cases [55]. Given the seeming immunity to the pandemic strain in older age groups (who usually are at higher risk of severe disease and death), it is quite possible that the overall CFR for this pandemic will be lower than the one for seasonal influenza. Whether there will be more actual deaths than experienced in a seasonal influenza winter remains to be seen. The mortality trend data from Australia show little difference from their 2008 winter [73]. In contrast, in the United States, the rates for deaths from influenza and pneumonia have risen steeply this autumn [74].

Of more relevance for public health planning are estimates of mortality per 100 000 population and that is the approach recommended by ECDC's Advisory Forum. This also overcomes the problem that numbers of symptomatic cases are so difficult to derive. The data available from the southern hemisphere (Oceania, South America and Africa/Indian Ocean) have been summarised in an editorial published in *Eurosurveillance* [15]. With a few outliers, population mortality was estimated to have been between 0.4 and 1.5 deaths per 100 000 population. The review by WHO gave a range of 0.2 – 1.4 per 100 000, with the high value (for Argentina) being an outlier

and the next highest being 0.9 per 100 000 for Australia [29]. Applying the data for England and the USA to the latest estimated global population, gives estimates for the pandemic so far of 0.27 and 3.18 deaths per 100 000 population, respectively. Though of course these figures will rise with time. There are important social differences, giving rise to considerably higher rates among indigenous communities such as Native Americans and Pacific Islanders [75, 76].

Data on mortality among severe cases has also recently become available. These were very similar in Australia/New Zealand and Canada (14% and 17%, respectively) [41, 43], but higher in Mexico (41%) [45]. The study in Mexico, however, was smaller and a selection bias for the inclusion of the most severe cases might have occurred. This is due to the fact that the Mexican study was conducted in the six reference hospitals that specialised in the treatment of severe influenza cases. In the US, 7% of 272 hospitalised patients with confirmed pandemic influenza are known to have died [77].

Contrast with seasonal influenza

It remains the case that because influenza-associated deaths are occurring in a younger population than usual and involve people who might not normally be expected to die from seasonal influenza in such numbers (pregnant women, previously healthy people), these deaths are regarded as unusual by society. For example, the number of children dying from pandemic influenza has risen steeply in countries experiencing their first pandemic wave, therefore age-specific mortality will be important to measure. Though calculations have yet to be undertaken, it is likely that the number of life years lost may approach those accounted for by seasonal influenza which causes the highest mortality in people in their 70s and older.

A recent analysis from the UK has shown that the overall estimated case fatality rate was 26 (range 11 – 66) per 100 000 cases. It was lowest for children aged 5 – 14 (11 (range 3 – 36) per 100 000 cases) and highest for those aged ≥ 65 (980 (range 300 – 3200) per 100 000 cases) [56].

The level of pre-existing immunity against the 2009 pandemic influenza A(H1N1) virus in humans is much lower than against seasonal influenza, especially in the youngest age group. The serological and epidemiological studies indicate that persons under the age of 30 years showed very little evidence of cross-reactive antibodies to the pandemic virus, while this proportion increase with age, showing a relatively high titre of cross-reactive antibodies in the elderly (see section 2.1.2). Other similarities and differences between the current seasonal influenza and this pandemic influenza are shown in Table 1. Note also the series of similarities or 'known knowns' listed in Figure 2.

Table 1: Similarities and differences

Parameter	Seasonal influenza (2008/9) A(H2N3), A(H1N1), B viruses	2009 pandemic influenza A(H1N1)
Highest transmission rates	All ages affected but more transmission among the young.	Children highest, then young adults, quite uncommon among older individuals.
Underlying immunity (prior to immunisation)	Some immunity in most age groups, highest in those immunised, lowest in young children.	Pre-existing immunity in older people (born after around 1950).
Clinical features	Simple and complicated influenza disease. Viral pneumonia very rare.	Many mild cases, simple and complicated influenza disease. Some more diarrhoea than usual. Viral pneumonia and Acute Respiratory Distress Syndrome occurring .
Asymptomatic infections	Occur in about 30% of people infected	Seemingly in a higher proportion than for seasonal influenza.
Antiviral resistance for neuraminidase inhibitors	Very common in A(H1N1), rare in A(H3N2) and not present in B.	Rare in the pandemic strain.
Effectiveness of seasonal influenza vaccines	Depends on degree of match between vaccine and circulating virus .	Expected to be very high because perfect match between vaccine and virus.

2.2.8 Planning assumptions, including pressure on hospitals

From the above considerations, it is possible to revise previous generic 'reasonable worst case' planning assumptions and these were published by at least two European countries in July and then updated in September [51]. In both cases, the assumed rates of disease, hospitalisations and deaths declined in the light of available data. Working with a series of countries and advised by WHO specialists, ECDC has produced some planning estimates for the EU/EEA [78] (Figure 8).

Table 2: EU reasonable worst case planning assumptions for the 2009 pandemic first year to mid-May 2010

Potential effects of 2009 pandemic influenza A(H1N1) infection for the general population in countries and populations that have not experienced significant transmission in a first wave over the summer	
Clinical attack rate	Up to 20% of population
Hospitalisation rate	Up to 100 per 100 000 population of whom up to 25% could require intensive care at any given time
Case fatality rate	Up to 3 per 100 000 population
Peak absence rate	No different from what is seen in normal winters

Note: These estimates should not be used for predictions.

Some important points have to be made about these assumptions and are enlarged on in a separate ECDC publication [78]. The clinical attack rate and the other rates will be lower in countries and populations that did not experience significant transmission in a first wave over the summer. Also it has to be remembered that many of the disease episodes will be very mild and those cases will certainly not need to be seen by doctors. The hospitalisation rate is higher than that actually observed but that reflects differing traditions on who goes to hospital in some European countries. Though the absenteeism rates will not be higher than usual, it should be remembered that in ordinary winters other respiratory viruses combine with influenza causing people to be absent from work.

Pressure on hospitals

The proportion of hospitalised cases requiring intensive care and respiratory support is especially important information for determining the needs for higher levels of care in European countries. Strong evidence of this has recently become available from the southern hemisphere (Australia and New Zealand). Based on the analysis of all (722) confirmed 2009 pandemic influenza A(H1N1) cases requiring ICU admission over a period of three months (June–August 2009), the estimated incidence of ICU admission was 28.7 (95%CI 26.5–30.8) per million inhabitants [43].

Initial estimates reported in Figure 6 and Table 2 have been derived from experience in the UK and the southern hemisphere. They require careful interpretation bearing in mind that the UK estimates (25% of those hospitalised requiring ICU admission) represent the proportion at any one time. The risk of a hospitalised patient going into ICU will be lower; this is because patients admitted to ICU stay in hospital longer than other patients.

Experience from the United States shows that, in contrast to seasonal influenza, hospitalisations due to 2009 pandemic influenza A(H1N1) are more common among those under the age of 18 years (44%) than over the age of 65 years (5%) [19]. This observation suggests that hospitals should be well prepared with paediatric care facilities. Where these facilities are absent, proper adult care units can be adjusted for paediatric demand [79].

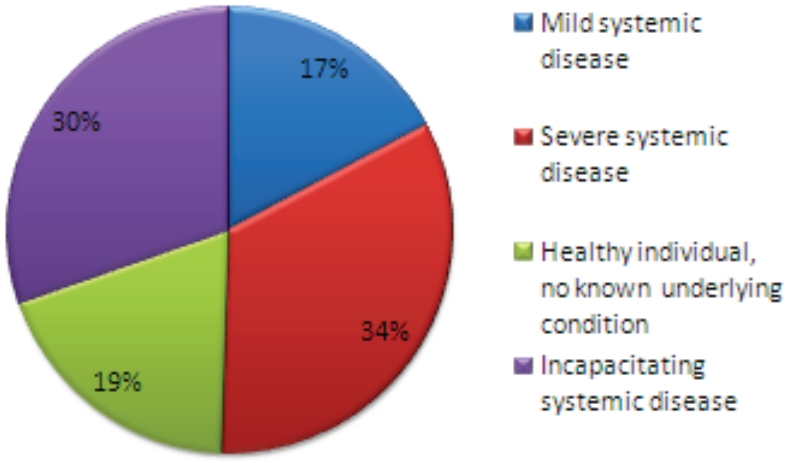
The Christmas and New Year holidays may present a period of vulnerability for countries still experiencing waves in December if primary care services are less available during this period. This could place an extra burden on emergency services and hospitals if they have to deal with people who would normally only seek primary care. Some European countries have planned for this.

2.2.9 Risk groups for hospitalisation, severe disease and death

There are growing amounts of relevant data on this from Europe, but when considering mortality from influenza, the best estimates are that 70–80% of deaths occurred in people with chronic underlying conditions and pregnant women.

The analysis of deaths from the UK [56] based on 138 cases in whom the confirmed cause of death was 2009 pandemic influenza A(H1N1), indicates that over a third of those who died were either previously healthy or had mild systemic disease that did not limit their activity. Two thirds had severe or incapacitating underlying systemic disease (Figure 8). Patients at the extremes of ages (< 5 and > 65) had poorer health status.

Figure 8: Pre-morbid health of patients of all ages who died from causes related to 2009 pandemic influenza A(H1N1) in England up to 8 November n = 138



Source. Data extracted from Donaldson L, et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ 2009. Available at: http://www.bmj.com/cgi/reprint/339/dec10_1/b5213

So far, there is only one large published study that attempts to compare the prevalence of risk factors among severely ill pandemic influenza cases with the prevalence of the same risk factors in the general population [40]. This study was conducted among all confirmed 2009 pandemic influenza A(H1N1) cases requiring ICU admission in Australia and New Zealand. It showed that the following risk factors were much more common among cases with confirmed severe influenza disease than the general population:

- Pregnant women (9% vs 1%)
- Obesity (defined as BMI greater than 35) (29% vs 5%)
- Asthma or other chronic pulmonary disease (33% vs 13%)

In New Zealand, another important finding showed that indigenous populations were at a higher risk of severe disease: Aboriginal and Torres Strait Islanders represented 9.7% of severe cases while they represent just 2.5% of New Zealand's population and Maori represented 25% of severe cases while they represent 13.6% of the population [43]. The data concerning the distribution of risk factors collected from influenza cases are likely to be more accurate than the information for the general population. This may have led to an overestimation of the role of risk factors (ascertainment bias). Even taking into consideration the possible influence of bias, these findings represent the strongest available evidence pointing towards specific risk factors for severe 2009 pandemic influenza A(H1N1).

In addition, these findings are consistent with what has been reported so far from other parts of the southern hemisphere, US and Canada.

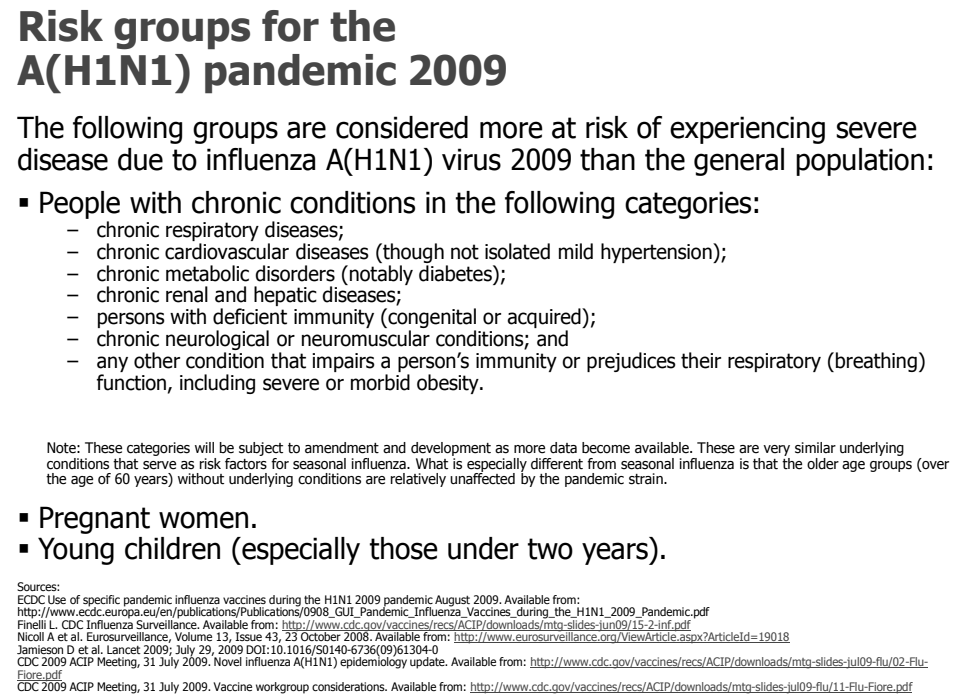
- **People with underlying chronic diseases**: In an initial published study from California, of 553 probable and confirmed infections with the 2009 pandemic influenza A(H1N1) virus, 30 people were hospitalised needing care. Nineteen of the 30 patients had underlying chronic conditions, which have been in decreasing frequency: asthma or chronic obstructive airways disease; diabetes; being immunocompromised; chronic cardiovascular disease (not simple hypertension); chronic renal failure; epilepsy (seizure disorders); and malignancy [37]. Another published study highlighted massive or morbid obesity in adults though it is increasingly considered that massive obesity is a proxy for other chronic medical conditions, such as respiratory insufficiency [80]. The largest dataset reported to date (n = 302) is based on deaths reported to the US CDC and this defines the current risk groups as pregnant women, children under two years of age and people with the chronic underlying conditions listed above, plus chronic neurological and neuromuscular disorders. These underlying conditions are present in 70% of the people dying or experiencing severe disease [9,59].
- **Pregnancy**: There is consistent evidence showing that pregnancy is a risk factor for severe disease during the 2009 influenza A(H1N1) pandemic . In addition to the data described above from Australia and New

Zealand, among 272 hospitalised patients in the USA, pregnant women accounted for 7% of cases and 16% of fatal cases [77]. A published study from the USA has identified pregnant women infected with the pandemic virus as being four to five times more likely to be hospitalised than pregnant women not infected, even though the absolute risk for infected pregnant women being hospitalised remains low (around 0.32 per 100 000). This is somewhat higher than the heightened risk noted for women experiencing seasonal influenza [81]. When considering the risk of going into intensive care, the relative risk rises to ten [82]. Risk of hospitalisation rises as pregnancy progresses. A rather contrasting set of data are from England which showed that pregnant women only accounted for 5 of 138 deaths [56].

- **Age**: Children under the age of 15 have experienced higher rates of infection than other age groups and, as a consequence, this age group also accounts for the largest proportion of hospital admissions in most of the available reports. In Australia and New Zealand, the highest age-specific incidence of ICU admission was among infants (0 to 1 year of age), whereas the highest number of ICU admissions was among patients 25–49 years [43]. In the USA, a total of 95 deaths in children (0–17 years) associated with 2009 pandemic influenza A(H1N1) have been reported to the CDC [48]. A more in-depth analysis of 36 of these children revealed that 19% were < 5 years old and 67% had one or more underlying conditions. Of the 24 children with underlying conditions, 92% had a neurodevelopmental condition often associated with co-morbid pulmonary conditions. Forty-three per cent of all children who died had a documented bacterial infection [48]. However, the children who died with no underlying condition were older than would usually be expected with seasonal influenza [48]. It was also observed that hospitalised younger children without underlying conditions often experienced a short stay in hospital; far shorter than their adult counterparts.
- **Obesity**: The data from Australia, New Zealand and the United States indicate that obesity is a strong risk factor for severe 2009 pandemic influenza A(H1N1). However, it remains unclear whether this is only because of the high prevalence of co-morbidities in obese individuals. The analysis of hospitalised cases in the US seems to confirm the latter hypothesis. In a series of 100 adults admitted to hospital with confirmed pandemic influenza, 29 (29%) were obese, and 26 (26%) were morbidly obese; 26 of the obese patients (90%) and 21 of the morbidly obese patients (81%) had an underlying medical condition. The association of obesity with other underlying conditions seems less strong among children: Of 61 children, 18 were obese (30%) and of those, 12 (67%) had an underlying medical condition.

From these data and analyses it is possible to derive a list of risk groups, i.e. groups experiencing more severe infections than the general population.

Figure 9. Risk groups for the 2009 pandemic influenza A(H1N1)



2.2.10 Older people

There are a number of analyses indicating that people 65 years of age and older are noticeably underrepresented in reported infections and hospitalisations compared with what is seen for seasonal influenza [36, 54, 83-85]. Normally, in the United States, people 65 years of age and older would account for nearly 50% of hospitalisations with confirmed seasonal influenza, but for 2009 pandemic influenza A(H1N1) the figure has so far been less than 5% [72]. This is consistent with the fact that many older people are immune due to prior exposure to a similar virus in the 1950s or earlier [22]. However, older people are more likely to be in clinical risk groups and, as might be expected, when one of the minority of older people who is susceptible becomes infected with the pandemic virus, there is a high likelihood that they will need hospital care and stay in hospital longer. The case fatality rate is higher than for any other age group. For this reason, when considering who is hospitalised for influenza on any particular day in a hospital, the age pattern is more even than would be expected from the age pattern of cases seen in Figure 3 [22].

2.2.11 People without risk factors

There are significant numbers of cases of severe disease and deaths in people without any reported underlying disease or other conditions. It should be remembered that these also occur with seasonal influenza [86-88]. Among deaths reported to be attributable to or associated with the pandemic influenza in the UK (England), in the first ninety or so cases, between 20 and 30% of the cases (of all ages) were in those with either no reported underlying condition (19%) or only mild conditions (17%) (Figure 8) [56].

The United States has published analyses of the first 36 child deaths [48]. These findings showed 10 children (28%) with no reported underlying condition. The age span of these children was also surprising: four of the ten were two years of age or under (ages of 2–4 months and one and two years). However, the other six were between nine and fifteen years of age, indicating that older, healthy children are also at risk of death from this virus.

2.3 Features of the virus

2.3.1 Genetic stability

Recently, several countries worldwide have reported on the finding of a specific mutation (known as D222G) in the haemagglutinin (HA) gene of the 2009 pandemic influenza A(H1N1) virus [89]. The variant has been found in some of the severe cases (including deaths) but also in mild cases of the disease.

Unless well designed epidemiological studies show otherwise, it is likely that the finding of D222G variants in a small proportion of severe cases of 2009 pandemic influenza A(H1N1) infection only shows a natural variation of the virus and does not have an association with the disease course. The current data suggest that the variant cases described in different parts of the world are unrelated and each mutation probably occurred independently in the infected individual as a consequence of the natural variability of influenza viruses. The current evidence gives no indication of spread of these variants and they have not been shown to directly affect the severity of the disease. It is important to note that genetic variation leading to point mutations causing amino acid changes in viral proteins is an inherent property of influenza viruses and similar cases can be expected in the future.

2.3.2 Susceptibility to antivirals and antiviral resistance

Based on genetic evidence, the indications are that the neuraminidase inhibitors oseltamivir and zanamivir will provide effective treatments, but that the virus will be resistant to adamantanes (amantidine). With many people taking antivirals, it is to be expected that some viruses will appear with markers of antiviral resistance as it has been seen with other human influenzas. Indeed, over 40 isolates of the pandemic virus have been reported resistant to oseltamivir. All of the isolates have been susceptible to zanamivir. Three secondary cases were detected in Europe and four in Japan, where there is particularly close surveillance [90]. Only one case of community transmission of oseltamivir resistant viruses has been reported so far in Viet Nam in July 2009 [91]

With the end of November HPA has reported a cluster of oseltamivir resistant infections on a hospital ward in Wales among patients with haematological problems which resulted in immuno-suppression either because of the disorder or the chemotherapy given to treat the disorder. Because the risk of oseltamivir resistance is always greater in immunosuppressed patients and confined settings such as hospital ward favour spreading it was very highly possible that person to person transmission has occurred. Up to date further follow-up of cases and their close contacts has not indicated transmission in the community. The isolates were sensitive to zanamivir which is commonly being used as an alternative antiviral [85, 92].

2.3.3 Pathogenicity of the virus and severity of the pandemic

Many national authorities like to have an assessment of the 'severity' of a pandemic so as to determine a proportionate response [28, 93]. However, it is difficult to classify because the experience and perception of

people, organisations and societies are different. Severity can vary from country to country and even from place to place within a country. It can also change over time and there are important social and societal factors, including the vulnerability of populations, a society's capacity for response, the availability of healthcare and the level of advance planning and preparedness. Severity can also be seen either from the individual perspective (people who are infected experience a severe disease—even though they may be only a few), or from a societal view (many people are away from work and essential services are threatened—even though the disease may be relatively mild).

What is known so far concerning the severity is as follows:

- **Hospitalisation and case fatality rate**. Recent data from the United States suggest hospitalisation rates varying with age in the range of 5 – 25 per 10 000 population [84]. The limited information to date for Europe (mostly from the UK) suggests similar rates [21]. Because of the seeming underrepresentation of older people among those infected, the overall fatality rate in Europe may be less or similar to a moderate influenza season, like 2008–09. However, age-specific rates are expected to show a very different picture, with higher mortality in younger age groups. Also the absolute numbers of hospitalisations could be higher, especially because of the short hospitalisations of young children. Experience from southern hemisphere countries shows that particular pressures will be felt by hospital services, specifically paediatric services, the services for critically ill patients who might benefit from intensive care, artificial ventilation and extracorporeal membrane oxygenation (ECMO) [94].
- **Number of people being ill with respiratory illnesses at any one time**. This correlates to the pressure on the health services to deal with these patients. The experience so far suggests this is manageable as long as the public are not seeking medical attention unnecessarily and there are no epidemics of other illnesses taking place [68]. European health services have come under more pressure in the autumn and winter but there are no reports of European countries experiencing unmanageable healthcare pressure. A particular problem can arise when numbers of people bypass primary care and go directly to hospitals; this happened for a short time in New York City [45,64].
- **Critical services functioning**. So far, there have been no reports of any problems in any affected countries globally.
- **Certain groups experiencing severe illness or dying unexpectedly**. There is both an underrepresentation of older people compared with seasonal influenza and three groups that are more severely affected than would normally be expected: namely people under age 65 with chronic but treatable illnesses, pregnant women and very young children (see Figure 8). These three groups are overrepresented among those falling ill and dying in the United States.

Given this experience, it would seem that most well prepared European Member States should be able to cope with this pandemic in its present form. [81].

2.4.1 Potential worsening of severity

Historically however, it must also be remembered that pandemic viruses are quite capable of worsening their impact over time (this happened in 1918–19 and 1968–69 in some European countries). Severity will need to be monitored, especially given the possibility of the virus acquiring genetic material associated with pathogenicity or antiviral resistance in humans [94].

3 Areas of particular uncertainty

3.1 The proportion of people that have been infected

This is especially difficult to estimate because of the mild nature of infection. Serological data following the first waves are uncommon but such data as are available suggest that many more people may have been infected than previously estimated [16].

3.2 Likely timing and pattern of spread of the virus in Europe in the winter and spring

This depends on 3.1 and so is imponderable at present though it is becoming more possible to make some comments. A number of European countries experienced initiation phase outbreaks over the summer months [71]. Schools have been especially associated with outbreaks and so transmission was limited by the closure of schools over the summer. School amplification has now resumed [95]. Given the experience in the southern hemisphere, it was predictable that pandemic waves would affect the European countries and now a general west to east trend can be seen. What remains uncertain is exactly how high peak attack rates will be though these will be lower where there has been prior transmission. An important determinant will be the level of asymptomatic infection or very mild disease that has been experienced. This will only be determined by serological studies which are

underway in a few countries (Mika Salminen, personal communication). It was prudent of European countries to prepare for early pandemic waves [70,74]. Countries in their final planning stages still need to recall that local epidemics will be shorter but sharper than the overall pandemic wave in the country (having higher incidence of people needing care and being unavailable for work) [94, 96] (see also section 2.2.4).

A typical wave of seasonal influenza activity is usually in the shape of a bell curve which goes up, peaks and then goes down.(Figure 6) The analysis of pandemic waves in different countries shows that influenza activity started earlier than a typical seasonal influenza period, but the pattern and dynamics were different across countries.

Up to now in Australia there was one wave starting in mid-May and lasting until mid-September with its significant peak in July (the middle of southern winter) [73]. In the northern hemisphere, the USA has experienced increasing activity from the end of August, reaching its peak in mid-November, while at week 50 influenza activity was still above national baseline. In Canada, two waves have been observed: the first from April to September and the second from September to December. At the beginning of December in Europe, widespread and increasing transmission of pandemic influenza virus was observed across much of the continent. Some countries, for example the UK, have experienced two peaks of pandemic influenza and most European countries are currently experiencing the first wave.

It is impossible to predict the exact number and time of peaks in every particular country. This will depend on several factors such as the level of infections (both symptomatic and asymptomatic) that has been experienced, the proportion of pre-existing immunity among the population, the percentage of people who have been immunised, Christmas holidays and winter breaks in schools. The Australian example indicates that with the end of winter pandemic influenza activity was significantly reduced. However, it can not be excluded that with the end of summer the next wave of pandemic influenza could come (whether with a higher or lower proportion of seasonal influenza virus) as has been seen during past pandemics.

3.3 Mix of influenza and other viruses that will circulate this winter in Europe

Some statements can now be made about this. In Europe to date there have been very few seasonal viruses though respiratory syncytial viruses have started to appear as usually happens late in the autumn [61]. The pattern in the southern hemisphere in their winter (April to October 2009) was mixed. In a number of countries, the pandemic virus has increasingly predominated while in others the pattern is more mixed [70]. In Australia and New Zealand, there were contributions by both influenza A(H3N2) and the 2009 pandemic influenza A(H1N1), but the latter came to predominate. Also it is not clear what sampling and testing strategies are being used by the countries concerned (for example whether B viruses are being included). Current data are regularly published by the United States CDC and WHO*. It is recommended by WHO and European national authorities that plans for immunising conventional risk groups with the seasonal vaccine go ahead in northern hemisphere countries [54, 83]. In at least one southern hemisphere country (Chile), respiratory viruses other than influenza (such as respiratory syncytial viruses) added to the pressure on health services as can happen in any winter.

In the northern hemisphere, the proportion of cases related to seasonal influenza A(H3N2) continues to decline in Asia (apart from China where significant numbers are still being reported) while the proportion related to the 2009 pandemic influenza A(H1N1) virus is increasing significantly [97]. The trend of supplanting seasonal influenza subtypes with pandemic influenza strain is evident in Europe and United States, where in October and November, the percentage of 2009 pandemic influenza A(H1N1) virus samples tested constituted over 80% of influenza subtypes† [98].

That said, what cannot be ruled out are late epidemics of A(H3N2) and B viruses in the late winter after the pandemic waves have passed.

3.4 Shedding the virus and infectivity

The outbreak investigation study at the US Air Force Academy [99] shows that the presence of viable virus among patients with confirmed 2009 pandemic influenza A(H1N1) infection was highest in those with the nasal-wash samples obtained on days 1–3 after symptom onset and declined with each proceeding day, beginning on day two. Among 29 samples obtained seven days from symptom onset ,seven (24%) contained viable 2009 pandemic influenza A(H1N1) virus. Among 106 samples obtained from patients with a temperature lower than 37.7°C at the time of sample collection, 31 (29%) contained viable 2009 pandemic influenza A(H1N1) virus, as did 11 (19%) of the 58 samples obtained from patients who reported being symptom-free for longer than 24 hours. However, the

* See http://www.cdc.gov/h1n1flu/updates/international/map.htm

† See http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Pages/EISN_Bulletin.aspx

period of viable virus shedding does not necessarily mean the virus can be transmitted (the period of infectiousness is shorter than the period of virus shedding). These findings should be taken into consideration for informing infection control activities in high-risk settings and the community.

3.5 Relative and attributable risk of more severe disease

While the risk groups are becoming clearer, there are as yet no new estimates from Europe of relative, attributable risk or absolute risk. More is known about the risk for pregnant women [81]. The attributable individual risk—'how much more likely am I (or my child) to be hospitalised if I am infected with this virus?'— is especially important to enable the public and clinicians to make informed choices about early treatment with antivirals or vaccination.

3.6 Pathological processes underlying severe disease and individual vulnerability

There is no information as yet on whether the causes of death and responses to the infections in humans are the same as for seasonal influenza or otherwise, though the numbers of severe viral pneumonias suggest that some people are experiencing unusual illnesses. This is important for informing treatment strategies and for determining why most people experience mild disease but some even previously healthy people get so ill.

3.7 Population level mortality attributable to the pandemic virus in Europe

There are significant numbers of deaths attributable to seasonal influenza each year. The groups most affected are older people and people with chronic medical conditions [83]. Population data and especially age-specific data are not yet available for European countries.

3.8 Protective value of early treatment with antivirals

No trials can be undertaken in these circumstances but it is noticeable that of the patients that have been hospitalised, most patients have not received the effective antivirals, oseltamivir or zanamivir (Department of Health, London UK – unpublished data). Thorough controlled analyses remain to be undertaken. However, observational studies of seasonal influenza and the collective experience of those treating cases with the pandemic strain point to the success of early treatment with oseltamivir in preventing severe outcomes [46, 100].

3.9 Impact of seasonal immunisation

A serological study conducted by Hancock, K [101] and his group shows that vaccination with recent seasonal influenza vaccines, even when formulated with adjuvants, provide hardly any protection against 2009 pandemic influenza A(H1N1). This is due to the genetic and antigenic differences between the seasonal influenza A(H1N1) virus included in the 2008/09 and other recent seasonal vaccines and the pandemic vaccine [101].

This lack of protection confirms the results of an earlier seroepidemiological study conducted in the US [22] and other observational studies.

A series of epidemiological studies have now confirmed the ineffectiveness of the seasonal 2008/09 vaccine against the 2009 pandemic influenza A(H1N1) virus [26].

3.10 Data and analyses concerning patient numbers in hospitals and information on children

Though some information has come from southern hemisphere countries, there are few details that allow European countries to undertake planning [40]. There are also a number of anecdotal reports indicating that the clinical course in children may be different from that in adults and from that observed with seasonal influenza [48].

Next steps for ECDC

In addition to close surveillance of cases in the EU, ECDC will continue to closely monitor the situation in Europe as well as North America, China and Japan. ECDC will continuously provide information through its website and update this risk assessment as needed. For rapid updates, please see the Daily Updates published on weekdays on the ECDC Pandemic 2009
website: http://ecdc.europa.eu/en/healthtopics/Pages/Influenza_A(H1N1)_Outbreak.aspx

Date of next planned update

Late January 2010. If important changes take place these will be incorporated earlier.

For further information and comment, contact: PHE.H1N1v@ecdc.europa.eu **(preferably marked "Interim Risk Assessment" in the subject field).**

References

[1] CDC. Swine influenza A (H1N1) infection in two children--Southern California, March-April 2009. Mmwr. 2009 Apr 24;58(15):400-2.

[2] Mexico SdS. Situación actual de la epidemia; June 2009.

[3] Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, Hernandez M, Quinones-Falconi F, Bautista E, et al. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. The New England journal of medicine. 2009 Aug 13;361(7):680-9.

[4] Maines TR, Jayaraman A, Belser JA, Wadford DA, Pappas C, Zeng H, et al. Transmission and pathogenesis of swine-origin 2009 A(H1N1) influenza viruses in ferrets and mice. Science (New York, NY. 2009 Jul 24;325(5939):484-7.

[5] Nava GM, Attene-Ramos MS, Ang JK, Escorcia M. Origins of the new influenza A(H1N1) virus: time to take action. Euro Surveill. 2009 Jun 4;14(22).

[6] Trifonov V, Khiabanian H, Greenbaum B, Rabadan R. The origin of the recent swine influenza A(H1N1) virus infecting humans. Euro Surveill. 2009 Apr 30;14(17).

[7] Newman AP, Reisdorf E, Beinemann J, Uyeki TM, Balish A, Shu B, et al. Human case of swine influenza A (H1N1) triple reassortant virus infection, Wisconsin. Emerging infectious diseases. 2008 Sep;14(9):1470-2.

[8] Olsen CW, Karasin AI, Carman S, Li Y, Bastien N, Ojkic D, et al. Triple reassortant H3N2 influenza A viruses, Canada, 2005. Emerging infectious diseases. 2006 Jul;12(7):1132-5.

[9] WHO. Pandemic influenza preparedness and response; WHO guidance document. available from: http://www.who.int/csr/disease/influenza/pipguidance2009/en/index.html; April 2009.

[10] WHO. Recommended composition of influenza virus vaccines for use in the 2010 southern hemisphere influenza season; September 2009.

[11] ECDC. The public health risk from highly pathogenic avian influenza viruses emerging in Europe with specific reference to influenza type A/H5N1; 1 June 2006

[12] ECDC. Influenza Surveillance in a Pandemic - Paper from ECDC Working Group; August 2007.

[13] ECDC. Meeting report: Surveillance and studies in a pandemic: Fourth meeting of the SSiaP working group; July 2009.

[14] CDC, Flu View, 2009-2010 Influenza Season, Week 47 ending November 28, 2009, available at:http://www.cdc.gov/flu/weekly/.

[15] Baker M, Kelly H, Wilson N. Pandemic H1N1 influenza lessons from the southern hemisphere. Euro Surveill. 2009;14(42).

[16] HPA. Pandemic (H1N1) 2009 in England: an overview of initial epidemiological findings and implications for the second wave. 2 December 2009.

[17] Kelly H, Grant K. Interim analysis of pandemic influenza (H1N1) 2009 in Australia: surveillance trends, age of infection and effectiveness of seasonal vaccination. Euro Surveill. 2009 Aug 6;14(31).

[18] A(H1N1)v Ewgoi. Preliminary analysis of influenza A(H1N1)v individual and aggregated case reports from EU and EFTA countries. Euro Surveill. 2009 Jun 11;14(23):19238.

[19] Dawood FS, Jain S, Finelli L, Shaw MW, Lindstrom S, Garten RJ, et al. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. The New England journal of medicine. 2009 Jun 18;360(25):2605-15.

[20] Fiore A. Novel influenza A (H1N1)Epidemiology Update. Advisory Committee on Immunization Practices Meeting; 29 July 2009; 29 July 2009.

[21] ECDC. Analysis of influenza A(H1N1)v individual case reports in EU and EEA countries - ECDC surveillance report; June 2009.

[22] CDC. Serum cross-reactive antibody response to a novel influenza A (H1N1) virus after vaccination with seasonal influenza Mmwr. 2009 May 22;58(19):521-4.

[23] Effectiveness of 2008-09 trivalent influenza vaccine against 2009 pandemic influenza A (H1N1) - United States, May-June 2009. Mmwr. 2009 Nov 13;58(44):1241-5.

[24] Iuliano AD, Reed C, Guh A, Desai M, Dee DL, Kutty P, et al. Notes from the field: outbreak of 2009 pandemic influenza A (H1N1) virus at a large public university in Delaware, April-May 2009. Clin Infect Dis. 2009 Dec 15;49(12):1811-20.

[25] Kelly H, Carville K, Grant K, Jacoby P, Tran T, Barr I. Estimation of influenza vaccine effectiveness from routine surveillance data. PloS one. 2009;4(3):e5079.

[26] ECDC, Scientific Advice, Effectiveness of trivalent seasonal influenza vaccine against pandemic influenza (H1N1) 2009 infection, available at: http://www.ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=687&RootFolder=%2Fen%2Factivities%2Fsciadvice%2FLists%2FECDC%20Reviews.

[27] Garcia-Garcia L, Valdespino-Gomez JL, Lazcano-Ponce E, Jimenez-Corona A, Higuera-Iglesias A, Cruz-Hervert P, et al. Partial protection of seasonal trivalent inactivated vaccine against novel pandemic influenza A/H1N1 2009: case-control study in Mexico City. BMJ (Clinical research ed. 2009;339:b3928.

[28] WHO. Considerations for assessing the severity of an influenza pandemic. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations. 2009 May 29;84(22):197-202.

[29] WHO, Weekly Epidemiological Report, Transmission dynamics and impact of pandemic influenza A (H1N1) 2009 virus, 13 November 2009, available at: http://www.who.int/wer/2009/wer8447.pdf.
[30] WHO. Media Briefing with Dr Keiji Fukuda, Assistant Director-General for Health Security and Environment; May 2009.
[31] Nishiura H, Wilson N, Baker MG. Estimating the reproduction number of the novel influenza A virus (H1N1) in a Southern Hemisphere setting: preliminary estimate in New Zealand. The New Zealand medical journal. 2009;122(1299):73-7.
[32] Fraser C, Donnelly CA, Cauchemez S, Hanage WP, Van Kerkhove MD, Hollingsworth TD, et al. Pandemic potential of a strain of influenza A (H1N1): early findings. Science (New York, NY. 2009 Jun 19;324(5934):1557-61.
[33] Munayco CV, Gomez J, Laguna-Torres VA, Arrasco J, Kochel TJ, Fiestas V, et al. Epidemiological and transmissibility analysis of influenza A(H1N1)v in a southern hemisphere setting: Peru. Euro Surveill. 2009;14(32).
[34] McBryde E, Bergeri I, van Gemert C, Rotty J, Headley E, Simpson K, et al. Early transmission characteristics of influenza A(H1N1)v in Australia: Victorian state, 16 May - 3 June 2009. Euro Surveill. 2009;14(42).
[35] CDC, Recommendations for the Amount of Time Persons with Influenza-Like Illness Should be Away from Others, October 23 2009, Available at: http://www.cdc.gov/h1n1flu/guidance/exclusion.htm.
[36] CDC. Surveillance for the 2009 pandemic influenza A (H1N1) virus and seasonal influenza viruses - New Zealand, 2009. Mmwr. 2009 Aug 28;58(33):918-21.
[37] INFOSAN. The influenza outbreak in humans caused by Influenza A/H1N1 - considerations at the human-animal interface; 30 April 2009.
[38] Greenberg ME, Lai MH, Hartel GF, Wichems CH, Gittleson C, Bennet J, et al. Response after One Dose of a Monovalent Influenza A (H1N1) 2009 Vaccine -- Preliminary Report. The New England journal of medicine. 2009 Sep 10.
[39] CDC. Update: novel influenza A (H1N1) virus infections - worldwide, May 6, 2009. Mmwr. 2009 May 8;58(17):453-8.
[40] Baker MG, Wilson N, Huang QS, Paine S, Lopez L, Bandaranayake D, et al. Pandemic influenza A(H1N1)v in New Zealand: the experience from April to August 2009. Euro Surveill. 2009;14(34).
[41] Kumar A, Zarychanski R, Pinto R, Cook DJ, Marshall J, Lacroix J, et al. Critically Ill Patients With 2009 Influenza A(H1N1) Infection in Canada. Jama. 2009 Oct 12.
[42] Thompson WW, Shay DK, Weintraub E, Brammer L, Bridges CB, Cox NJ, et al. Influenza-associated hospitalizations in the United States. Jama. 2004 Sep 15;292(11):1333-40.
[43] The ANZIC Influenza Investigators Critical Care Services and 2009 H1N1 Influenza in Australia and New Zealand. The New England journal of medicine. 2009 Oct 8.
[44] WHO. Clinical features of severe cases of pandemic influenza. Available at: http://www.who.int/csr/disease/swineflu/notes/h1n1_clinical_features_20091016/en/index.html. 2009.
[45] Dominguez-Cherit G, Lapinsky SE, Macias AE, Pinto R, Espinosa-Perez L, de la Torre A, et al. Critically Ill Patients With 2009 Influenza A(H1N1) in Mexico. Jama. 2009 Oct 12.
[46] Uyeki T. Antiviral treatment for patients hospitalized with 2009 pandemic influenza A (H1N1). The New England journal of medicine. 2009 Dec 3;361(23):e110.
[47] WHO. Human infection with pandemic A (H1N1) 2009 influenza virus: clinical observations in hospitalized patients, Americas, July 2009 - update. Releve epidemiologique hebdomadaire / Section d'hygiene du Secretariat de la Societe des Nations = Weekly epidemiological record / Health Section of the Secretariat of the League of Nations. 2009 Jul 24;84(30):305-8.
[48] CDC. Surveillance for pediatric deaths associated with 2009 pandemic influenza A (H1N1) virus infection - United States, April-August 2009. Mmwr. 2009 Sep 4;58(34):941-7.
[49] CDC. Questions and Answers: 2009 H1N1 and Pneumococcal Disease in the News available at: http://www.cdc.gov/h1n1flu/vaccination/qa_pneumococcal_disease.htm. 25 November 2009.
[50] Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. Jama. 2009 Oct 12.
[51] Hayward A. The community burden of influenza and influenza-like illness in England - early results from the MRC Flu Watch Study. Poster at Third European Influenza Conference (1332256) 14-17 September 2008, Vilamoura, Portugal [Unpublished]; 14-17 September 2008; 14-17 September 2008.
[52] Hygiene NYCDoHaM. Health Department Survey Suggests that 7% of New Yorkers Had Flu-like Illness in May. June 10th 2009 [cited; Available from: http://www.nyc.gov/html/doh/html/pr2009/pr041-09.shtml
[53] CDC. Hospitalized patients with novel influenza A (H1N1) virus infection - California, April-May, 2009; 2009 May 22. Report No.: 1545-861X (Electronic).
[54] Fiore AE, Shay DK, Broder K, Iskander JK, Uyeki TM, Mootrey G, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices (ACIP), 2009. MMWR Recomm Rep. 2009 Jul 31;58(RR-8):1-52.
[55] CDC Estimates of 2009 H1N1 Influenza Cases, Hospitalizations and Deaths in the United States, April – November 14, 2009. Availavle at: http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm. 2009.
[56] Donaldson L. , et al. Mortality from pandemic A/H1N1 2009 influenza in England: public health surveillance study. BMJ (Clinical research ed. 8 December 2009.
[57] Preliminary descriptive epidemiology of a large school outbreak of influenza A(H1N1)v in the West Midlands, United Kingdom, May 2009. Euro Surveill. 2009 Jul 9;14(27).
[58] Guinard A GD, Durand C, Schwoebel V. . Outbreak of influenza A(H1N1)v without travel history in a school in the Toulouse district, France, June 2009. Eurosurveillance. 09 July 2009;Volume 14(Issue 27).

[59] Weisfuse I. Presentation to ECDC on Outbreak of Influenza A(H1N1)v in New York. 6 July 2009 [cited; Available from: http://ecdc.europa.eu/en/press/Pages/ECDC_Webcast.aspx
[60] HPA. Weekly National Influenza Report, 03 December 2009 (Week 49), available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1259152086900.
[61] ECDC. ECDC Eexecutive Update, Pandemic influenza (H1N1) 2009, Issue 22, 7 December 2009, available at: http://www.ecdc.europa.eu/en/healthtopics/Documents/091207_Influenza_A(H1N1)_Weekly_Executive_Update.pdf.
[62] New South Wales public health network, Progression and impact of the first winter wave of the 2009 pandemic H1N1 influenza in New South Wales, Australia. Euro Surveill. 2009;14(42):pii=19365.http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19365.
[63] Malaguti A. Pandemic H1N1 influenza in Brazil: Analysis of the first 34,506 notified cases of influenza-like illness with severe acute respiratory infection (SARI), Eurosurveillance, Volume 14, Issue 42, 22 October 2009
[64] HPA. Weekly epidemiological update. Summary for 10 December 2009 (Week 50). Available at:http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1259152217308 2009.
[65] HPA. Weekly National Influenza Report (Week 44); 29 October 2009, Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1256639861726.
[66] ECDC. Revised pandemic 2009 planning assumptions for Europe. Available at: http://www.ecdc.europa.eu/en/healthtopics/Documents/091111_Pandemic_(H1N1)_2009_Planning_Assumptions_for_EU_EEA_countries.pdf. 2009.
[67] ECDC. Planning Assumptions for the First Wave of Pandemic A(H1N1) 2009 in Europe. Public Health Development 29 July 2009 [cited; Available from: http://ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=633
[68] Vaillant L, La Ruche G, Tarantola A, Barboza P. Epidemiology of fatal cases associated with pandemic H1N1 influenza 2009. Euro Surveill. 2009;14(33).
[69] WHO. Situation Report No 58. July 7th 2009. [cited; Available from: http://www.who.int/csr/don/2009_07_06/en/index.html
[70] Mott J. Novel influenza epidemiology update – International. ACIP Meeting; July 31 2009; July 31 2009.
[71] HPA. Weekly National Influenza Report (Week 29); 16 July 2009
[72] ECDC. Surveillance and studies in a pandemic in Europe; June 2009.
[73] Australian Government, Department of Health and Ageing, Australian influenza report 2009 - 5 to 11 September 2009 (#18/09), available at: http://www.health.gov.au/internet/main/publishing.nsf/Content/cda-ozflu-no18-09.htm.
[74] CDC. FluView – 2008-2009 Influenza Season Week 44 November 1, 2009.
[75] Castrodale L. , et al. Deaths Related to 2009 Pandemic Influenza A (H1N1) Among American Indian/Alaska Natives - 12 States, 2009. Mmwr.December 11, 2009 / 58(48);1341-1344.
[76] La Ruche G, Tarantola A, Barboza P, Vaillant L, Gueguen J, Gastellu-Etchegorry M. The 2009 pandemic H1N1 influenza and indigenous populations of the Americas and the Pacific. Euro Surveill. 2009;14(42).
[77] Seema J, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. Hospitalized Patients with 2009 H1N1 Influenza in the United States, April-June 2009. The New England journal of medicine. 2009 Oct 8.
[78] ECDC. ECDC Health Information, Pandemic (H1N1) 2009 planning assumptions to end of May 2010 for EU/EEA countries, 11 November 2009, available at: http://www.ecdc.europa.eu/en/healthtopics/Documents/091111_Pandemic_(H1N1)_2009_Planning_Assumptions_for_EU_EEA_countries.pdf.
[79] Ercole A, Taylor BL, Rhodes A, Menon DK. Modelling the impact of an influenza A/H1N1 pandemic on critical care demand from early pathogenicity data: the case for sentinel reporting. Anaesthesia. 2009 Sep;64(9):937-41.
[80] CDC. Intensive-care patients with severe novel influenza A (H1N1) virus infection - Michigan, June 2009. Mmwr. 2009 Jul 17;58(27):749-52.
[81] Jamieson DJ, Honein MA, Rasmussen SA, Williams JL, Swerdlow DL, Biggerstaff MS, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. Lancet. 2009 Aug 8;374(9688):451-8.
[82] WHO. Experts advise WHO on pandemic vaccine policies and strategies. [cited; Available from: http://www.who.int/csr/disease/swineflu/notes/briefing_20091030/en/index.html
[83] Nicoll A, Ciancio B, Tsolova S, Blank P, Yilmaz C. The scientific basis for offering seasonal influenza immunisation to risk groups in Europe. Euro Surveill. 2008 Oct 23;13(43).
[84] CDC. Update: influenza activity--United States, April-August 2009. Mmwr. 2009 Sep 18;58(36):1009-12.
[85] ECDC. Weekly influenza surveillance overview, December 11, 2009. available at: http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Newsletter/091211_EISN_Weekly_Influenza_Surveillance_Overview.pdf (accessed on 16/12/2009). 2009.
[86] CDC. FluView – 2008-2009 Influenza Season Week 35 ending September 5, 2009. 2009 [cited; Available from: http://www.cdc.gov/flu/weekly/weeklyarchives2008-2009/weekly35.htm
[87] Klimov A. Virology and Immunology Update. July 29 2009.

[88] ECDC. Pathogenicity and transmissibility of pandemic influenza A(H1N1)v – results from an animal model. Scientific Advice 04 Jul 2009 [cited; Available from: http://ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=625

[89] WHO, Public health significance of virus mutation detected in Norway Pandemic (H1N1) 2009 briefing note 17, available at: http://www.who.int/csr/disease/swineflu/notes/briefing_20091120/en/index.html.

[90] WHO. WER Oseltamivir-resistant pandemic (H1N1) 2009 influenza virus, 30 October 2009. [cited; Available from: http://www.who.int/wer

[91] Mai Lea. A community cluster of oseltamivir-resistant cases of 2009 H1N1 influenza. Published at www.nejm.org December 9, 2009 (10.1056/NEJMc0910448) The New England journal of medicine. 2009.

[92] Healt Protection Agency, HPA statement on possible transmission, 20 November 2009, available at:http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1258560561316?p=1231252394302.

[93] WHO. Summary report of a High-Level Consultation: new influenza A (H1N1). May 18th 2009.

[94] Jakab Z. ECDC's future look and risk assessment. Briefing to the Swedish Presidency Informal Council. Jönköping, Sweden 5 July 2009.

[95] Cauchemez S, Ferguson NM, Wachtel C, Tegnell A, Saour G, Duncan B, et al. Closure of schools during an influenza pandemic. The Lancet infectious diseases. 2009 Aug;9(8):473-81.

[96] ECDC. Meeting Report: European pandemic planning assumptions. January 2009. .

[97] WHO. Pandemic (H1N1) 2009 - update 71. [cited 28 October 2009]; Available from: http://www.who.int/csr/don/2009_10_23/en/index.html

[98] ECDC. Weekly influenza surveillance overview, 23 October 2009. [cited; Available from: http://www.ecdc.europa.eu/en/activities/surveillance/EISN/Newsletter/091023_EISN_Weekly_Influenza_Surveillance_Overview.pdf

[99] Witkop CT, Duffy MR, Macias EA, Gibbons TF, Escobar JD, Burwell KN, et al. Novel Influenza A (H1N1) Outbreak at the U.S. Air Force Academy Epidemiology and Viral Shedding Duration. American journal of preventive medicine. 2009 Oct 21.

[100] Hanshaoworakul W, Simmerman JM, Narueponjirakul U, Sanasuttipun W, Shinde V, Kaewchana S, et al. Severe human influenza infections in Thailand: oseltamivir treatment and risk factors for fatal outcome. PloS one. 2009;4(6):e6051.

[101] Hancock K, Veguilla V, Lu X, Zhong W, Butler EN, Sun H, et al. Cross-reactive antibody responses to the 2009 pandemic H1N1 influenza virus. The New England journal of medicine. 2009 Nov 12;361(20):1945-52.