ECDC RISK ASSESSMENT

Seasonal influenza 2010–2011 in Europe (EU/EEA countries)

January 2011

Contents

Stockholm, January 2011

The Risk assessment was corrected on 6 May 2011: Page 4 'Risk assessment' paragraph 3. Spain added to the sentence 'notably France, the Netherlands, Norway and Spain.'

Executive summary

The 2010/11 seasonal influenza epidemics in Europe are dominated so far by the A(H1N1)2009 viruses which emerged in the 2009 pandemic, although these are now considered seasonal viruses. There are also some B viruses circulating. Both are causing some severe disease and premature deaths but the preliminary data indicate that 90% of the fatalities are due to A(H1N1)2009

This is the first European influenza season after the 2009 pandemic. Many of the features and required countermeasures are the same as for the previous seasonal influenzas (which ran until the 2008/09 season). However, there are important differences which Europe needs to take into consideration, notably the type of people who are most affected and experiencing severe disease.

In the first affected country (the United Kingdom) there have been higher numbers of people seeking care than on average with seasonal influenza. Also, the number of people with severe disease has been considerably higher than during the pandemic with at its peak 1.4 persons/10^5 population requiring higher level (intensive) hospital care at one time. The reason for the latter finding is unclear. Part of the reason for the increased demand in primary care has been persons seeking immunisation or treatment as information on the severe cases became apparent to the public. These phenomena have also been observed in other countries in Western Europe, albeit at lower levels.

A broad pattern of west to east progression of influenza epidemics is underway, such as has been seen in previous years. Hence the experience of the Western countries can inform those further to the east of the European Union. All these considerations constitute the justification for this Interim ECDC Risk Assessment, which will be updated at intervals.

Those mostly reported as experiencing severe disease or dying prematurely are those adults below the age of 65 years and children in the clinical risk groups. These constitute over 80% of cases reported. Severe disease also affects some pregnant women. There are also some previously entirely healthy people, who account for 20% of the deaths in the UK, and higher percentages requiring higher-level (intensive) hospital care in France. As in the pandemic, there have been some older people experiencing severe disease but reported cases have been low in numbers.

Numbers of severely ill cases requiring care are now declining in the UK but they are rising in other countries. It cannot be anticipated whether those countries will experience the same rates as the UK.

The circulating viruses have not as yet changed or mutated, and it is expected that the seasonal vaccines will be effective in preventing disease. ECDC-coordinated studies in the pandemic found up to 80% effectiveness for vaccines containing A(H1N1)2009. Other observational studies have confirmed this. Indeed there are encouraging data suggesting that significant protection develops within a week of immunisation. Data on the early deaths in the UK indicate that the vaccines in use are also effective in preventing influenza-related deaths.

Recent surveys of pandemic and seasonal vaccine coverage by Member States indicate that there are many people in the clinical risk groups in Europe who remain unvaccinated, either with the pandemic vaccine or the 2010 seasonal vaccine.

In the UK, there is a rise in laboratory reports of two or more severe invasive bacterial diseases; pneumococcal disease and group A streptococcal disease has been observed. Rates of invasive streptococcal disease rose to 0.33/10^5 population in December 2010 compared to 0.19/10^5 in an average year. To date, this has not been reported elsewhere in Europe. It is unclear whether this rise is associated with the influenza epidemics and contributing to the high numbers of severe cases in the UK, but that is a possibility.

The scientific evidence to date provides justification for the following countermeasures already adopted by some countries in addition to the usual influenza personal protective measures (early self isolation, respiratory hygiene and hand-washing):

- Continued vaccination of all those recommended for vaccination following national guidelines but especially clinical risk groups, including pregnant women, especially as it seems that the vaccine provides some protection even just a week after injection. However, there may be vaccine availability, logistical and administrative issues that will make this difficult in some settings.
- Use of antiviral treatment in those presenting with severe influenza-like illness, pending virological confirmation, and in those with risk factors with milder disease.
- Alerting higher level healthcare services of potential increased numbers of influenza patients this winter, potentially already in the next few weeks.
- Advising clinicians to be vigilant to the possibility of severe illness due to bacterial co-infection with influenza, including invasive group A streptococcal, pneumococcal and meningococcal infection, and to be aware of the possibility of such bacterial co-infection in people with flu-like illness.
- Use or creation of clinical networks for surveillance, evaluation and sharing of clinical experience.

This is an interim risk assessment and will be up-dated at intervals as more data and analyses emerge.

Source, and type of request

ECDC internal decision: urgent; replacing a previous internal threat assessment.

Questions

Main questions

What are the main features, risks to human health and likely course of the 2010/2011 influenza season in Europe and how likely is it that the initial experience in the first affected countries will be replicated in other EU/EEA countries in terms of a) the pattern of infection and b) the impact on the health services?

What possible countermeasures and actions do the scientific and public health data and analyses support being taken by authorities?

More specific questions

- Why have a number of community and hospital indicators of influenza activity risen to levels higher than that seen in the 2009 pandemic despite the same virus (AH1N1)2009 being seen to be the main driver in both?
- Can changes in the viral mix be anticipated later this season?
- Has there been any change in the virology of the A(H1N1)2009 virus?
- Has there been any emergence of antiviral resistance?
- What is likely to be the effectiveness of influenza vaccines and antivirals?
- Is the observation of increased incidence of two types of invasive bacterial infections in the UK likely to be related to influenza?
- Is an observed rise in all-cause/all-age mortality observed in a number of the Western European countries likely to be related to influenza?

Consulted experts

Internal to ECDC: Epidemic intelligence, influenza and communication functions.

Specific contributions from: Eeva Broberg, Bruno Ciancio, Andrew Amato Gauci, Johan Giesecke, Kari Johansen, Angus Nicoll (guarantor), and Pasi Penttinen.

External to ECDC:

- Preben Aavitsland, Norwegian Institute of Public Health (FHI), Oslo, Norway
- Caroline Brown, World Health Organization (WHO) Regional Office for Europe, Copenhagen, Denmark
- Bruno Lina, University of Lyon and National Influenza Centre (Southern France), Lyon, France
- Marianne van der Sande, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands
- John Watson, Health Protection Agency (HPA), London, UK

ECDC is very grateful for the expert input from the persons above. They were consulted as individuals on the basis of their expert knowledge and experience rather than as representatives of their institutions or countries. It should also be noted that responsibility for the Risk Assessment is with ECDC rather than with these individuals, and that this Risk Assessment will be updated frequently.

Evidence accessed

Global and European Data and Analyses

WHO. Influenza update – 14 January 2011, available from: http://www.who.int/csr/disease/influenza/2011_01_14_GIP_surveillance/en/index.html

National data from EU/EEA Member States as reported to ECDC and appearing in the Weekly Influenza Surveillance Overviews (WISO), Week 2, 21 January 2011.

CNRL-ECDC Influenza virus characterisation, Dec 2010, available from: http://ecdc.europa.eu/en/publications/Publications/1012_Influenza_virus_characterisation_2010_December.pdf

EUROMOMO – European monitoring of excess mortality for public health action. Pooled results are available from: http://www.euromomo.eu/results/pooled.html

More specific and detailed data from selected western EU/EEA countries

France: Institute de Veille Sanitaire; Ireland: Health Protection Surveillance Centre; Netherlands: RIVM 'Griep en verkoudheid' (influenza and colds); Norway: Public Health Institute (specifically a risk assessment and forecast, 11 January 2011 – English translation); UK: Health Protection Agency (HPA) – National Influenza Weekly Reports (specifically Week 2, 12 January 2011 and other information for health professionals; UK: Department of Health, 'Winterwatch' health data, 20 January 2011.

Regional and national influenza websites in temperate northern hemisphere countries

WHO Regional Office for Europe (Euroflu Elecronic Bulletin), Canada (PHAC-Fluwatch), China (CCDC), Japan (NIID), USA (CDC-FluView), EUROMOMO European Mortality Project (Weekly mortality bulletin).

See also references below.

Risk assessment

Epidemiological situation and impact on the health services

EU/EEA countries. See latest Weekly Influenza Surveillance Overview (WISO). Increasing levels of influenza transmission have been reported in the majority of EU/and EEA countries. The first country to report increases in consultations was the UK in week 47/2010. As of week 1/2011, 17 EU/EEA countries participating in the European Influenza Surveillance Network (EISN) (Belgium, Bulgaria, Denmark, Estonia, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovenia, and Spain) were reporting increasing primary care consultations, influenza-like illness and/or acute respiratory infections (ILI/ARI) above baseline levels. As of week 2, the first country that reported rises, the United Kingdom, was now reporting a downward trend and a number of other countries reported that their levels were now unchanging ('stable'), albeit at high levels (WISO, week 2). The highest incidence of consultations for ILI/ARI has been observed among individuals below 65 years of age.

Looking over time, and taking into account the effect of the Christmas and New Year holiday period on transmission and reporting, there is a broad pattern of west to east progression across Europe, such as has been seen in many but not all previous years (1).

There are a number of reports of severe cases from individual countries with over 1700 cases of hospitalised severe acute respiratory infections (SARI) as of week 2 reported to ECDC from eight countries (Austria, Belgium, France, Ireland, Portugal, Romania, Slovakia and Spain). In addition there are analyses on national web sites on a number of countries, notably France, the Netherlands, Norway and Spain. In Ireland as of the latest surveillance report (Week 2/2011)(29) there were 52 cases requiring higher level (intensive) care. This is equivalent to $1.2/10^5$ population, while rates have been lower in the Netherlands. However, all these analyses are difficult to interpret since such reporting is either new or was only introduced from the pandemic (2009) onwards and hence knowledge of baselines (what is normally experienced) is limited. Similarly, there was previously no report of impact on health services.

It was fortunate that the UK has experienced some of the first effects of this year's epidemics since it has one of the more developed and timely surveillance systems worldwide. Key entry points to the results of these are the Health Protection Agency's National Influenza Weekly Reports, the Department of Health's (England) Winterwatch and their equivalents in the so-called devolved administrations[1]. In the UK the rises in community consultations were preceded by the detection of severe cases of influenza, an increase in ITU-bed occupancy and use of ECMO facilities when rates of consultations with influenza-like illness (ILI) or acute respiratory infections (ARI) were still low. This led to the UK alerting the rest of Europe. A similar phenomenon was seen in the Netherlands (see RIVM 'Griep en verkoudheid' (influenza and colds) website). This pattern of severe cases preceding obvious community epidemics might be considered unusual, though the early impact of influenza epidemics on secondary care has not been well described in any country. Subsequently in the UK, community indicators (e.g. calls to help lines) and levels of consultation in primary care rose steeply to higher levels than seen in any winter since the intense A(H3N2) winter epidemics of 1999/2000. Equivalent levels of consultations were experienced in the spring/summer wave of 2009 in England and Wales, but that was a period of intense awareness, case finding and care seeking. Trends and comparisons of consultations rates for

[1] Northern Ireland, Scotland, and Wales

illnesses that might be influenza (ILI/ARI) have to be interpreted with care as they are very sensitive to awareness by the public and doctors and media information. As a consequence, more patients with mild symptoms consult who might not ordinarily do so. Hence the 'multipliers' (the figures for converting from consultations to true incidence) can change significantly even within a season (30). Subsequently in the UK, community indicators have started to decline. Within this national pattern there have been some important regional differences as there were during the pandemic but it is not yet clear whether places that were more affected in 2009 are less affected now, as was observed in New Zealand (see below).

On 6 January 2011, there were nearly 800 patients with confirmed or suspected influenza in higher-level care (NHS critical-care beds) in England. This was equivalent to $1.4/10^5$ population and about 20% of capacity. The latter percentage statistic needs to be interpreted in the context of the national *higher-level care* (intensive care) capacity which varies considerably in Europe (2). As of 20 January, this prevalence of cases requiring care had declined to around 400 cases (see Department of Health (England) Winterwatch, 20 January 2011). The characteristics of these patients seemed similar to that seen in the pandemic and different to the prior seasonal epidemics. More than 80% of patients were below the age of 65 years. This caused some disruption to higher-level care services in some parts of the UK and led to cancellation of elective surgery, with hospitals adopting plans for dealing with increased pressures. These rates (severe influenza cases per 10^5 population) were considerably higher than what was experienced in the 2009 pandemic. The reasons for this are not clear at present but it could be because there were both A(H1N1)2009, B and other viruses circulating, or that in the pandemic, transmission in the UK was extended over a number of months, interrupted by the closure of schools in the summer (3), while now transmission is being condensed into the usual few weeks of winter epidemics (4). In addition in 2010/11 transmission is happening in the winter when incidence of other infections (including that by potentially invasive bacteria) is more common, and so this may also be increasing.

No other country is reporting the volume of severely ill influenza patients that have been seen in the UK intensive care units. However, there are specific reports of numbers of severe influenza cases, cases requiring intensive care, and deaths from Denmark, France, Ireland, and the Netherlands. In addition, six other countries (Austria, Belgium, Spain, Portugal, Romania, and Slovakia) as well as France and Belgium are reporting SARI cases to ECDC (see below for more detail). In a French hospital, the sentinel reporting system indicated that around 40% of people needing higher-level care were previously healthy and outside the risk groups (31).

The increase cannot be explained by any reduction in vaccination coverage rates in the UK. As of week 2/2011, seasonal vaccination coverage in England was reported to be little different from what was seen in 2008 and 2009, especially in the most important population: people in clinical risk groups (5) cases (see Department of Health (England) Winterwatch, 20 January 2011).

Table 1. Interim vaccine coverage in the UK (England) in 2010 compared to previous years

	Older people			Clinical risk group under 65 years		
Pandemic vaccination 2009 (14)	Not targeted			37.6%		
Seasonal vaccine (as of week 2/2011 (1))	2009	2010	2011	2009	2010	2011
	74%	72%	72%	46%	51%	48%

Characteristics of the deaths – UK and elsewhere. As of 20 January 2011, more that 250 premature deaths identified to be associated with influenza this season have been reported to the HPA. Around 80% have been people in risk groups (including those for pandemic and seasonal influenza) under the age of 65 years. Conversely, around 20% of deaths have been among previously healthy people. Only 26% have been over 64 years of age. Most cases (over 90%) have been associated with influenza A(H1N1)2009 but for about 7% the association is with influenza B viruses. All the viral isolates from severe cases that have been subtyped are matched well by the seasonal influenza vaccine (1,8). Clinical anecdotes from the UK indicate that the severe disease in adults is mostly acute respiratory distress syndrome and invasive bacterial disease. However there is reason for caution since it should not be assumed that there is no influenza-related premature mortality taking place in older people aged over 65 years. Apart from the UK, there is currently only limited information on the incidence and character of severe acute respiratory infections, mortality, case fatality rate, and risk factors for severe illness in Europe in 2010/11. However, some countries are reporting this now (see latest Weekly Influenza Surveillance Overview (WISO)). ECDC has asked all countries both for data from sentinel reporting of Severe Acute Respiratory Infections (SARI), and in addition for data from intensive care units. A number of countries (Austria, Belgium, Spain, France, Portugal, Romania, and Slovakia) are making this available to ECDC. Reports from other European countries (Ireland, Netherlands, and France) conform to a similar pattern for deaths or severe disease.

All-cause deaths. In England and Wales (UK), the Netherlands and some other countries in Western Europe, all-cause/all-age deaths rose above the expected normal upper level for the time of year. In England and Wales, this occurred for a number of four consecutive weeks (49–51). However, only a proportion of this will be attributable to influenza, and that proportion could be quite small (1). Other contributions will be from other respiratory infections and the cold weather over the Christmas period. During the pandemic, there were only changes in all-cause mortality in

some age-specific groups (6). However, in other years, increases in all-cause/all-age mortality occur regularly in winter. The last occasion being the bad A(H3N2) winter of 2008/09.

The EUROMOMO pilot project monitors age-specific mortality rates for a collection of seven EU/EFTA countries[2]. Individual country data are then put together and reported as pooled results on the EUROMOMO website. Unlike in the UK and the Netherlands, no rises were initially seen in the rates this winter as of week 2. However, it needs to be kept in mind that the countries involved were at an earlier stage of their winter epidemics than the UK (K Mobak, personal communication to ECDC).

A rise in some invasive bacterial infections – UK. In the UK, routine laboratory reporting has found recent increases in two or three of the four routinely and commonly reported invasive bacterial infections in England. These are pneumococcal infections and invasive group A streptococcal infection (iGAS). Meningococcal infections have also increased but only to a level which was seen in 2008 – after a very low year in 2009. There has been no rise in invasive staphylococcal disease. All these infections may occur as co-infections with influenza. The broad age groups from which the invasive specimens are obtained are the same as for severe influenza disease. The rise in reports of invasive group A streptococcal (IGAS) infection is above levels observed in previous winters (see UK HPA website: Group A streptococcal infections: seasonal activity 2010/11). Numbers of invasive streptococcal disease rose to 185 (a rate of $0.33/10^5$ population) in December 2010 compared with 106 ($0.19/10^5$) on average for the years from 2002 to 2008, and an annual range of 80 to 157 reports. However, it is unclear whether there is an association with influenza, and it needs to be seen whether there are any similar findings in other countries (7).

An earlier observational analysis in the pandemic period found that early use of oseltamivir was associated with a reduced risk of invasive bacterial disease (28), which in turn is consistent with a recent re-analysis of an earlier controversial meta-analysis by Kaiser et al (8,9). Further investigations are underway in the UK, but the rise was sufficient to elicit an alert to be issued by the authorities to all doctors to be on the look-out for these infections and to treat them early (UK Chief Medical Officer Alert, 10 January 2010).

Virological situation in the EU/EEA

See latest Weekly Influenza Surveillance Overview (WISO) – Week 2 2011.

Among specimens collected by sentinel physicians participating in EISN, the percentage that tested positive for influenza was 43% in week 2/2011. For combined sentinel and non-sentinel influenza positive specimens, 72% were type A and 28% were type B. Ninety-nine per cent of sub-typed influenza A viruses were A(H1N1)2009. However, there was some variation from country to country. For example France has been experiencing more B viruses than Europe overall. France (INVS) and Norway (Public Health Institute) are seeing mostly influenza B viruses.

Overall respiratory syncytial virus (RSV) detections in countries reporting to ECDC started to rise during week 44/2010 were highest during week 51/2010, but have since declined.

Since week 40/2010, 559 influenza viruses from sentinel and non-sentinel specimens have been characterised antigenically: 320 (57.2%) as A/California/7/2009 (H1N1)-like; 56 (10.0%) as A/Perth/16/2009 (H3N2)-like; 172 (30.8%) as B/Brisbane/60/2008-like (Victoria lineage); and 11 (2.0%) as B/Florida/4/2006-like (Yamagata lineage).

Antiviral resistance and use of antivirals. Since week 40/2010 in the EISN system, a total of 185 influenza A(H1N1)2009 viruses and six influenza B viruses have been tested for susceptibility to neuraminidase inhibitors. Data were provided for either single location (e.g. H275Y only) or multiple location substitution analysis (full sequencing) and/or phenotyping (IC50 determination) and should be interpreted in this context. All but two viruses out of 185 were sensitive to both oseltamivir and zanamivir. Two A(H1N1)2009 viruses from the UK had the H275Y substitution known to confer resistance to oseltamivir while retaining susceptibility to zanamivir. Both viruses were from patients who had not been known to have been treated with oseltamivir.

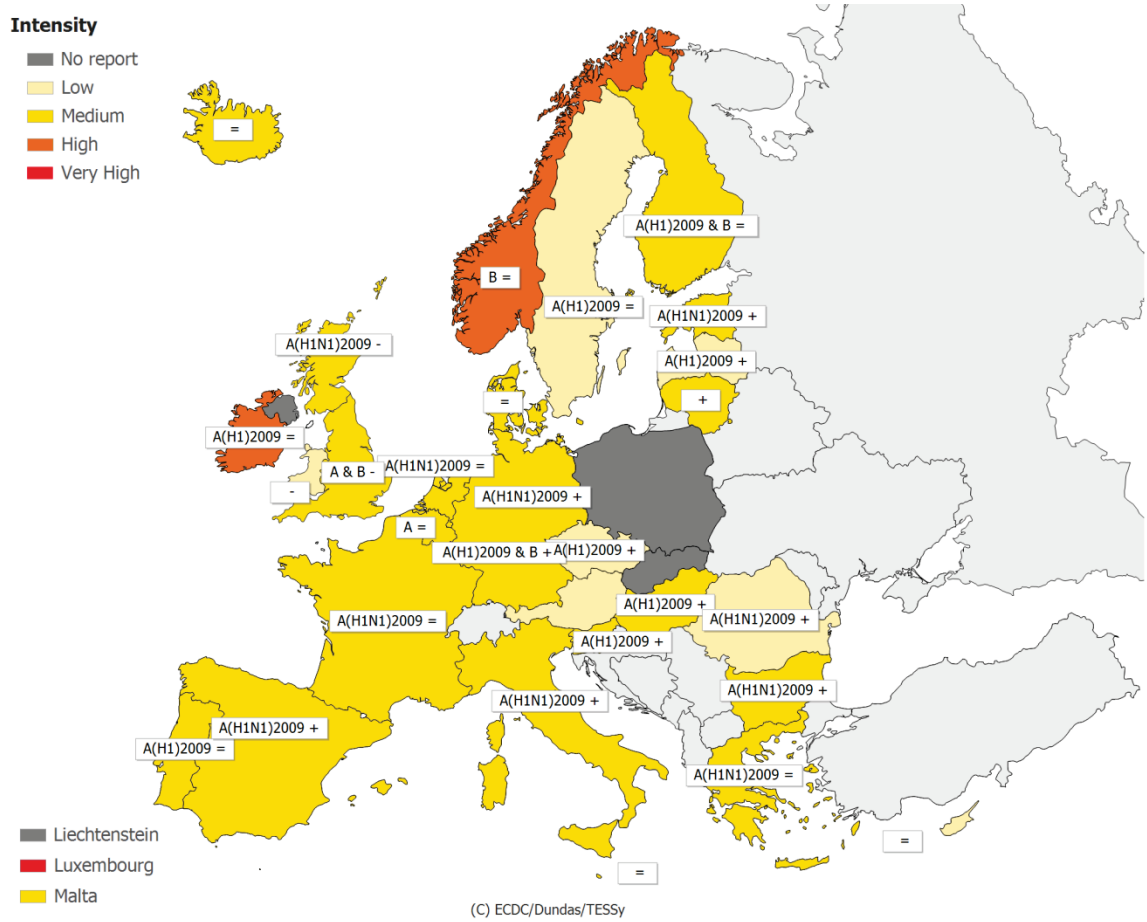
There are additional reports of antiviral resistance from the UK that have yet to enter the EISN system. In its 20 January report, the UK's Health Protection Agency included details of influenza A(H1N1)2009 viruses that had been tested for antiviral susceptibility since week 40/2010. 27 have been found to carry the H275Y mutation, which confers resistance to the antiviral drug oseltamivir. Fifty-one H1N1 (2009) viruses have been fully tested for susceptibility, one of which was found to be phenotypically resistant to oseltamivir (included in the 17), while all 51 retained sensitivity to zanamivir. In addition, three influenza A(H3) viruses and fifty-eight influenza B viruses have been fully tested for susceptibility and found to be sensitive to oseltamivir and zanamivir. Further investigations are underway to determine what proportion of the individuals have been prescribed oseltamivir. At least a proportion of these have been from individuals known not to have received antivirals, which means there are a least some freely transmitting A(H1N1)2009 viruses circulating. There has been considerable use of, and demand for, this treatment in the UK since awareness rose concerning the severe cases. Following the observation of these cases, the UK authorities encouraged the use of antivirals for early treatment, initially of those with disease in the risk groups. When it became apparent that there was a substantial proportion of severe cases and deaths in healthy individuals, doctors were given more freedom to use their discretion on whom to

treat (see HPA website, Information for health professionals. The amount of antivirals used cannot readily be quantified, but a release from a national antiviral stockpile was necessary to supplement pharmacy supplies.

Viruses from the first fatal cases in the UK have been analysed and the results published (10). No unique mutations have been associated with severe or fatal cases of influenza A(H1N1)2009. The genetic drift that has taken place has been as expected (gradual natural viral evolution). Further comprehensive analyses are underway (8).

Maps of intensity and spread, EU/EEA countries

Map 1: Intensity for week 2/2011

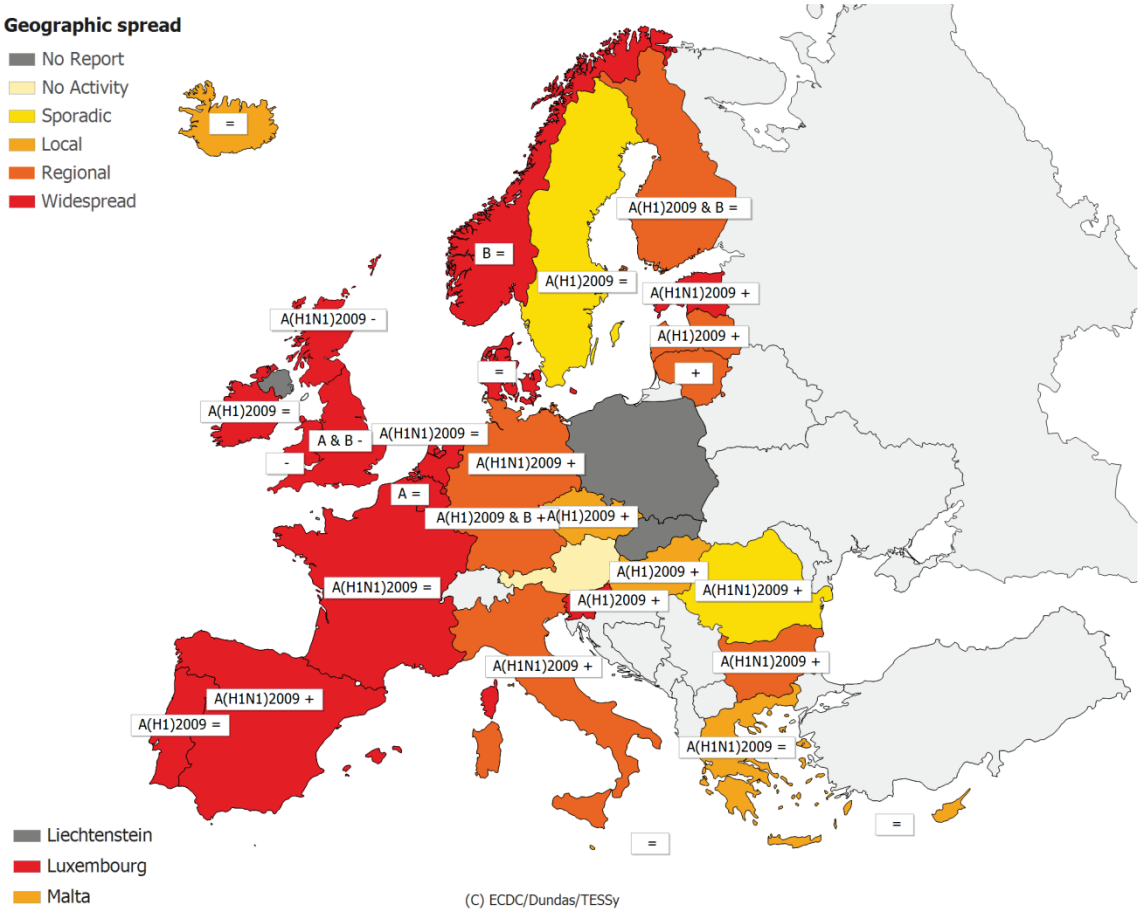


* A type/subtype is reported as dominant when > 40 % of all samples are positive for the type/subtype.

Legend:

Low	No influenza activity or influenza at baseline levels	**-**	Decreasing clinical activity
Medium	Usual levels of influenza activity	**+**	Increasing clinical activity
High	Higher than usual levels of influenza activity	**=**	Stable clinical activity
Very high	Particularly severe levels of influenza activity	**A**	Type A
		A & B	Type A and B
		A(H1)2009	Type A, Subtype (H1)2009
		A(H1)2009 & B	Type B and Type A, Subtype (H1)2009
		A(H1N1) 2009	Type A, Subtype (H1N1)2009
		B	Type B

Map 2: Geographic spread for week 2/2011



(C) ECDC/Dundas/TESSy

* A type/subtype is reported as dominant when at least ten samples have been detected as influenza positive in the country and of those > 40 % are positive for the type/subtype.

Legend:

No activity	No evidence of influenza virus activity (clinical activity remains at baseline levels)
Sporadic	Isolated cases of laboratory confirmed influenza infection
Local outbreak	Increased influenza activity in local areas (e.g. a city) within a region, or outbreaks in two or more institutions (e.g. schools) within a region (laboratory confirmed)
Regional activity	Influenza activity above baseline levels in one or more regions with a population comprising less than 50% of the country's total population (laboratory confirmed)
Widespread	Influenza activity above baseline levels in one or more regions with a population comprising 50% or more of the country's population (laboratory confirmed)

-	Decreasing clinical activity
+	Increasing clinical activity
=	Stable clinical activity
A	Type A
A & B	Type A and B
A(H1)2009	Type A, Subtype (H1)2009
A(H1)2009 & B	Type B and Type A, Subtype (H1)2009
A(H1N1) 2009	Type A, Subtype (H1N1)2009
B	Type B

International virological picture

WHO (Influenza Update – 14 January 2011); WHO Regional Office for Europe (Euroflu Weekly Electronic Bulletin, Week 1, 14 January 2011), Canada (PHAC-Fluwatch), China (CCDC), Japan (NIID), USA (CDC-FluView), EUROMOMO European Mortality Project (Weekly mortality bulletin).

The influenza virus mix observed in the EU/EEA countries has been different from that in North America and northern China, where reports show an influenza season dominated by A(H3N2) and B viruses. Most recently though there has been a report of increasing proportions of A(H1N1) in Japan and South Korea ,though not in northern China (southern China has more of an equatorial pattern of influenza transmission) (WHO Report, 14 January). No reports of significant impact on health services have come to WHO at regional or global level equivalent to that which has been seen in the UK. However, it has to be kept in mind that reporting of impact on health services is relatively new and difficult to interpret (see WHO Influenza update – 30 December 2010).

Likely immunity to circulating viruses: natural and acquired immunity – serosurveys

There are limited contemporary seroepidemiologial data published and only for A(H1N1)2009 antibodies for a few countries (Finland, Norway, UK) Hence a comprehensive serological analysis for European vulnerability is not possible. Also some of the results are confusing or difficult to interpret. For example in Norway in the over-70 year age group there were only about 10% of persons with antibodies to A(H1N1)2009 before the pandemic(11). However there were very few cases in that age group in Norway (Norway: risk assessment). Clearly there is more to immunity to influenza than is reflected in simple influenza antibody seroprevalence surveys.

Some idea of the duration of anti-body based immunity may also be inferred from the Norwegian serosurveys where population seroprevalences (HAI >= 20) of 7 %, 59 % and 45 % were found for August 2009, January 2010 and August 2010, respectively (the figures for HAI >=40 were 3%, 45 % and 26%) (Norway: risk assessment). This indicates some sustained duration of protection is likely at this time.

An international review by WHO after the 2009 pandemic suggested that between 5% and 60% of populations in different continents across the age groups had antibodies against the A(H1N1)2009 virus. The seropositivity was highest in children and teenagers (20-60%) as well as in the elderly older than 80 years (20-40%). Pre-existing or cross-reactive antibodies against the virus are present mostly in sera of older people born before the late 1950s that could have encountered the 1918 pandemic influenza A(H1N1) virus(12). These data remain difficult to interpret for a number of reasons, different in testing methods and standards and whether the presence of antibodies excludes other non-humoral protection, such as cell-based immunity. However one important point is that the second round of serology in the UK indicated enough susceptibility to support the observed transmission(13).

Vaccine coverage

Further information relevant to particular vulnerabilities in Europe can be inferred from the coverage of seasonal and pandemic vaccines, especially among the risk groups experiencing severe illness this season.

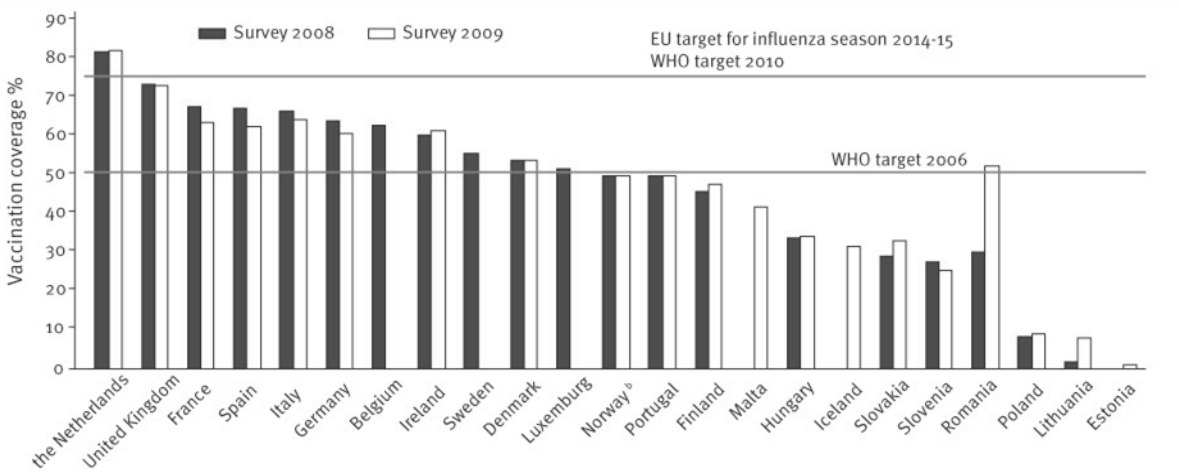
Seasonal influenza vaccines in use include antigens for the A(H1N1)2009 influenza virus, A(H3N2) and a B virus. Seasonal influenza vaccination coverage in risk groups in EU/EEA countries has been variable in earlier years and such variability can be expected to be present also during the current 2010/11 season (see Figure 1 for older people). Coverage among the people in the clinical risk groups is less well known but where data are available it is always lower than in older people in the same countries.(14-15) The current coverage rates in Europe for the new trivalent seasonal vaccine will not be known ahead of the annual VENICE survey later this year except for some countries that can report in season such as the UK where the coverage rates held up well (see above). However, given the poor experience with pandemic vaccination in some other countries (Figure 3) and controversy over even the need for pandemic vaccination, it may be that coverage may not be as good in 2010 as in previous years. Given that the coverage in the clinical risk groups is usually below 50% in countries that can measure this, it is most likely that there are many people in these groups in Europe that did not receive the new seasonal vaccine in 2010.

Pandemic vaccine A(H1N1)2009 coverage rates among Member States in the EU were highly variable, ranging from zero to over 60% of the population (see Figures 2 and 3) (14). This indicates that there are four Nordic countries that could have significant population protection against A(H1N1)2009, especially when naturally acquired infection is added in. It is not yet established how enduring the protection is conferred by pandemic vaccination. Similarly it is unclear whether the herd immunity though vaccination, natural and acquired immunity will be sufficient to reduce transmission compared to what is seen in countries which took the approach of protecting those most at risk.

However countries with overall low coverage of clinical risk groups will seem more likely to experience higher numbers of severely ill patients than those with higher coverage. This seems to be especially likely given the high effectiveness of the pandemic vaccine in preventing infection (see below).

Again, as for seasonal vaccination there will be many people in the clinical risk groups who were not immunised with the pandemic vaccine in 2010 (Figure 3).

Figure 1: Vaccination coverage for seasonal influenza among the elderly in EU/EEA countries: national seasonal influenza vaccination surveys in Europe, January 2008 and July 2009.



WHO: the World Health Organization.

[a] For 23 EU/EEA Member States.

[b] Vaccine coverage calculated for the over 65 age group and clinical risk groups together.

Vaccine coverage data for Survey 2008: Belgium – 2003-4 influenza season; Germany, Poland – 2005-6 influenza season; the remaining countries – 2006-7 influenza season.

For Survey 2009 all countries reported vaccination coverage data for the 2007-8 influenza season.

The age limit for elderly varies by country from between 50 and ≥65.

Source: Mereckiene J, Cotter S, D'Ancona F, Giambi C, Nicoll A, Levy-Bruhl D, et al. Differences in national influenza vaccination policies across the European Union, Norway and Iceland 2008-2009 . Euro Surveill. 2010 Nov 4;15(44). Available from: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=19700

Figure 2: 2009 pandemic vaccination coverage in the population of 21 EU/EEA countries, VENICE survey 2010.

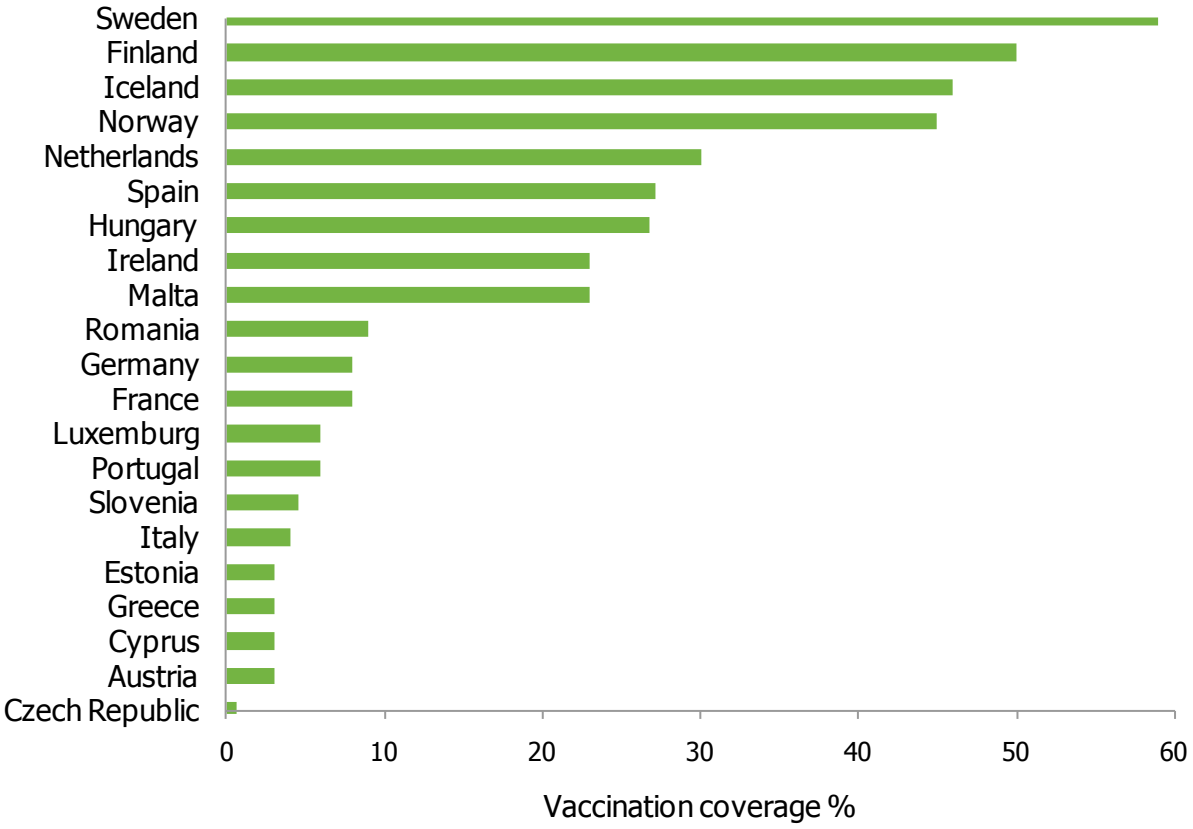
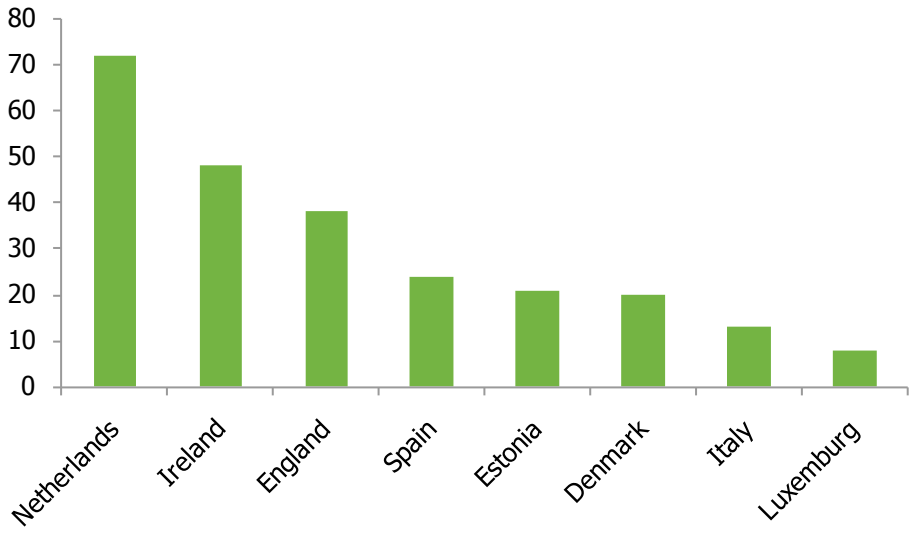


Figure 3: 2009 pandemic vaccination coverage in the at-risk population of eight EU/EEA countries, VENICE survey 2010.



These data suggest that unless there has been very widespread infection (which is not supported by the serological data) there are many vulnerable people out there in Europe.

Impact on health services

As yet the UK has a unique experience in terms of both pressures in primary care, hospital pressures and impact on all-cause/all-age mortality (though that certainly will not just reflect influenza potential: additional factors contributing to this excess include recent cold weather and other circulating respiratory viruses(2)). The main pressure has been on the hospitals, and they have coped, albeit with some use of emergency plans. Although primary care consultation rates have risen, they are reported to be manageable. Other EU countries have reported growing pressure on intensive care (France, the Netherlands and Denmark) but nothing that cannot be managed, and overall pressure is less than in the UK.

The southern hemisphere experience

Looking to the southern hemisphere countries and the winter they experienced in mid-2010, the most obvious similarities are to New Zealand which uniquely had a winter entirely dominated by A(H1N1)2009, though its level of hospital activity was less than in its pandemic winter (2009) (16). A notable comment from the New Zealand winter was that – although overall the numbers of severely ill cases were lower than in the pandemic winter of 2009 – there were regional and local differences, with a tendency for places that were affected less in the 2009 winter to be more affected in 2010 (32).

The southern hemisphere experience in 2010 (the first winter with seasonal influenza after the pandemic) was variable. Both Chile and Australia experienced later epidemics of A(H3N2) and B viruses, following initial transmission of A(H1N1)2009, so that should be considered a possibility for Europe (16).

Likely effectiveness of countermeasures including vaccination and antivirals

There is no reason to expect that the normal trio of personal countermeasures (early self-isolation of those with symptoms, respiratory hygiene, and regular hand-washing) will be any more or less effective this season (see ECDC health information: Personal protective measures for reducing the risk of acquiring or transmitting human influenza and WHO). Equally, the usual immunisation of healthcare staff and infection control measures (stringent measures including mask wearing, according to national and local guidance) will be important in some healthcare settings.

According to the antigenic characterisation data available through the EISN and data recently published in Eurosurveillance, the influenza A(H1N1)2009, which is currently circulating in Europe, is antigenically homogeneous and similar to the A(H1N1)2009 virus included in the 2010/11 seasonal influenza vaccine (10), i.e. the vaccine and the circulating virus match well.

Estimates of pandemic vaccine effectiveness in Europe showed good protection conferred by the vaccine, as would be expected when a good match is present between the vaccine strain and the circulating virus. Estimates of vaccine effectiveness from field epidemiology varied by age and risk group, but were all above 70% (17-20)(21-22). An

especially important finding is that some protection was apparent even a week after vaccination. These studies, with the exception of a small study done in in Castellón, Spain (21), mostly had mild influenza illness as the endpoint.

An important factor for analysis is the vaccination history among those with severe disease or those who have died from influenza. This is being looked at first in the UK. As of week 3, a report by the HPA of fatal cases with available information on immunisation history states that 59 of 71 (83%) cases had not received 2010/11 trivalent influenza vaccine this season. Thirty-eight of 40 cases with available information had not received monovalent pandemic influenza vaccination last season. This is much less than what would be expected by chance, given the reported coverage of vaccination in the clinical risk groups with the pandemic and seasonal vaccines in 2009 and 2010 respectively (Table 1). Hence these findings are compatible with results that describe the vaccines as protecting against fatal outcome as well as mild disease. Studies to estimate vaccine effectiveness for the 2010/11 trivalent vaccines are currently ongoing in eleven EU countries as part of the I-MOVE collaboration. Preliminary results from a large I-MOVE cohort study involving 152 581 individuals (2010/11 seasonal vaccine coverage: 34%) in one region of Spain shows good protection against medically attended ILI and ILI (confirmed as influenza induced) by the 2010/11 vaccine during the period week 43/2010 and week 2/2011 (Dr Jesús Castilla, personal communication to ECDC, January 2011).

Although having received pandemic vaccine last season is expected to provide some protection against the currently circulating A(H1N1)2009 virus, there is no precise estimate on how effective previous pandemic vaccination will be in protecting individuals in different age and risk groups or what effect it might have on transmission.

There are a number of observations from the pandemic indicating that early use of antivirals was associated with a better outcome in people with influenza disease due to A(H1N1)2009 than people who did not receive antivirals or received them later (23,24). Though even late application was associated with improved survival and less likelihood of admission to an ITU (24,25). Also, a formal re-analysis of an earlier and latterly controversial meta-analysis of trial data by an independent group has essentially reproduced the earlier findings (8,9).

Safety of interventions

There is no indication of any Adverse Event Following Immunisation (AEFI) safety signal related to the 2010/11 trivalent seasonal influenza vaccines being used in EU. For the monovalent 2009 pandemic vaccines)which are currently hardly being used in the EU apart from in the UK), multicountry investigations of two signals associated with the pandemic vaccine are underway concerning Guillain-Barré Syndrome (GBS) and narcolepsy in children. The results of the GBS study are reassuring (they are yet to be published). Work on a narcolepsy signal is underway. This is almost entirely involving children immunised with one product. The signal is predominately from two Nordic countries (Finland and Sweden). A preliminary review on the narcolepsy signal undertaken by the European Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency concluded there was no convincing evidence of additional risk at this stage though additional research was needed (33). Such work is underway, funded by ECDC. There have been no convincing adverse event signals reported for the neuraminidase inhibitors the antivirals used in Europe (34).

ECDC scientific and public health advice

What countermeasures do these scientific and public health data and analyses support?

Vaccination. Since there are many people unvaccinated in the clinical risk groups, there will be advantages to continuing vaccination particularly for these persons. This seems especially advantageous in view of findings:

- that the A(H1N1)2009 vaccines are effective and very safe;
- that they protect against fatal disease outcome as well as mild disease; and
- that protection starts in as short a period as a week after vaccination.

It also should be recognised that there may be vaccine availability, logistical and administrative issues that make implementation of this policy difficult in some settings.

Antivirals. The available data support the early use of antiviral treatment in all those presenting with severe influenza-like illness pending virological confirmation, and in those with risk factors with milder disease.

The occurrence of severe disease and even deaths in entirely healthy adults and children poses a problem. If it was felt that all people with early infection should be treated, the amount of antivirals that could be used would be considerable.

Higher-level care. The early experience makes it seem prudent to alert hospital – and especially intensive healthcare services – of potentially increased numbers of influenza patients needing hospital care/intensive care in the next few weeks, even though it is not clear as to whether this surge will materialise and at what level.

A number of the countries affected early this season have already pursued or re-emphasised these measures.

Invasive bacterial infections. While the association between the influenza epidemics this year and the rise in two or three types of bacterial infections in not proven, clinicians could usefully be alerted to be vigilant to the possibility of the appearance of severe illness due to invasive bacteria, including invasive group A streptococcal, pneumococcal and meningococcal infections. They could also be made aware of the possibility of such bacterial co-infection in people with

flu-like illness. One of the implications of this is the benefits of giving antivirals as well as anti-bacterial agents to such patients. There is some support for this from trials and observational analyses (8,9,28).

Clinical networking. To use clinical networks for surveillance, evaluation and sharing of clinical experience (26).

Interpretation of the current situation, specific questions, remaining uncertainties, and priorities for further investigation

Q1. How likely is it that the initial experience in the first affected country (UK) will be replicated in other EU/EEA countries in terms of a) the pattern of infection and b) the impact on the health services?

The picture that emerged in the UK in December, with stress on higher-level care (1.4 prevalent cases/10^5 population due to influenza) when community consultation rates were low, seems unusual. It is a new development in Europe to gather hospital epidemiology on influenza patients, and so it is hard to state what is and what is not normal. However, this could be consistent with the characteristics of the A(H1N1) virus: mild disease in most, but very severe disease in a very few.

The first affected country managed to cope through some reconfiguring of services and activation of reserve plans. It should be borne in mind that it does not take very many severely ill patients to strain and disrupt higher-level services, especially when added on top of other 'winter pressures'. Also, such pressures have to be considered against the provisions of higher-level care beds and 'surge capacity', which vary considerably across Europe (26-27). A plausible reason this season is resulting in greater stress than the pandemic 2009 is that instead of being stretched out over six months, interrupted by the school summer holidays, the period when influenza transmits intensely is now being compressed into a normal six to eight weeks in the winter when there are additional possible contributing factors of cold weather and circulation of other respiratory viruses.

The increased circulation of influenza A(H1N1)2009 and B viruses will have contributed to the excess all-cause mortality in a number of consecutive weeks: 49/2010 to 1/2011 observed in the UK (England and Wales), the Netherlands and elsewhere. However, other respiratory diseases and cold weather will also have contributed, probably more so. While no excess all-age/all-cause mortality was detected during the 2009 pandemic, waves of such excesses are quite common in other winters in Europe. What is especially uncertain this season is the extent of severe disease and mortality among older people (aged over 65 years) where diagnostic tests are less used and reporting of individual cases is weak (35).

The observation of a number of influenza cases requiring admission to an ITU is relevant and shows that preparations may be advisable to deal with the increased demand for high-level treatment during this winter's influenza epidemics. Although the UK authorities feel what they are seeing is unusual, it will be difficult at present to entirely verify that numbers of admission are higher than what was seen during previous influenza seasons in the absence of historical data and dedicated surveillance systems for monitoring incidence of severe cases in hospital.

What can be anticipated for the rest of the season? (20 January 2011)

In the past, a rough progression of increased influenza incidence from west to east and from north to south has been observed in Europe, though the trend usually breaks down as transmission moves further east (4). This pattern of spread is occurring also in the 2010/11 season. Most of the countries are currently experiencing increased reporting of ILI/ARI but epidemics are more advanced in the western countries (see Maps 1 and 2). It should be expected that in the coming weeks increased levels of ILI/ARI consultation rates will be observed in the rest of Europe. Influenza activity will intensify in countries that have not yet reached their peaks.

However it simply cannot be determined whether countries will experience higher or lower incidence of severe cases than the UK. On the positive side, the evidence that higher levels have not happened to date would seem to be reassuring. It could be that the UK simply experienced two or three pressures coinciding (influenza, other respiratory viruses, and very cold weather) though why this should affect people in a certain age group more than others is difficult to explain. Increased ILI/ARI consultation rates usually last for four to six weeks at national level, but there are variations from year to year and between countries. It also needs to be recalled that hospital pressures usually lag behind the ILI/ARI consultation rates by one to two weeks. Equally, no country epidemics have been running this year as long as the UK's, which began around week 47/2010, and it could be the experience is yet to come in some other countries. Also on the positive side, there are the four Nordic countries that vaccinated well and should have higher levels of protective immunity (Figure 2). On the negative side, there should be a number of countries with considerably lower numbers of immunised people than the UK (14).

Heightened need for hospital care at higher levels of dependency may be experienced in some countries. On the other hand, the levels of immunisation in the UK with seasonal vaccines are higher than in most countries. Given the predominance of influenza A(H1N1)2009 and B Victoria lineage in the current season, and given the preliminary surveillance data available, it is expected that the 2010/11 influenza season is characterised by a more similar epidemiology to that observed during the pandemic waves in 2009/10 than the previous seasonal influenza.

Whether there will be changes in the predominant viruses in European countries this season cannot be anticipated at this stage. In the southern hemisphere 2010 winter, two countries (Australia and Chile) experienced late A(H3N2) waves, while it is quite often observed that B viruses come to predominate late in some influenza seasons (16). Equally though in New Zealand the dominant viruses throughout were A(H1N1)2009. This northern hemisphere season, the predominant A virus has just changed in Japan from A(H3N2) to A(H1N1) (see NIID website). The only consistent finding is that the old pre-2009 A(H1N1) virus is entirely absent this season. Hence the importance of protecting against all three viruses in the seasonal vaccine 2010. This is relevant as there are stocks of pandemic vaccine remaining in Europe, and at least one country (the UK) had to use these due to problems in distribution and supply of seasonal vaccines (36). Since the majority of severe disease is due to A(H1N1)2009 that is certainly the most important antigen to vaccinate with if no seasonal vaccine is available. However, the evidence available suggests that seasonal vaccine 2010 would be the preferred option.

Q2. Has there been any change in the virology of the A(H1N1)2009 viruses?

To date there is no evidence of a significant change in the circulating viruses (11) (see Weekly Influenza Surveillance Overview (WISO) – Week 3 2011.).

Q3. Has there been any emergence of antiviral resistance?

Some resistant A(H1N1) 2009 viruses have emerged almost entirely of the A(H1N1) H275Y type associated with oseltamivir resistance (37) (see also UK HPA Weekly National Influenza Report, 20 January 2011 – Week 3). This needs careful attention to determine if there are growing numbers of transmitting resistant viruses.

Q4. What is likely to be the effectiveness of influenza vaccines and antivirals?

To date there has been no change in the virology, and the effectiveness of the current vaccine should be good. Whether it will be as high as in 2009, with a non-adjuvanted vaccine being used now, remains to be seen. The same is true for the expected effectiveness of antivirals, although the low but increasing numbers of resistant viruses will need close study.

Q5. Can changes in the viral mix be anticipated later this season?

This is a possibility that should not be dismissed. Some seasons B viruses emerge and predominate, and in two southern hemisphere countries epidemics of A(H3N2) followed waves of A(H1N1). This would support the use of trivalent seasonal vaccines over pandemic vaccine unless there is none of the former available.

Q6. Is the observation of increased incidence of two types of invasive bacterial infections in the UK of importance and likely to be related to influenza?

This is an important question but it is not one that ECDC can answer directly as it does not yet receive data on these infections. It will need to be tackled at a Member State level. It is important as early care and treatment can be crucial, and there are some data compatible with early antiviral treatment being associated with a better outcome (28).

Q7. Is an observed rise in all-cause/all-age mortality observed in a number of the Western European countries likely to be related to influenza?

Influenza will certainly have made a contribution but it may only be a minor one.

Other uncertainties

It is uncertain whether influenza attack rates in older people who were relatively spared during last season will continue to be low also during the 2010/11 season.

Though there have been anecdotal reports of severe disease due to A(H1N1)2009 in pregnant women in Europe and there are strong studies from the USA, there is a lack of analytic studies showing this in Europe. It is also important to be able to distinguish between healthy pregnant women, and pregnant women with underlying disease.

Evaluation of severity, based on indicators such as case fatality rate, case hospitalisation rate, SARI incidence, excess all-cause and P&I (pneumonia and influenza) mortality are missing, and this does not allow a proper assessment of this season's influenza as yet.

Next update

We will review this risk assessment in two weeks' time with a view to updating. For more information, please contact: influenza@ecdc.europa.eu, where comments on this Risk Assessment are also invited.

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