ECDC FORWARD LOOK RISK ASSESSMENT

Likely scenarios for influenza in 2010 and the 2010/2011 influenza season in Europe and the consequent work priorities

Contents

Stockholm, March 2010

Executive summary

Work has been undertaken by ECDC with substantial input from its Advisory Forum, other European experts and WHO in order to inform EU stakeholders as to the likely scenarios for influenza transmission (pandemic and inter-pandemic) in Europe in the immediate future.

Specifically, this work has been looking at what can most reasonably be expected in the first half of 2010 and to the end of the 2010/11 influenza season. It has also identified the further information that needs to be gathered through surveillance and research in order to determine vaccine strategies, including implementation of the new EU Health Council Recommendation on seasonal influenza immunisation.

Evidence, data and information were considered from a number of sources including prior pandemics, the European experience during this pandemic, sero-epidemiology, modelling and especially what happened in the Southern Hemisphere in 2009/10 following their initial autumn/winter wave.

On the basis of this it seems unlikely that there will be another spring/summer pandemic wave in Europe unless there are significant unrecognised uninfected populations or the virus changes and becomes more transmissible. Serological surveys (measuring the levels of immunity in the community) could help reduce this uncertainty. However, only a limited number of Member States are currently using this tool to assess susceptibility. Other important data and analyses are lacking and hence priority work has been identified for Member States and ECDC to undertake, especially to inform vaccination strategies using the currently authorised monovalent pandemic vaccines and the anticipated 2010/2011 seasonal trivalent influenza vaccines (which will include the pandemic H1N1 strain).

It seems highly likely that even when WHO judges the post-peak and post-pandemic phases to have been reached, Europe will continue to experience low-level transmission and small outbreaks of the pandemic 2009 A(H1N1) influenza. This is the most likely scenario throughout the whole of 2010. However, larger outbreaks cannot be excluded given the lack of information from seroepidemiology.

Epidemic transmission of the pandemic virus is highly likely in the next (2010/2011) winter season, at least in very young children and other susceptible individuals. It is also most likely that pandemic influenza A(H1N1) will become the dominant virus in the coming winter season along with influenza B viruses, though the presence of influenza A(H3N2) viruses as well cannot presently be excluded. By then Europe will probably be referring to this combination as the 'new seasonal influenza'.

There is currently no evidence of a changed pathogenicity of the circulating pandemic influenza virus. No significant genetic or antigenic changes to the pandemic influenza virus have so far been reported and so patterns in morbidity and mortality similar to those seen during the pandemic should initially be expected from this virus next winter though numbers of cases will be considerably smaller because of the previous transmission and vaccination.

In summary, the implications for vaccination strategies from this conservative forward look is that transmission of the pandemic virus will continue through 2010 albeit at low levels, and that this will be the predominant influenza A virus causing seasonal influenza in the winter of 2010/2011. At present the currently authorised monovalent pandemic vaccines and the new 2010/2011 seasonal influenza vaccines are likely to be effective against the 2009 A(H1N1) strain for the coming 6–10 months. Therefore, for Member States wishing to protect unimmunised citizens in the spring of 2010 and autumn/winter of 2010–2011, there will be advantages to continuing to offer these vaccines (or trivalent vaccines with the pandemic antigen when they are available) to their chosen risk and target groups. ECDC's advice to EU citizens remains to accept influenza vaccination when it is offered to them.

Influenza viruses are notorious for their unpredictability and so this forward look risk assessment must not be seen as representing anything more than the most likely scenario. It will also be updated as relevant and significant data become available.

There are a number of uncertainties about the new seasonal influenza that Europe will face in the winter of 2010/11 concerning the burden of disease, the clinical picture and the groups at higher risk of experiencing severe disease. It should not be assumed that this will be the same as the previous seasonal influenza. ECDC has identified eight priority areas for surveillance and research where it advises work should be undertaken to clarify these uncertainties, particularly in support of the new EU Health Council Recommendation on Seasonal Influenza Immunisation.

This document represents guidance from ECDC and does not necessarily represent the opinions of those who contributed to the work or their employing institutions. Comments on this forward look are welcomed and should be sent to influenza@ecdc.europa.eu.

Rationale of this risk assessment

This work is needed for a number of planning purposes, notably to inform decisions on short- and long-term influenza vaccination strategies. It is urgently required because:

- authorities need to decide whether to continue pandemic vaccination in 2010;
- it cannot be assumed that the pandemic is over;
- previous recommendations about risk and target groups in the EU should be revisited, preferably before the summer, as the ones for the previous seasonal influenza may no longer entirely apply [1].

Source, date and type of request

ECDC internal decision informed by discussion at the ECDC Advisory Forum No. 20 (8 December 2009).

Objectives

Specific objectives of the work are:

- to inform Member States, the European Commission, the European Medicines Agency and others as to possible scenarios for influenza transmission (pandemic and inter-pandemic) that can reasonably be expected, or excluded, in the first half of 2010 in Europe and more tentatively through to the end of the 2010/2011 influenza season; and
- to determine what further information is needed to inform vaccine strategies including implementation of the new EU Health Council Recommendation on seasonal influenza immunisation[i].

The processes that this will inform (though not necessarily determine) are:

- Planning for possible pressures on health services in early 2010.
- Decisions on continuation of vaccination with the specific pandemic vaccines.
- Selection of the vaccine components and formulation for the 2010/2011 season[ii].
- Elaboration of more detailed seasonal vaccine strategies, including identification of the risk groups and other groups to be offered seasonal vaccination.

Consulted experts

Internal ECDC experts. ECDC Advisory Forum members or individuals nominated by them, World Health Organization, relevant experts and specialists from EU and other countries, notably from WHO and EU pandemic modelling groups (Annex 1).

[i] Council Recommendation of 22 December 2009 on seasonal influenza vaccination (2009/1019/EU). Official Journal of the European Union. OJ L 348, 29 December 2009. http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2009:348:0071:0072:EN:PDF

[ii] Note the components of the vaccine are determined during meetings convened by WHO and EMA but information and analyses such as those contained here contribute to that process. WHO published their latest recommendation on 18 February: Recommended viruses for influenza vaccines for use in the 2010-2011 northern hemisphere influenza season. See also ECDC Public Health Development (19 February 2010).

Background

This work is similar to that which ECDC undertook with its Advisory Forum (AF) (or their nominated representatives), WHO and other contributors for revising pandemic planning assumptions to fit the parameters of the 2009 pandemic. The outcome of that work was published in November on the ECDC website[i]. There are also links with ECDC's 2009 Pandemic Risk Assessments[ii] and work undertaken by an ECDC Pandemic Modelling Group and a global group convened by WHO [2].

The members of the group advising ECDC are listed in Annex I. There is continuity with the group which undertook the work on planning assumptions. However, ECDC again invited all AF members to join in the process or to nominate representatives[iii]. ECDC would like to thank all those who contributed to this work at what was an exceptionally busy period. A number of European countries have also been generous in sharing unpublished analyses and data and one of these appears as Annex II.

Terminology and assumptions

For this pandemic, ECDC finds it preferable to use the terms spring-summer wave and autumn-winter wave rather than first wave, second wave, etc. This is because the latter can be taken to imply that all countries will experience two or more pandemic waves which may not be the case

Previous experience is that all pandemics 'settle down' and dominate the new pattern of inter-pandemic influenza (also known as seasonal influenza), which can be significantly different in its characteristics from what was experienced prior to the pandemic (Table 1, Figure 1). The timeframe for the transition from a pandemic to a seasonal pattern is uncertain. As explained below, it can happen quite quickly (1957 pandemic) or take two seasons (1918 and 1968 pandemics) [3]. The formal name of the transition phase (which is still in the pandemic period) is 'post-peak' and it is followed by a post-pandemic phase, sometimes interrupted by a renewed wave (Table 2) [4].

Methodology, available information and evidence assessment

The methodology used was simple, to consider all relevant sources of data and analyses. Four data sources or types of analyses are available:

- Observations of what happened in the Southern Hemisphere temperate countries in their 2009/2010 spring and summer [Australia, Chile, New Zealand and South Africa][iv]. What is happening in other regions of the world [5] and in Europe in the winter of 2009/2010 [6,7].
- Observations of what happened during previous pandemics and inter-pandemic periods (Figure 1), with particular attention being paid to the 1957 and 1968 pandemics [Italy, Spain, Sweden, UK and USA].
- Estimations of the likely numbers and proportions of people who are immune due to prior immunity, by having been infected during this pandemic or from being immunised [France, Germany, UK]. Hence, from these estimations, whether there are sufficient susceptible individuals to sustain transmission. Because of the difficulties of dealing with overlapping estimations and the indeterminate sizes of the overlap, particular attention should be paid to the serological data becoming available.
- Mathematical modelling based on the above assessments. Especially, estimations of the proportions of the population that are needed to be immune for transmission to terminate given the transmission characteristics (especially the values for R) observed to date [EU Modeling Group, Germany, UK] [2,8].

[i] http://ecdc.europa.eu/en/healthtopics/Documents/0901_Pandemic_Influenza_European_Planning_Assumptions.pdf

[ii] http://ecdc.europa.eu/en/healthtopics/H1N1/Pages/risk_assessment.aspx

[iii] The names of those in the earlier group are at the bottom of the front page of the planning document. In addition, other members of the Advisory Forum, though unable to participate, expressed interest in the outcome and/or contributed to national data or analyses.

[iv] Information in [square brackets] means the countries or larger grouping from which data were made available either in published form or in confidence.

In addition, there is important information on the apparent risk group and mortality data which differ somewhat from that seen for the previous seasonal influenza [9,10,11,12].

Further, to determine the risk and target groups for immunisation, data will be needed from the experience with the 2009 pandemic A(H1N1), especially concerning the risk factors associated with experiencing severe disease and death from this infection.

The 2009 pandemic in Europe

The epidemiology of this pandemic has not been uniform across Europe. This is documented in ECDC's 'Situation Reports', then the 'Daily Updates' and the 'Weekly Influenza Surveillance Overview', as well as a set of downloadable powerpoint slides[i], as well as many national data presentations [France, Italy, the Netherlands, Spain, and the UK] and the regular reports on the WHO website [5]. As the pandemic spread globally in the spring and early summer, all EU/EFTA countries noted imported cases and then experienced in-country transmission. Because of the mild or even asymptomatic nature of many infections, the extent of the spring/summer transmission is especially difficult to determine for this pandemic without the benefit of serology [13-15]. However, early case-reporting, reports of deaths and serology indicated that the spring/summer wave was particularly heterogeneous between and within countries. According to their reports, parts of two countries, Spain and the United Kingdom, were especially affected during the period May to July, after which transmission probably declined in all EU/EFTA countries, seemingly in parallel with the closure of schools for the summer holiday. Transmission picked up again in September in the western countries, soon after schools re-opened. This is evidenced by national primary care and virological reports from Member States, reporting to the European Influenza Surveillance Network (EISN) with outputs in successive Weekly Influenza Surveillance Overviews (WISO) and by surveillance of deaths announced by EU/EFTA Member States and published in the ECDC Daily Updates. These data are now presented graphically on the ECDC Pandemic website. The reports showed a series of autumn/winter waves that appeared in all countries with a rough west to east and north to south progression similar to that often observed with inter-pandemic influenza [16], though with many variations between and within countries. More details on the characteristics of the cases are available in the ECDC Risk Assessment, though it is important to note some substantial differences from the preceding inter-pandemic (seasonal) influenza (Table 1) [1].

Current situation

Up to week 51, the primary care indicators of influenza-like illness (ILI) and acute respiratory infection (ARI) in most EU and EFTA Member States showed that community transmission was declining. This picture was not universal and was most often the case in the western and northern countries rather than in the eastern and south-eastern countries, seemingly because the pandemic waves were more advanced in the former. Because hospitalisations and deaths lag behind community transmission, countries that had passed the peak of the autumn wave were still experiencing significant numbers of patients in hospital in mid-December. Similarly, until the holiday period deaths were continuing to be announced by Member States, with the highest number of any week to date announced in week 50 (see ECDC Executive Update 14 December). Given the sensitivity of this pandemic to transmission in schools, it was significant that in many countries the decline in indicators of transmission took place *before* the closure of schools for the Christmas holidays.

As of week 6 2010, and after the usual disruption of surveillance and reporting of surveillance data during the Christmas/New Year holidays, the primary care parameters have predominately stayed low in all Member States apart from some eastern EU countries. **However, it is important to note that there is some continuing low-level transmission in all countries and confirmed pandemic influenza deaths are continuing to be announced on national websites, albeit in diminishing numbers [7]**.

The evidence

Observations from the Southern Hemisphere, 2009/2010, and other regions

Surveillance reports from the Southern Hemisphere countries indicate that there have been no additional waves of transmission following the end of their winter waves, though transmission of the 2009 pandemic A(H1N1) virus has continued at a low level. There have been sporadic outbreaks and hospitalisations attributable to A(H1N1), but no additional pandemic waves or even sustained community transmission (Figure 2). Also, reports of other

[i] ECDC's pandemic influenza materials are available from http://ecdc.europa.eu/en/healthtopics/H1N1/Pages/home.aspx

influenza viruses have indicated only low levels of influenza B viruses, very low levels of influenza A(H3N2) and that the previous seasonal influenza A(H1N1) has become almost nonexistent [17-20,5].

Elsewhere in the world, there are data from many Northern Hemisphere countries well summarised by WHO and its FluNet system and well presented by the US Centers for Disease Control and Prevention (CDC) and WHO (global presentation). These indicate that through the season the proportions of non-pandemic viruses have been steadily diminishing in almost all countries reporting. Exceptions are China, Vietnam and Cambodia, where the proportions of influenza A viral isolates that are A(H3N2) initially remained significant, but even in those countries that proportion has fallen over time. There has also been a rise in influenza B viruses in China so that of late they have predominated over the pandemic virus. That has also been seen recently in Bangladesh, emphasising the continuing risk posed by the B viruses [5, 27]. What remains unknown and unknowable is what is circulating in many equatorial countries with weak influenza surveillance.

Observations on previous pandemics and inter-pandemic periods (France, Italy, Spain, Sweden, UK, USA)

1957 pandemic A(H2N2)

From the limited historical data and analyses for Europe, this seemed to be the most straightforward pandemic. Indeed, there are considerable similarities (but some important differences) with the 2009 pandemic [21,10, 29]. The importance of school-focused transmission in both pandemics is noticeable and the age profiles of the cases are similar [11] (Figure 3). There was a single up and down wave though with an intriguing rise in the number of deaths reported in the early months of 1958 in Sweden, the UK (Figure 4) and the US data. However, in the most complete analysis found to date, that rise was not reflected in widespread community transmission, but rather seemed to be attributable to cardiovascular deaths due to influenza in older individuals [22].

1968 pandemic A(H3N2)

There are now convincing data indicating that the virus became more transmissible between its first and second winter in Europe. This had been apparent from the many more cases (UK) and deaths (Italy) that occurred during the second winter (1969/1970) than the first (1968/1969) (Figure 5) [23]. Supportive unpublished data were also made available to the group by France and Spain. It has recently been calculated that the influenza circulating in the winter of 1969/1970 must have been considerably more transmissible than the one circulating in the winter of 1968/1969 [24]. This seems to have been due to a real change in the virus rather than to the fact that the virus circulating during the first winter was a blend of the new pandemic virus and the preceding seasonal A(H2N2) virus [25].

Estimations of numbers and proportions of people likely now to be immune

Whether or not transmission increases in the spring of 2010 or the autumn/winter depends on whether there are enough people to sustain transmission given the observed low transmissibility ('R' value) of A(H1N1) [8]. There are three possible types of immunity:

- Pre-existing immunity – principally in people born before the mid-1950s.
- Immunity after infection during the current pandemic.
- Immunisation.

These three groups overlap to varying extents, and particular attention needs to be paid to serological data to overcome that difficulty. However those data are rare and an additional difficulty arises here because for a key group, children and adolescents, it is especially difficult to obtain serological data at a population level and data obtained on them from outbreaks can be misleading [13, 15].

Contributing data and calculations come from France for estimates of those infected and immunised along with serological data [26,14] from Germany (Annex II) and the UK [13,15].

Estimations of the numbers and proportions of population groups that have been immunised with the pandemic vaccine are becoming available and they are currently being gathered by the European Medicines Agency, together with data that are being sent from Member States to the European Commission (Directorate-General for Health and Consumers, Unit C3). A difficulty is simply the rapid speed with which some countries undertook immunisation and the general lack of immunisation population registers were such that data collection and analysis will take some time to catch up in many countries. Hence estimates of the proportions of the population

immunised, especially the crucial younger populations are not yet available and may not be available for some time.

Because of the widely varying proportions of the population that have been offered and have accepted 2009 pandemic vaccine (from over 60% to zero) it is possible to imagine a very heterogeneous set of risks of enduring or reappearing transmission across the EU with almost a need for country-by-country analyses. This will depend on how extensive immunity is in countries where there has been no or very little vaccination. However, an important indication that there are not sufficient susceptibles to sustain large-scale continuing transmission is that there has been no major resurgence of transmission in most of Europe in January 2010 though there has been continuing low-level transmission in all European countries.

Mathematical modelling (Germany, EU modelling group)

Modelling has been done to provide estimations of the proportions of the population that are needed to be immune for transmission to terminate, given the transmission characteristics observed to date. The most extensive work is from the UK and those analyses have been shown to the group undertaking this project. It was apparent that the probability of another wave of transmission in the spring/summer of 2010 was very low, at least for the UK. That was also the consensus opinion for the EU/EFTA countries from the EU pandemic modelling group convened by ECDC. However, there are significant caveats:

- The UK work concerns a single country where it is known that transmission has been different in timing and perhaps extent from the rest of the EU.
- There are indications that transmission is continuing at a low level along with deaths.
- There may be populations in the EU relatively unaffected by transmission of the pandemic virus in 2009.
- There is always the possibility of the virus changing its transmission characteristics (as it did in 1968–1970) or its pathogenicity [24].

Germany (Robert Koch Institute, see Annex II) has demonstrated that there needs to be an immunity threshold in the population to make continued transmission unlikely. This threshold is determined by R_o which they assumed to be 1.4–1.6, resulting in a necessary immunity level of 29–38% to prevent transmission. Then Germany tried to estimate the level of immunity in the German population based on: (a) infected through transmission (current estimate was: 1.5% seeking healthcare, divided by 0.3 (30% are seeking healthcare) = 4.5%, times two (asymptomatic rate = 50%) = 9%); (b) immune because of vaccination (current data suggest 8%); and (c) pre-existing immunity (estimated 8% of the population). Altogether this would give a sum of 25%, being close to the necessary threshold. The risk factor and mortality data becoming available suggest significant differences between the pandemic and the prior seasonal influenza (Table 1) though it is not clear whether all of these will be sustained into the new seasonal influenza [1].

Most likely scenarios to the end of the pandemic season (week 20, 2010)

Pandemic influenza

This remains difficult to predict because of the paucity of information on the proportions of the susceptible populations remaining uninfected or unimmunised. Serological data are vital but they are only becoming available slowly through initiatives like those of SéroGrippeHebdo and the Health Protection Agency, UK [14,15]. However, the fact that many countries experienced declining waves before the holiday season (see accompanying series of curves) is probably significant[i]. Also, the Southern Hemisphere surveillance reports, such as those from Australia (Figure 2) and PAHO show no resumption of the wave after their 'mid-winter break'. Certainly, there was no spring wave in temperate southern hemisphere countries after their winter wave had subsided. Therefore, it is suggested that the default position is that another pandemic wave in Europe this spring or summer, though not impossible, is unlikely. [4]. Caveats here are if there are populations yet to be affected or if the virus' characteristics change. However, it is important to note here that there may be groups who are continuing to be at some risk through the spring and summer due to sporadic infections and for whom it is still worthwhile to consider immunisation. This especially includes children, pregnant women and those in clinical risk groups.

[i] See Weekly Influenza Surveillance Overviews (February 2010). http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/EISN_Bulletin.aspx

Seasonal influenza and other respiratory pathogens

As usual, as the winter progressed in Europe, the incidence of other respiratory pathogens in the EU (including bacterial pathogens) in the community probably increased. However, the only EU data on this are for respiratory syncytial virus (RSV) and the incidence of these is now declining[i] [6]. While it remains unclear whether any of the current seasonal influenzas will emerge this season in Europe, to date they have not done so in any number. Again the experience in the Southern Hemisphere was that even in absolute terms there were few influenza A viruses apart from the pandemic strain. There were some of the new A(H3N2) viruses, which do not fit the A(H3N2) antigen recommended for this season and more B viruses [17,19,20,27].

Likely scenarios for the influenza season 2010/2011

It is important to think of this now given that WHO has made recommendations on the strain selection [27]. However, as above, making predictions will be even less easy than for the end of the 2009/2010 season. It will be necessary to prepare for more than one scenario. For example, it cannot even be assumed that there will be both an A(H3N2) and an influenza A(H1N1). Up until the mid-1970s, we believed that there was usually only one predominant A virus in addition to B viruses (Figure 1). However, it is undoubtedly safer to include an A(H3N2) for the seasonal influenza vaccine strain selection for season 2010/2011 as WHO recommended for the 2010 Southern Hemisphere vaccine [8] and indeed that has been the WHO recommendation for a Northern Hemisphere trivalent vaccine (which will need to be confirmed by the European Medicines Agency) [27,28]. If pandemic influenza A(H1N1) predominates, and does not change its current characteristics (Table 1), then we might have a different spectrum of disease and a different set of risk groups than now, albeit overlapping with the current ones. It is even possible to imagine the worsening scenario as seemed to happen in the last pandemic (1968/1969) where in the European countries for which data are available the second winter of the pandemic saw many more transmissions and deaths than the first winter (Figure 5) [1].

Implications for vaccination

One important implication of these findings is that from this conservative forward look it is most likely that transmission of the pandemic virus will continue in 2010 and that this virus will be the predominant influenza A virus causing seasonal influenza in the winter of 2010/2011. That is not forgetting influenza B viruses. The most likely group to experience transmission will be young children born recently but other uninfected and unimmunised persons will be at most risk of infection. The possibility of major outbreaks cannot be excluded because of the paucity of sero-epidemiological information available in Europe. Unless the virus changes, the patterns of severe morbidity and mortality can be expected to be similar to that of the pandemic virus, at least in the first few winters.

At present, the only vaccines that are likely to be effective against the 2009 A(H1N1) strain are those based on the new A(H1N1) viruses. Therefore, for Member States wishing to protect their citizens in 2010 and in the 2010/2011 winter there will be advantages to continuing to offer these vaccines in 2010 to their chosen risk and target groups. ECDC's advice to EU citizens remains to accept vaccination should it be offered to them (See ECDC Key Messages), then to accept the new seasonal vaccines when they become available in the autumn.

Work to be undertaken in 2010

Arising from the above consideration and uncertainties as demonstrated both in this document and the ECDC Risk Assessment on the 2009 Pandemic [11], work, including surveillance and research, is advised for the following areas (among others), with varying degrees of ECDC coordination and support:

[i] See Weekly Influenza Surveillance Overviews (February 2010). http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/EISN_Bulletin.aspx

- Continue primary care and virological surveillance in the EU throughout the whole of 2010, with particular emphasis on looking for significant changes in the 2009 virus – *all countries*;
- Conduct quality assured serological studies to determine age group-specific immunity after the autumn/winter wave and share the analyses with other Member States ahead of publication– *as many countries as possible with particular ECDC coordination*;
- Retrospectively review risk groups in EU Member States through surveillance data on severe acute respiratory infection and deaths so as to review the previous recommendations on risk and target groups. Special attention may need to be paid to the 'new' risk groups: young children, pregnant women and those with morbid obesity – *as many countries as possible*;
- Establish and strengthen surveillance for severe acute respiratory infection and deaths so that it is found routinely on a sentinel basis in more countries in the EU – *as many countries as possible*;
- Determine whether there are any additional deaths attributable to influenza in specific age groups both during the pandemic and subsequently through routine death monitoring – *individual Member States and EU-level work*;
- Estimate the actual levels of additional risk of illness for the individual citizen from the pandemic – *volunteering countries*;
- Determine the mortality in age group and risk groups and compare this with previous seasonal influenza using parameters like Years of Potential Life Lost – *volunteering countries and ECDC*;
- Closely monitor the situation in the Southern Hemisphere during its 2010 winter (June to September) – *ECDC and WHO*.

Tables and figures

Table 1: Differences between prior seasonal influenza and 2009 pandemic influenza in Europe

	Seasonal influenza (to 2008/09 season)	2009 pandemic influenza
Circulating influenza viruses	Two A viruses (H1N1), (H3N2) & some B viruses	Almost exclusively the pandemic A(H1N1) viruses, a few A (H3N2) viruses & some B viruses
Antiviral resistance	Common and transmissible oseltamivir resistance in A(H1N1)	Rare and to date only transmitting very rarely in certain circumstances
Setting for transmission	Probably any setting where people come together	Schools are considered especially important, along with homes
Experiencing severe disease	Those in clinical risk groups and older people	Young children, pregnant women and those in clinical risk groups. But 20–30% of people experiencing severe disease were outside any risk group. Many people born before the mid 1950s seem to be immune but those who are not do experience severe disease, more so than any other age group
Acute respiratory distress syndrome	Extremely rare	Uncommon but occurring, even in young fit adults
Mortality	Few confirmed deaths reported each year in official statistics Estimates of up to 36 000 in a more severe year from statistical methods	Substantial numbers of confirmed deaths announced by Member States Not yet calculated for the EU but reported in the US*

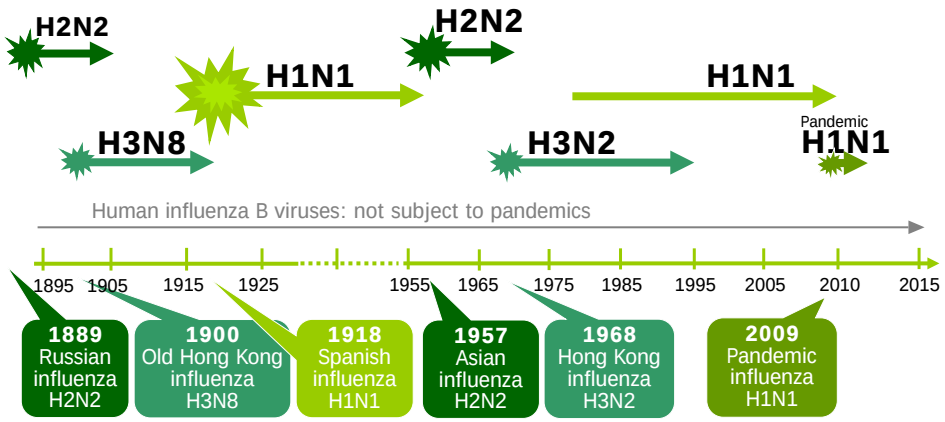
**See http://www.cdc.gov/h1n1flu/estimates_2009_h1n1.htm*

Table 2: WHO global pandemic phases (2009 Guidance)

Phases	Descriptions
One	No animal influenza virus circulating among animals has been reported to cause infection in humans.
Two	An animal influenza virus circulating in domesticated or wild animals is known to have caused infection in humans and is therefore considered a specific potential pandemic threat.
Three	An animal or human-animal influenza reassortant virus has caused sporadic cases or small clusters of disease in people, but has not resulted in human-to-human transmission sufficient to sustain community-level outbreaks.
Four	Human-to-human transmission of an animal or human-animal influenza reassortant virus able to sustain community-level outbreaks has been verified.
Pandemic	
Five	The same identified virus has caused sustained community level outbreaks in two or more countries in one WHO region.
Six	In addition to the criteria defined in Phase 5, the same virus has caused sustained community level outbreaks in at least one other country in another WHO region.
Post-peak	Levels of pandemic influenza in most countries with adequate surveillance have dropped below peak levels.
Possible new wave	*Level of pandemic influenza activity in most countries with adequate surveillance rising again.*
Seasonal influenza	
Post-pandemic	Levels of influenza activity have returned to the levels seen for seasonal influenza in most countries with adequate surveillance.

Adapted from Pandemic influenza preparedness and response: a WHO guidance document.2009. http://www.who.int/csr/disease/influenza/PIPGuidance09.pdf

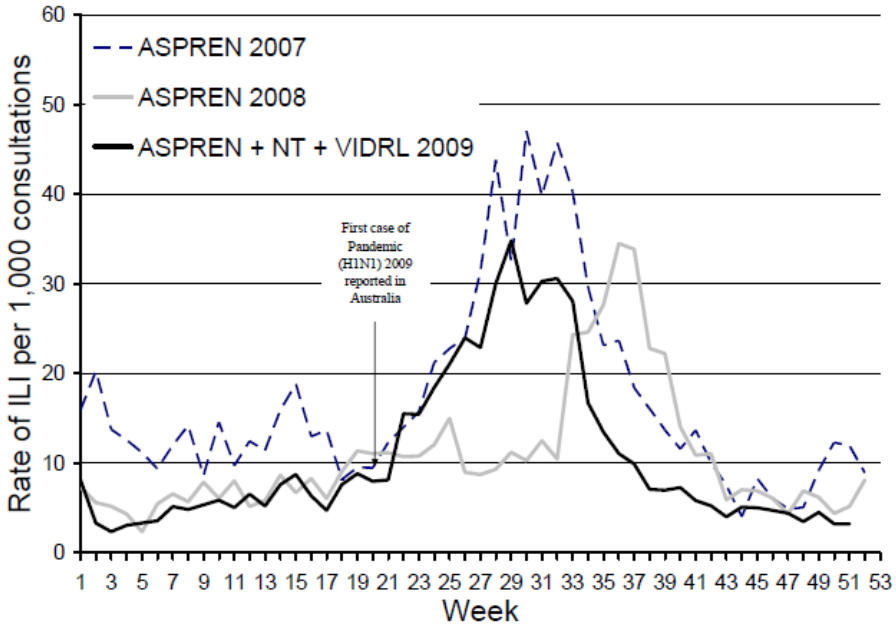
Figure 1: Previous pandemics and inter-pandemic (seasonal) influenza



The major current seasonal influenzas in any season are represented by the arrows running horizontally at the time so that in 1960 it was A(H2N2) viruses. In 1970 A(H3N2) viruses and in 1980 onwards until 2008/9 A(H3N2) and A(H1N1) viruses. There are also influenza B viruses each year as indicated.

Reproduced and adapted (2009) with permission of Dr Masato Tashiro, Director, Center for Influenza Virus Research, National Institute of Infectious Diseases (NIID), Japan.

Figure 2: Weekly rate of influenza-like illness reported from GP ILI surveillance systems, Australia, 2007–2009



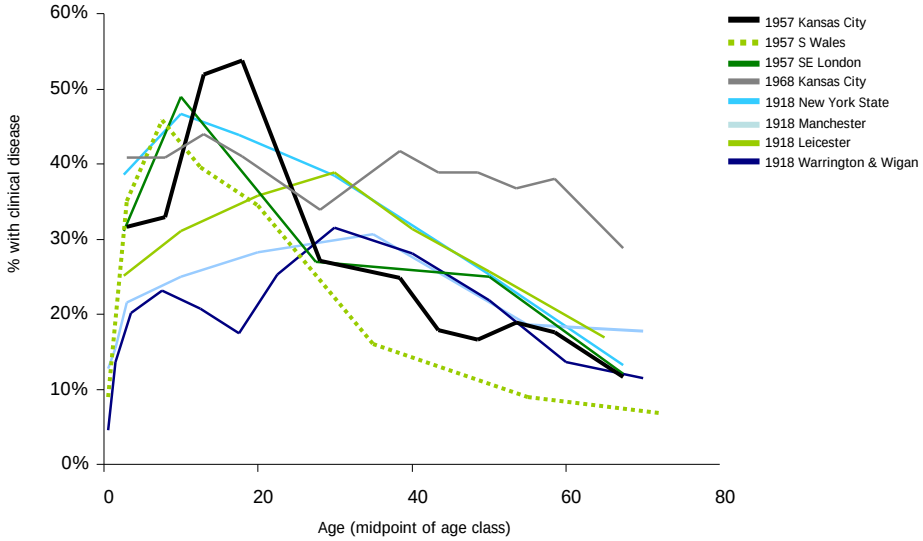
* Delays in the reporting of data may cause data to change retrospectively. As data from the NT and the VIDRL surveillance systems are combined with ASPREN data, rates may not be directly comparable across 2007, 2008 and 2009.

SOURCE: ASPREN, NT, VIDRL

Source: Australian Government, Department of Health and Ageing. Australian influenza surveillance summary report. No 33, 2009, reporting period 19 December 2009 – 1 January 2010. http://www.healthemergency.gov.au/

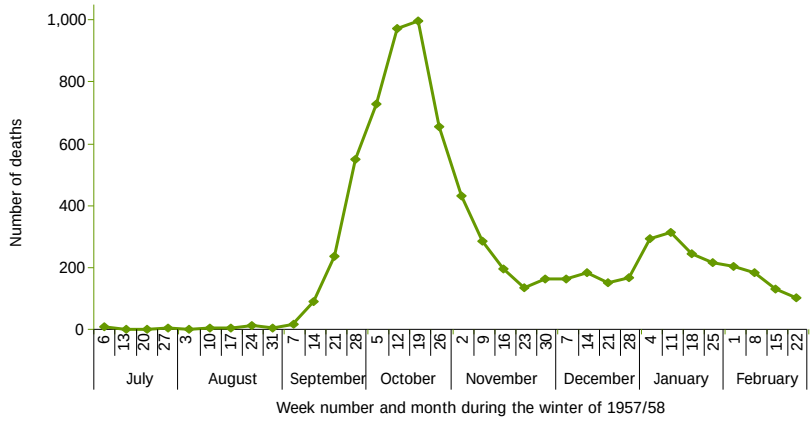
Figure 3: Estimated age-specific attack profiles from 1918, 1957 and 1968 pandemics

The 2009 pandemic most closely resembles that of 1957 [11]



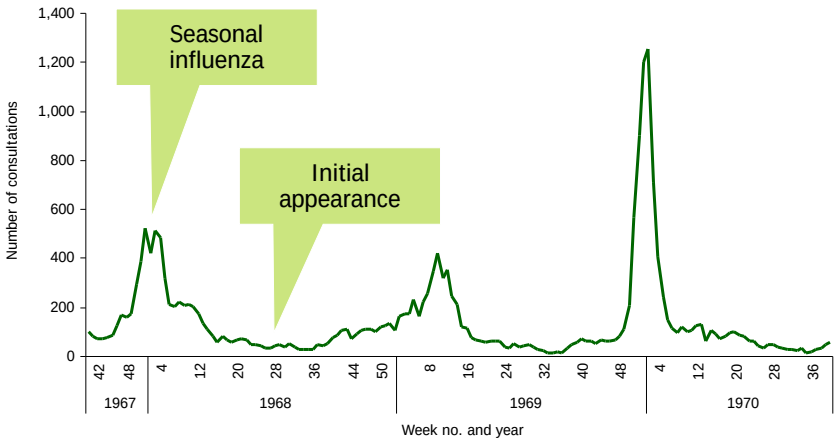
Source: Peter Grove, Department of Health, UK.

Figure 4: Recorded deaths from influenza, England and Wales, 1957/58



Source: Health Protection Agency, UK.

Figure 5: Number of GP consultations with influenza-like illness per week, England and Wales, 1968/69



Source: Health Protection Agency, UK.

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Annex 1
Working Group Members

Active participants from the Advisory Forum: Natalia Kerbo (Alternate, Estonia), Outi Lyytikäinen (Alternate, Finland), Jean-Claude Desenclos (Member, France), Ágnes Csohán (Member, Hungary), Darina O'Flanagan (Member, Ireland), Derval Igoe (Alternate, Ireland), Marianne van der Sande (Alternate, Netherlands), Hanne Nøkleby (Alternate, Norway), Irena Klavs (Member, Slovenia), Marta Vitek (Alternate, Slovenia), Pedro Arias Bohigas (Member, Spain), Jana Petrenko (European Patient Forum).

Participants, experts and observers: Antoon Gijsens (European Commission, Directorate General for Health and Consumers, Unit C3), Maria Van Kerkhove (Imperial College London, UK, representing the WHO informal mathematical modelling network for H1N1pdm), Guy Walker (UK Department of Health, for Peter Grove), Peter White (UK-nominated expert), Caterina Rizzo, (Italy-nominated expert, ISS), Udo Buchholz (Germany-nominated expert, RKI), Amparo Larrauri Camara (Spain- nominated expert, ISCIII), Daniel Levy-Bruhl (France-nominated expert, INVS), Tony Mounts (WHO Headquarters).

Participants, ECDC: Johan Giesecke (Chief Scientist), Angus Nicoll (Influenza Coordinator – accountable writer of report), Pasi Pentinnen (PHE Crisis Manager & Senior Expert), Mika Salminen (PHE Crisis Manager & Senior Expert), Tommi Asikainen (Mathematical modeller and convenor of EU Modelling Group), Bruno Ciancio (Senior Expert), Judit Bak (Cabinet – Secretariat).

Annex 2
Considerations towards the probability for another pandemic wave in the beginning of 2010

Robert Koch Institute, Germany

Regarding the question about the probability of the likelihood of another wave in early 2010 we thought that in principle there are two questions that need to be taken into account: (a) has the virus changed so much that any acquired immunity (through infection or vaccination) becomes irrelevant or near irrelevant? (b) is there a susceptible portion of the population that is sufficiently large to allow sustained transmission of the virus? The latter could be the case if (i) there are sufficiently large geographical heterogeneities, e.g. urban-rural, that would generate large enough pockets of susceptible population permitting the build-up of a veritable wave; or if (ii) intervention measures have dampened the autumn wave substantially and these measures have now been lifted; or if (iii) there are climatic factors at work which have resulted in an autumn wave that was smaller than a wave that would have occurred in winter. Also a combination of (i)–(iii) is possible.

While these three questions are difficult to address we attempted to roughly estimate the proportion of the population that is already immune. In general, the immunity threshold that needs to be reached by a population so that an infectious agent cannot maintain transmission depends on R_0 and can be calculated by the formula $1 - 1/R_0$ (Bootsma, PNAS 2007). At the moment WHO and others seem to reach consensus on the R_0 of the pandemic virus of about 1.4–1.6. Thus, the threshold of the immune population would need to be between about 29% (R_0=1.4) and 38% (R_0=1.6).

We tried to calculate the proportion of the population that is immune due to (i) infection at the end of the autumn wave, (ii) vaccination and (iii) pre-existing cross-protection:

(i) Immunity due to infection: Although ECDC has suggested as worst case scenario for planning a 20% clinical attack rate and the wave seems to be rather moderate, we assumed a 5–10% clinical attack rate. Assuming that 50% of infected persons become ill, approximately 10–20% of the population would be infected.

(ii) Immunity due to vaccination: The proportion of vaccinated until year's end surveys show that these may reach approximately 10%. Assuming an effectiveness of 50–100%, about 5–10% of the population would be vaccinated. We have assumed that persons vaccinated and persons infected do not overlap.

(iii) Immunity due to pre-existing cross-protection: Cross-immunity in the population against A/H1N1 is possible (MMWR, May 2009) and would be about a conservative 5% in younger adults and 30% in older adults. This would result in 50 million (population) x 5% (cross-immunity) = 2.5 million persons among younger adults, and in 20 million (population) x 30% = 6 million persons among the elderly. These proportions must be reduced by the number of people that are vaccinated, but there should be no overlap with those infected in (i) because those with pre-existing immunity could not be infected. Vaccination *and* pre-existing cross-protection might be a random event. For younger adults this would mean that (→ 5% (cross-immunity) x 10% (vaccination rate) =0.5%) 0.25 million need to be deducted, in the elderly we assume that these were more willing to be vaccinated (assume conservatively 30%), so that (30% (cross-immunity) x 30% (vaccinated)=9%) 1.8 million need to be deducted. Thus, cross-immunity would amount to 2.25 million (2.5–0.25) in the younger adults and 4.2 million (6–1.8) in the elderly, together 6.45 million (=8% of the population).

These numbers are shown again in the Table, below. These calculations can be refined with more information, in addition it should be also taken into account that the major portion of the population that is assumed to be cross-immune is among the elderly which is not the driver of transmission. At any rate it seems that the proportion of the population that is immune is near the threshold where another wave in early 2010 is statistically unlikely to occur.

U Buchholz (December 2009)

Annex Table: Immunity threshold needed to 'prevent' another wave in early 2010 with assumed R_0 and acquired/existing immunity in the population due to different mechanisms

		Min		Max
Immunity threshold to be reached		29%		38%
Immunity in % after the autumn wave				
(1) due to infections				
1.1 clinical attack rate	5%		10%	
1.2 infection attack rate (if 50% asymptomatic)		10%		20%
(2) vaccination	10%		10%	
Effectiveness	50%		100%	
Effectively vaccinated		5%		10%
(3) pre-extisting cross-immunity		8%		8%
Sum		**23%**		**38%**