



SPECIAL REPORT

The 2009 A(H1N1) pandemic in Europe

A review of the experience

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Suggested citation: European Centre for Disease Prevention and Control. The 2009 A(H1N1) pandemic in Europe . Stockholm: ECDC; 2010.

First published November 2010

Revised December 2010: Number of deaths reported to ECDC as quoted on page 27 was corrected from 2900 to 1975

ISBN 978-92-9193-225-2

doi 10.2900/35415

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Table of contents

List of figures/List of tables	iv
Executive summary	1
1 Introduction	3
1.1 Background	3
1.2 Previous influenza pandemics	4
1.3 Interpandemic influenza	5
1.4 First reports of the 2009 influenza A (H1N1) pandemic	6
2 Methods	8
2.1 The interpandemic influenza surveillance systems in the EU/EEA	8
2.2 The influenza surveillance systems reinforced for the pandemic	8
3 Results	12
3.1 Epidemiology and virology of the recent interpandemic flu in European Union and European Economic Area countries.....	12
3.2 Epidemiology of the 2009 pandemic in the EU/EEA countries.....	14
3.3 Detailed analyses of the initial cases	18
3.4 Virology of the novel virus	20
3.5 Antiviral susceptibility.....	22
3.6 Variants, severe disease and D222G substitution	24
3.7 Pandemic influenza and interpandemic influenza—similarities and differences.....	24
3.8 Severity of the pandemic.....	25
3.9 Hospital sentinel surveillance of severe acute respiratory infection cases	25
3.10 Mortality attributable to influenza and disease burden.....	26
3.11 Epidemiologic parameters of the pandemic for modelling and forecasting	28
3.12 Clinical attack rates, case fatality rates and planning projections.....	29
3.13 Performance of the influenza surveillance systems during the pandemic.....	29
4 Discussion: European preparation and response.....	31
4.1 Adjusting the prepared responses.....	31
4.2 Personal measures.....	31
4.3 Containment and mitigation.....	31
4.4 Effectiveness of seasonal vaccines against the pandemic virus	32
4.5 Limitations of this EU/EEA data	33
5 Conclusions and lessons learned.....	36
5.1 Main conclusions	36
5.2 What next?.....	40
References.....	41

List of tables

Table 1: Data collected for the EU/EEA Weekly Influenza Surveillance Overview

Table 2: Antiviral resistance by influenza virus type and subtype, over the last two seasons (weeks 40/2008–18/2010) in samples collected by primary care sentinel networks in the EU/EEA.

Table 3: Planning projections - summary of impact to prepare for a reasonable worst case over the course of the first year of the pandemic. (ECDC and EU/EEA countries, November 2009)

Table 4: What was positive about the 2009 A(H1N1) pandemic for Europe and what could have been worse

List of figures

Figure 1: Recent human influenza pandemics, 1898 to 2009.

Figure 2a: Portugal: distribution of sentinel ILI notification rates, last two seasons

Figure 2b: Bulgaria: distribution of sentinel ARI notification rates by age group. Week 16/2009 to week 16/2010

Figure 2c: France: distribution of sentinel ARI notification rates, last two seasons

Figure 2d: Belgium: distribution of sentinel ILI notification rates by age group. Week 16/2009 to week 16/2010

Figure 3a: Trends of the ILI consultation rates per 100 000 population; UK (England), 1996/97 to 2009/2010

Figure 3b: Trends of the ILI consultation rates per 100 000 population, Spain, 1996/97 to 2009/2010

Figure 4: Geographic spread of influenza in Europe in week 3/2009

Figure 5: Percentage weekly reported sentinel ILI caseload, cumulative for 25 MS (weeks 40/2008 to week 15/10).

Figure 6: Frequency of countries reporting their peak sentinel ILI consultations in the autumn/winter waves by week, seasons 2008/9 (n= 23 ILI reporting countries) and 2009/2010 (n= 24 ILI reporting countries)

Figure 7: Comparison of the distribution of sentinel ILI notification rates between the UK and The Netherlands (seasons 2008/2009 and 2009/2010).

Figure 8: Distribution of EU/EEA sentinel ILI (n=724038, 20 countries) and ARI (n=5831365, 10 countries) notification rates per 100 000, by age group, wk16/2009 to wk16/2010.

Figure 9: Reported laboratory confirmed cases of the 2009 pandemic influenza in EU/EEA, by week of onset of disease, from week 16 to week 39/2009 (n=8328).

Figure 10: Distribution of the number of sentinel samples submitted and the percentage found positive for influenza, seasons 2008/2009 to 2009/2010, 28 EU/EEA countries.

Figure 11: Distribution of virus types isolated from sentinel samples, seasons 2008/2009 and 2009/2010 in the EU/EEA.

Figure 12: Number of SARI cases by week of onset in nine EU countries, season 2009/2010 (n=8443)

Figure 13: Officially announced and reported deaths due to 2009 pandemic A(H1N1) in the EU/EEA, by week of report, season 2009/2010.

Figure 14: Cumulative confirmed fatal 2009 pandemic influenza A(H1N1) cases (announced and reported deaths), by reporting EU/EEA Member State, as of week 17, 2010.

Figure 15: Global pandemic (H1N1) 2009 vaccine: Planned vs actual production (As of 10 January 2010).

Executive summary

This extended report aims to provide a broad overview of the epidemiology and virology of the 2009 pandemic in the European Union and European Economic Area (EU/EEA) countries (27 EU Member States (MS) and Norway and Iceland). Relevant background information on influenza epidemics and pandemics, notably their variability and unpredictability, is provided. The main trends and information are derived from the analysis and interpretation of the epidemiological and virological data and other analyses provided to the European Centre for Disease Prevention and Control's (ECDC) European Surveillance system (TESSy) through the European Influenza Surveillance Network (EISN).

These data and analyses show that, following its emergence in North America, the pandemic virus started to be transmitted in Europe around week 16/2009. This virus met the previously determined criteria for a pandemic in Europe as it did elsewhere. Surveillance suitable for the pandemic was rapidly developed and agreed upon by ECDC and the EU/EEA MS, with input from the World Health Organization (WHO) and countries already affected from outside Europe. This built on pre-existing systems, but included new elements to monitor the situation among those severely affected by the pandemic virus. In addition, epidemic intelligence and targeted science-watch methods were employed to determine, as early as possible, important parameters needed for informed risk assessments, adjusting projections and informing counter-measures.

The European Influenza Surveillance Network reported an initial spring/summer wave of transmission that appeared in most countries, but was only striking in a few countries, especially the United Kingdom. The rate of transmission briefly subsided as the summer progressed, but then accelerated again in the early autumn just after the re-opening of schools. This time it affected all countries, as an autumn/winter wave was seen to progress from west to east across the continent. The World Health Organization officially declared the pandemic over in week 32 of 2010.

In most countries, the autumn/winter wave of infection was sharp in shape, lasting approximately 14 weeks and was accompanied by a similar wave of hospitalisations and deaths. However, there was heterogeneity in the severity of disease as it varied from place to place, even within countries. In all, 2900 official deaths were reported by EU/EEA countries in the first 12 months during which the MS made extra efforts to collect these data. However, it is recognised this will be only a proportion of the true burden of deaths due to the pandemic. An excess of all-cause deaths in school-aged children was detected. Though this was an influenza virus never seen previously, prior exposure to a presumably antigenically similar influenza virus circulating before the mid-1950s ensured that many older people in Europe had some prior immunity. This fact, not unique to the 2009 pandemic, explains two of its notable differences from interpandemic, or seasonal, influenza: the overall lower mortality and the higher than expected relative burden of illness and fatality rates in young people. Though many older people appeared to be protected, those that were not showed the highest case fatality rates of any age group.

The pandemic virus displaced the previously dominant interpandemic influenza A viruses in Europe; though influenza B viruses still appeared at a low level late in the season. Only a low number of pandemic viruses were found to be resistant to oseltamivir and of these, very few seemed to be capable of being transmitted from one human to another. Though the pandemic viruses are not identical, there is little evidence of significant drift or the emergence of dominant new variants to date. One variant—A(H1N1)-D222G—has been suggested to be associated with more severe disease, though causation has not been established.

Although anecdotal evidence suggests that there were more mild and asymptomatic cases in comparison to the interpandemic influenza, there were enough cases of acute respiratory distress syndrome (ARDS)—a condition very rarely seen with interpandemic influenza—to stress intensive-care services in many places. Young children experienced the highest rates of disease, and country reports reveal that the highest rates of infection were in school-aged children. These high rates of illness passed particular burdens onto primary services, hospital paediatric services and especially intensive-care units in some localities.

Some limited data from serological surveys are now becoming available and support the surveillance data indicating higher rates of transmission than suspected from the clinical signs. However, these are not yet sufficient to make reliable predictions concerning what will happen next winter (2010/2011), and for this purpose the experience of the Southern Hemisphere temperate countries in the European summer period of 2010 has been most revealing.

At an early stage, the pandemic was much less severe than what had been feared. This was highlighted in the early ECDC Risk Assessments*, WHO reports and briefings given by ECDC to national and European authorities. With low rates of absenteeism, there was also little impact on services outside of the health sector. This and other features meant that this was arguably the most benign pandemic for which Europe could have hoped.

* Available here: http://ecdc.europa.eu/en/healthtopics/H1N1/risk_threat_assessment/Pages/risk_threat_assessment.aspx

As the 2009 pandemic was less of a threat than what many countries had prepared for, this tested the flexibility of existing plans. It occurred at a time when diagnostic tests were made quickly available, as were preventive pharmaceutical countermeasures like antivirals—which have little resistance to the neuraminidase inhibitors but almost complete resistance to older adamantanes—and appropriate vaccines that were developed quicker than ever before. Still, each of these developments brought their own problems and there were new challenges and surprises. As mentioned previously, there was a higher than expected rate of ARDS at a time when many intensive care units were already under pressure, without the rest of the hospitals necessarily being stressed. A more welcome surprise was that the rapidly prepared pandemic vaccines showed such a good immunological response that for many of the formulations only a single dose was needed in adults. They have also proved to be effective and acceptably safe, though post-marketing surveillance still needs to be maintained to determine exactly how safe they are. When the vaccines were made available they were greeted with variable enthusiasm to vaccinate among the health professionals. Reliable coverage data on an EU level are not yet available, but the impression is that coverage will be highly variable across Europe, with only some countries achieving high coverage among the whole population or targeted risk groups.

The lack of widespread acceptance of this vaccine is partly due to the difficulty in transmitting the complex risk communication message that essentially told people that unless they were in a risk group (young children, people with chronic ill health and pregnant women), the chance of severe disease following infection was very low. However because 25–30% of official deaths were in previously healthy people under 65 years of age, the second message was that there was a small but real risk of severe disease and death from the pandemic in all healthy adults and children. The challenges of risk communication were therefore considerable.

On balance, it is probably fair to say that the EU/EEA managed the response to the pandemic reasonably well. No country over-responded, while the systems developed by the Commission, WHO and ECDC for discussing and sharing information and analyses proved resilient and useful. The EISN virological and primary care-based surveillance worked well and served to augment the data emerging from the ECDC epidemic intelligence and targeted science watch sources. Less successful was the sharing of analyses from the countries first affected and it was fortunate that data and analyses were quickly available from North America and the Southern Hemisphere. Despite the many reviews and lessons-learned activities already underway, there are some general lessons that have become immediately apparent:

- agreed definitions of the severity of a pandemic are needed to improve the flexibility of preparedness plans;
- routine surveillance systems established prior to the pandemic will ensure that much less will need to be modified in a crisis, or even a pandemic;
- there should be better routine 'severe end' surveillance of people in hospitals and deaths;
- in the future, sharing early analyses from the first affected countries needs to work better;
- much work, including research and development, needs to take place to make seroepidemiology available in real time; and
- modelling during a pandemic should be more closely related to policy and operations across Europe, not just in one or two countries.

Pandemic planning will now need to be revisited as the occurrence of this pandemic does not exclude the possibility of another pandemic emerging in the near future; an H5 or H7 pandemic, for example. The next generation of plans need to include more flexibility for reacting to different severities and different combinations of ECDC pandemic 'known unknowns' (see section 1.4). This would be more feasible if some consensus on a European view of assessing severity was reached, matching levels of response to different scales and characteristics. These next plans must also provide for the consolidation and sustainability of the influenza surveillance systems introduced to meet the demands of the pandemic; in particular, severe acute respiratory infections, attributable mortality and, eventually, seroepidemiological surveillance. This surveillance work needs to be prioritised, given the right level of resources and subsequently allowed to develop and be tested during the interpandemic period so that they will be more resilient and effective by the time the next major crisis appears.

1 Introduction

This review describes the development, epidemiological course and initial response to the 2009 pandemic of influenza A(H1N1) in 27 European Union (EU) and two European Economic Area (EEA) countries (Norway and Iceland). This overview describes how and why pandemics emerge and gives some background on the virus, comparing the main features of the pandemic with those of interpandemic influenza. This report especially focus on the analyses of influenza surveillance data from 2008 to 2010 in the EU/EEA and uses these to indicate what has been learned about the important 'known unknowns' (see section 1.4) that have to be determined for every pandemic. Also, it broadly explains the impact of the pandemic and, in chronological order, some of the interventions that were undertaken in the EU/EEA, including the application of pharmaceutical (anti-viral and immunisation) policies, public health measures and the initial analyses of vaccine and antiviral safety and effectiveness. The review also identifies what has yet to be determined, including vaccine coverage and estimates of clinical morbidity and of premature death or years of life lost. This review is supported by a number of accompanying materials and downloadable slides on the ECDC web-site* including a structured time line, dynamic and static maps, and graphics showing the progression of the pandemic in terms of illnesses in the community and deaths. While not considering the lessons learned in detail, some observations on these are made in the conclusions.

This review includes a selection of the relevant scientific and grey literature (both published and country or agency reports) that were already collected and reviewed by the expanded influenza team at the European Centre for Disease Prevention and Control (ECDC) during the course of the pandemic. The analyses of the epidemiological and virological data presented here are a more extended examination than is usually available and published in the routine ECDC reports such as the Weekly Influenza Surveillance Overview (WISO). The WISO is produced with the data reported by the nominated disease specific experts in 29 EU/EEA countries that together make up the European Influenza Surveillance Network (EISN)[†], including the nominated virologists contributing to the Community Network of Reference Laboratories (CNRL)[‡].

1.1 Background

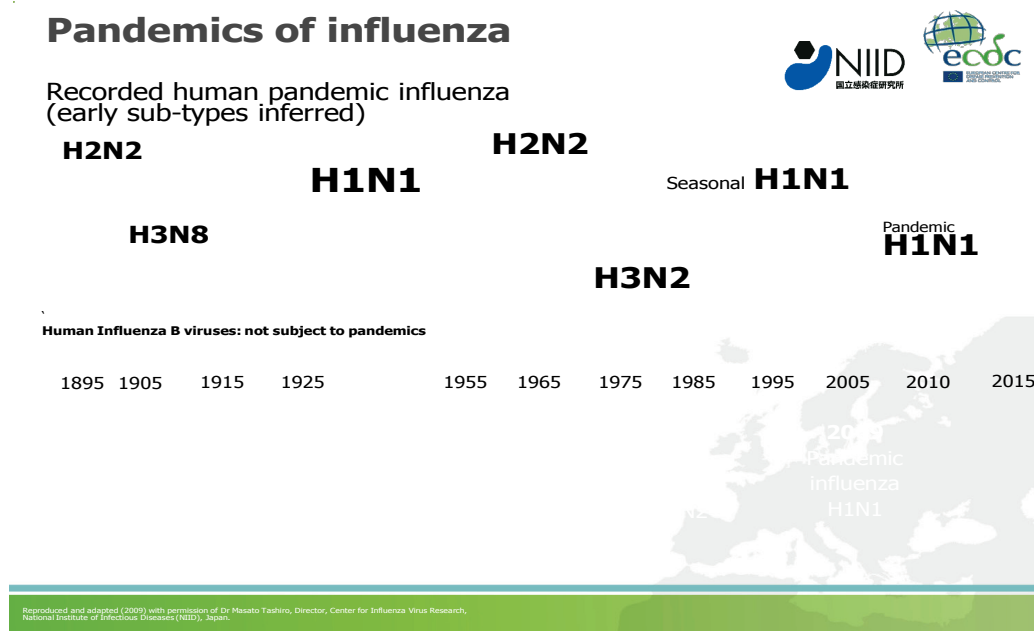
Most influenza A viruses circulate naturally as constantly evolving RNA-based avian influenza viruses among flocks of wild birds—especially ducks and waders. Some of these viruses have crossed species barriers and have become established in mammals, notably in humans (human influenza viruses) and pigs (swine influenza viruses) [1]. They are usually classified by the type of haemagglutinin and neuraminidase proteins present on the virus surface. Each strain may have any one of 16 known haemagglutinins (HA or H), and any one of nine neuraminidase (NA or N) varieties of protein. In any interpandemic period there is usually one, but sometimes two, predominant strains of influenza A viruses circulating in humans. It is infection with these plus the influenza B viruses (which have a less pathogenic human profile than the A viruses), that constitutes the interpandemic (seasonal) human influenza. The number of possible 'H' and 'N' combinations are quite large but since the 1918 influenza pandemic, humans have been infected by viruses with only seven of the 16 possible haemagglutinins (H1, H2, H3, H5, H7, H9 and H10), and four of the 9 possible neuraminidases (N1, N2, N3 and N7). Only three of the H types have successfully become human influenza (H1, H2 and H3), the others really being zoonoses (Figure 1) [2].

Historically, one of the earliest presumed pandemics affecting Europe is believed to have emerged around 1743 although there is some evidence of some occurring even earlier (see 'Previous influenza pandemics' below). Infectious diseases then were popularly thought to arise from the influence of the heavenly bodies (stars and planets). As waves of this contagious respiratory 'influence' affected Europe, including Italy, the name 'influence' (or *influenza*, in Italian) stuck. Causative organisms for human influenza were not isolated until two centuries later by Wilson Smith and colleagues in 1933 when they identified the influenza A viruses as members of the orthomyxovirus family [3]. Each influenza virion is 80–120nm in diameter (although the form varies from spherical to rod-like structures) and consists of eight RNA segments of the genome complexed with viral proteins. They have a complex structure with a host cell derived lipid membrane that harbours the haemagglutinin, neuraminidase, and M2 proteins that project from the virus surface. The core of the virus is comprised of the ribonucleoprotein (RNP) complex consisting of the viral RNA segments and the polymerase proteins (PB1, PB2 and PA) and of the nucleoprotein (NP). The matrix protein (M1) forms a layer between the envelope and the core [1]. The 'H' and 'N' proteins are of particular significance as protective antibodies produced by humans in response to infection are activated in response to these two proteins, hence they are a prime target for vaccines.

* For more information, click here: <http://ecdc.europa.eu/en/healthtopics/H1N1/Pages/home.aspx>

[†] For more information, click here: <http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx>

[‡] For more information, click here: http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/Methods_LabNetwork.aspx

Figure 1: Recent human influenza pandemics, from 1898 to 2009

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

Influenza viruses are RNA viruses with their viral RNA polymerases lacking the proofreading ability of DNA polymerases, so their mutation rate is high. This results in a minority of each next generation of influenza viruses being mutants, with point mutations of the antigens on the 'H' or 'N' antigens on the viral surface [4]. Over time, this may lead to 'antigenic drift' from the ancestral makeup and the new variant can come to dominate if it has an evolutionary advantage. This occurred, for example, when a new variant of the A(H3N2) virus subtype (named A/Fujian(H3N2)) emerged in 2003/2004 that was distinct from the preceding interpandemic strain [5]. Another characteristic of influenza viruses is that the division of their RNA genome into eight segments allows mixing or reassortment of these segments when more than one type of influenza virus infects the same cell. When two influenza viruses, human or animal, infect the same animal at the same time (and potentially both enter one cell), that animal can serve as a mixing vessel that may result in 'antigenic shift', with generations of novel influenza viruses having characteristics of both parent viruses. Thus, because of the deficiency in their RNA proofreading enzymes and the reassortment mechanism, a seemingly endless variety of new viruses with potentially new properties are continually being engineered in nature, usually with gradual changes (antigenic drift), but with an occasional abrupt change (antigenic shift) [6]. The larger, sudden changes may result in the emergence of a novel dominant human virus; a pandemic strain. An example of this is the A(H2N2), which replaced A(H1N1) (from the 1957 pandemic), when the former overcame the acquired protective historical herd immunity and out-competed the preceding influenza A viruses. Hence these two mechanisms explain the perennial waves of epidemic influenza of varying pattern and severity from season to season and the ongoing risk of an occasional pandemic strain emerging [7].

The reassortment process occurs for influenza A, B and C types but has not been observed between the three different types. Influenza B almost exclusively infects humans and is less prone to mutations than influenza A viruses [8]. Consequently, there is only one influenza B serotype with two lineages (Yamagata and Victoria) with much less genetic diversity and antibodies that are no longer cross protective. Therefore, it is no surprise that pandemics of influenza B do not occur as there is a limited host range combined with reduced rate of antigenic change (inhibiting cross species antigenic shift) [9]. Influenza C viruses are rare, although they infect humans, dogs and pigs, and are capable of causing mild disease in children [10].

1.2 Previous influenza pandemics

The first pandemic may have occurred as early as in 412 BC [11], and some authorities believe that the epidemics that can be attributed to influenza were first described in the late sixteenth century (1580) [11]. Since then, up to 31 influenza pandemics may have occurred. Nevertheless, there is only some degree of certainty over those occurring in the modern era, with start dates of 1889, 1900, 1918, 1957, 1968 and 2009; i.e., intervals of 11, 18, 39, 11 and finally 41 years (Figure 1) [11]. There is no predictable periodicity or pattern of pandemics. Also the modern pandemics all had important differences in their main characteristics and 'known unknowns' [2, 12]. This fact has important implications for the growing complexity of pandemic preparedness plans (that usually focus on

the worst-case scenario) with elaborate scenarios and countermeasures, that many countries started to elaborate on following WHO's lead in 1999 and 2005 [13, 14, 15].

The last three human 'true pandemics' were caused by different influenza A antigenic subtypes: A(H1N1) in 1918; A(H2N2) in 1957; and A(H3N2) in 1968, though all shared some ancestry with the 1918 strain (Figure 1) [6]. During the same era, there have been other notable influenza epidemics and events that didn't quite meet the pandemic criteria, demonstrating the unpredictability of influenza. These include an extreme intra-subtype drift in 1947, the mysterious re-emergence in 1977 of the old A(H1N1) primarily affecting children, and a small outbreak of swine influenza in 1976 that was feared to have pandemic potential but in fact never achieved human-to-human transmissibility [2, 16]. More recently the appearance, spread and persistence of the highly pathogenic avian influenza A(H5N1) in wild and domestic poultry in a series of locales (first in China around 1997, then Southeast Asia and subsequently elsewhere) made WHO declare pandemic Phase 3 in 2005. What made the A(H5N1) so disturbing was its ability to repeatedly cross the species barrier to infect humans, with an unprecedented case fatality rate (CFR) of over 60% [17, 18]. The development of extensive resistance to adamantanes in many human influenza strains in the 1990s, and the surprising detection of oseltamivir resistant A(H1N1) inter-pandemic influenza in Europe in 2008 have also been causes for concern [19].

1918 pandemic A(H1N1)

The 1918–1919 H1N1 influenza pandemic was one of the most serious catastrophes in recorded human health history. Estimates of its death toll vary, but it may have been responsible for the premature deaths of 50–100 million persons worldwide, many of whom were previously healthy young adults [20]. The estimated case fatality rate of 2–3% is believed, by one set of modellers, to have caused 86% excess deaths or 2.6 million deaths in Europe. This number represents 1.1% of the then European population, estimated at 250 million in 1918 [11].

The first wave occurred during the Northern Hemisphere spring and summer of 1918. At this time it had significant morbidity, but low mortality. The two following waves, in summer-autumn 1918 and the winter 1918–1919, had a considerably higher case fatality rate in all ages during these waves but the excess mortality was especially seen among previously healthy 20–40 year-olds, a group normally considered to be at low risk of death by this infection [21]. In the years that followed this pandemic, drift in the human H1N1 strain created less virulent strains, and therefore less severe epidemics. At the same time it is believed that the human strain crossed into pigs, perhaps to contribute to the genome that re-emerged in 2009.

1957 pandemic A (H2N2)

In comparison with 1918, the 1957 and 1968 influenza pandemics—both caused by lineages of the 1918 virus—produced relatively lower mortality overall and did not produce rapidly successive waves or multiple annual recurrences of high mortality. Like the 1918 virus though, they settled more quickly into familiar patterns of annual seasonal endemic circulation. The 1957 pandemic was the most 'straightforward' pandemic, with a single rise and fall in the wave of cases, although some countries—notably Sweden, the UK and the USA—also reported a rise in deaths in the early months of 1958, most likely due to this virus. In the most complete analysis found to date from the USA, that rise was not reflected in widespread community transmission, but rather seemed to be attributable to cardiovascular deaths due to influenza in the older more vulnerable individuals [22, 23]. There are some similarities with the 2009 pandemic; the importance of school-focused transmission in both pandemics is noticeable and the age profiles of the cases are similar, though the 2009 pandemic is missing infections and deaths in older people and so has a lower overall mortality and median age among those dying than the 1957 pandemic [23, 24, 25].

1968 pandemic A (H3N2)

In 1968, as in 1957, a new influenza pandemic arose in Southeast Asia and, in Europe, extended over two distinct winter waves. The first wave, in the winter 1968–69, showed some illness but not much more than in preceding winters due to inter-pandemic influenza. It was not associated with increased death rates. However, larger outbreaks and an increased number of deaths were experienced in the second winter (1969–70) of this pandemic in several European countries. Recent analyses indicate that this resulted from the virus becoming more transmissible, but not more pathogenic, in its second winter [23, 26].

1.3 Inter-pandemic influenza

Between the influenza pandemics in Europe there are annual epidemics, usually occurring each autumn/winter season, caused by a changing mix of influenza A and B viruses of varying severity depending on that year's strains. There is a long-term trend of declining viral severity between pandemics, seemingly as the last pandemic virus attenuates and adapts to the human host. The appearance of drift variants interrupts this pattern. After 1977 and the unexpected reappearance of the historic A(H1N1) viruses (Figure 1), the situation became more complicated than usual. This is because there were, for the period from 1977 to 2009, two inter-pandemic A viruses circulating simultaneously: A(H3N2) and A(H1N1). Both of these experienced drift, resulting in considerable season-to-season variation and notable phenomena like the severe winter of 1999/2000 (A(H3N2)), the emergence of a significant A(H3N2) drift variant—the so-called Fujian strain (2003–2004)—and the appearance and spread of oseltamivir

resistant A(H1N1) in 2008 [5, 27]. Consequently, the pattern of morbidity, mortality and groups experiencing most transmission was probably more variable in the period from 1977 to 2008/2009 than in previous interpandemic periods. This made the selection of appropriate annual vaccine strains more difficult. Still, there were some relative constants in Europe such as a tendency to progress from west to east [28–32], a substantial annual burden on healthcare services, the groups at higher risk of experiencing severe disease (older people and those in the clinical risk groups [33], and significant annual mortality [34, 35]. Over the period from 1977 to 2008, influenza A(H3N2) viruses appear to have caused more severe disease in terms of hospitalisation rates and mortality than the influenza A(H1N1) viruses [36, 37].

1.4 First reports of the 2009 influenza A (H1N1) pandemic

The initial warning of the 2009 pandemic came in a publication from the United States Centers for Disease Control and Prevention (CDC Atlanta) that appeared 21 April 2009. It described two children in southern California (USA) with febrile respiratory illnesses who were found to have been infected with a novel swine flu virus, but without any obvious contact with pigs [38]. Later, information emerged that showed that this new virus had already caused epidemics in Mexico unusually late in their influenza season (in early March 2009), having most likely first started* in the area of Veracruz [39]. However the significance of these epidemics were not fully appreciated until cases of severe influenza appeared in seemingly healthy people in Mexico City, at which point the virus was isolated. Further studies in Canada and the USA showed that the Mexican and Californian viruses were indistinguishable [40].

Declaration of a pandemic

When it became apparent that the new viruses causing the alarm in California and Mexico were in fact identical it was evident that this virus met the WHO criteria[†] for a pandemic strain. Thus by the time of its discovery the virus was well past WHO pandemic Phase 4[‡] and probably beyond any possibility of successful containment [41, 42]. On 25 April 2009, on the advice of an Emergency Committee convened under the International Health Regulations (IHR) 2005 [43], the Director-General of WHO, Dr Margaret Chan, declared that a Public Health Emergency of International Concern was underway[§], the first under the newly revised IHR, which came into force in 2007. Within a few days, the same pandemic virus had been reported outside of the Americas, but it was most likely reports of increasing transmission in New York City that led the same Director General, again acting on the advice from the WHO Emergency Committee (IHR), to declare Pandemic Phase 5 [44] on 29 April 2009** (week 18/2009). Since there are no qualitative differences between Phases 5 and 6, this implied that the pandemic was unstoppable and uncontrollable; though a number of more formal planned actions (such as switching to production of a pandemic strain vaccine) would not start until Phase 6^{††} was formally declared.

The initial reports on the new influenza A virus suggested that there were a significant number of severe respiratory illnesses and deaths in Mexico including among young, previously healthy, persons [40, 45]. This had prompted the Mexican authorities to take quite extreme measures early on, closing schools and banning public gatherings [46]. Once more detailed reports from the USA were available it became clearer that the new virus was, in fact, not causing much severe disease [47] as was reflected in ECDC's early risk assessment [48].

There was a considerable delay before pandemic Phase 6 was formally declared on 11 June 2009^{‡‡}, as even though it was quite clear that the epidemiological criteria for this phase had been reached, there had been pleas by some countries at the World Health Assembly in May for delay and more reflection^{§§}. This meant that by the time Phase 6 was actually declared, the ECDC estimated that 74 countries worldwide (26 of which were EU/EEA countries) had already reported over 27 000 cases of influenza A(H1N1), including 141 deaths [49]. With the declaration of Phase 6, a number of actions were automatically triggered at the country level, so many authorities needed to rapidly adjust their pandemic plans designed to deal with a more severe pandemic [50]. The formal end of the pandemic was declared by WHO on 10 August 2010 (week 32/2010)^{***}.

* More at: http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

† See summary at:

http://www.ecdc.europa.eu/en/healthtopics/H1N1/Documents/100503_health_topics_pandemic_definition_of_a_pandemic.pdf

‡ See a summary of the phases available from: http://www.ecdc.europa.eu/en/healthtopics/H1N1/Documents/100301_pandemic-phases_table_may_2009.pdf

§ More at: http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

** *ibid*

†† For more details of what this implies see: http://www.who.int/csr/disease/influenza/extract_PIPGuidance09_phase5_6.pdf

‡‡ More at: http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

§§ World Health Assembly, May 2009, see:

http://www.who.int/mediacentre/news/releases/2009/world_health_assembly_20090518/en/index.html

*** See the full statement at: http://www.who.int/mediacentre/news/statements/2010/h1n1_vpc_20100810/en/index.html

Naming the pandemic

The predominance of swine influenza genes in the new virus' genome prompted the initial labels of 'swine-origin influenza A (H1N1) virus (S-OIV)' or 'novel swine-origin flu' and later the simplified one of 'swine flu'. This label persisted in some countries, even though it became obvious that there was no link between most of the cases and pigs [42]. The finally accepted titles varied from 'pandemic (H1N1) 2009' to '2009 influenza A (H1N1) pandemic' or '2009 pandemic influenza A (H1N1)' and are all used in this article without any distinction.

The initial response in the European Union/European Economic Area countries

Vital information required for responding adequately to a pandemic has been collectively termed the 'known unknowns' [12]. These include a number of features like severity, groups at particular risk of severe disease and antiviral susceptibility that are essential to inform policy makers devising response strategies and that are known to differ from one pandemic to another* [12]. These features and specific characteristics cannot usually be easily gathered from conventional surveillance data. In addition, apart from a few countries (mainly the United Kingdom and Spain), most of the early experience with the pandemic was from outside Europe: North America and then the Southern Hemisphere. In order to better inform its early independent risk assessments, ECDC employed epidemic intelligence [51], science watch and media monitoring to gather targeted relevant information and analyses from the first countries affected.

In April, in response to the growing threat, the ECDC raised its level of general alert and started producing daily updates, a threat assessment and then regularly up-dated risk assessments, briefings and guidance on, for example, personal measures or case handling[†]. The daily updates were distributed to key stakeholders and published initially every morning for seven days a week, and later only on weekdays[‡]. Most EU countries entered into an emergency mode—as did the European Commission—that started holding regular meetings of the Health Security Committee and Stakeholders for the Early Warning and Response System. An urgent informal Health Council meeting was held under the Czech Presidency and briefings and a debate was held at the 2009 World Health Assembly in May with the active involvement of EU/EEA countries[§]. The World Health Organization reacted by accelerating the production of its suite of pandemic guidance that it had been developing since 2007 [13]. A uniform case definition for surveillance of individual cases was quickly agreed upon between all the EU/EEA countries and published in the Official Journal of the European Union (Commission Decision 2009/363/EC in OJ L 110 of 1 May 2009)^{**}.

Initially, an ad hoc, case-based reporting system was quickly set up within the secure platform of the European Commission's Early Warning and Response System (EWRS). The choice of variables and codes for this system were based on those recommended to be collected by WHO-Geneva, to ensure close compatibility of the European data. As the pandemic accelerated, individual case-reporting became impossible to sustain. It also became quite irrelevant globally, as the trends and the results of the analyses became more important than the numbers [12]. Hence, although the demand of the media and many decision makers for numbers was great, individual case reporting was suspended by agreement after week 39/2009, even though many EU/EEA countries had stopped reporting far earlier. The EU/EEA countries continued to report their data to the ECDC in the new format designed for the WISO, the weekly bulletin that pulled together a summary all the various types of data.

Because the pandemic viruses had been shared immediately following isolation, diagnostic tests were developed rapidly by the CDC Atlanta and were made available to all European countries and to the rest of the world. At the same time, the WHO Collaborating Centres for influenza, the Essential Regulatory Laboratories and other institutions developed candidate vaccine viruses under the coordination of the WHO.

* For more information, click here:

http://ecdc.europa.eu/en/healthtopics/Documents/0905_Pandemic_Influenza_Known_Facts_and_Known_Unknowns.pdf

[†] All available from: <http://ecdc.europa.eu/en/healthtopics/H1N1/Pages/home.aspx>

[‡] more at: http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

[§] ibid

^{**} For more information, see here:

http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

2 Methods

2.1 The interpandemic influenza surveillance systems in the EU/EEA

Multinational systematic surveillance of influenza in the EU began in 1987 with a sentinel surveillance network called the Eurosentinel scheme (1987-1991). This was followed by the ENS-CARE Influenza Early Warning Scheme (1992-1995) project. In 1996, a project called the European Influenza Surveillance Scheme (EISS) and funded by national governments took over these activities. Later this project was funded by the European Commission from 1999 until the end of September 2006.

In accordance with the desire of the EU/EEA countries to support all core surveillance systems on a more permanent and sustainable basis and to integrate all the European communicable disease surveillance activities into one system, the ECDC took over the funding of the EISS project from October 2006 until September 2008. Meanwhile, plans were being drawn up to integrate the project's epidemiological and virological surveillance data into the European Surveillance System (TESSy) platform. Since September 2008, the coordination of the former EISS network (with all the historical data) has been transferred to the ECDC, ending the reliance of this work on project-based funding and management. Hence the new programme, the European Influenza Surveillance Network (EISN), which consists of specifically nominated expert contact points for influenza surveillance (epidemiologists and virologists) proposed by the Competent Bodies for surveillance of the EU/EEA countries and coordinated and funded by the ECDC. Throughout the period of transition, care was taken to ensure that links and outputs to the WHO Global Influenza Surveillance Network (GISN)* were maintained.

2.2 The influenza surveillance systems reinforced for the pandemic

The agreed plan for EISN was to continue building on the previous influenza surveillance project's achievements and further develop the work carried out. This strategy for steady development was swept aside by the rapidly developing influenza pandemic that arrived just seven months after EISN was formally established. As described earlier, initial reports were based on individual cases to an ad hoc database, but it was clear to national authorities and to ECDC that this system would soon become unsustainable. Drawing on a previous ECDC work, 'Surveillance and studies in a pandemic' [52, 53, 54], ECDC and EISN held a meeting in July 2009 with experts from EU/EEA countries, WHO as well as the USA, Canada and Australia—who shared their early experiences of the 2009 pandemic virus [55]—to re-evaluate routine data flows and sources. A new reporting mechanism was designed to be in accordance with the WHO 2009 guidance on surveillance [56]. At the same time ECDC enhanced its epidemic intelligence, and targeted science watch and media scanning activities so as to obtain information that was unlikely to be revealed early by the more classical surveillance work [12]. This intensive information gathering was sustained from this period up to the end of April 2010, and included specific monitoring of official websites for announcements of confirmed cases and attributable deaths to complement the formal reports of cases and deaths due to influenza.

The new surveillance activities were reported in the WISO[†], incorporating qualitative and quantitative, aggregated or case based data as described in its first table. All the WISO data for week Y is reported to ECDC at the latest by week Y+3 days, analysed and reviewed and then the final WISO is published on week Y+4.5 days, or midday of the following Friday.

*For more informations, click here:

http://www.ecdc.europa.eu/en/healthtopics/seasonal_influenza/basic_facts/Pages/basic_facts.aspx

[†] Available from: <http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx>

Table 1: Data collected for the EU/EEA Weekly Influenza Surveillance Overview (WISO)

Type of data	Includes
Sentinel syndromic surveillance of influenza-like illness (ILI)/ acute respiratory infection (ARI)	Subjective assessment of intensity and degree of geographic spread as well as reporting of aggregated cases
Virological surveillance	Laboratory data of the results of tests requested by sentinel physicians and other respiratory specimens collected - describes the type and subtype of virus, the predominant strains, antigenic and genetic characteristics and their anti-viral susceptibility
Hospital sentinel surveillance of severe acute respiratory infection (SARI)	Case based data of the more severe forms of acute respiratory infection including influenza and other causes
Influenza deaths	Both case based deaths resulting from SARI as well as aggregated deaths reported by the countries ⁺
Qualitative reporting*	Planned to become the principle routine data to be collected should surveillance systems become overwhelmed and unable to generate the other data: includes subjective assessment of geographic spread, intensity, trend (as for ILI and ARI above) , and impact

*It was not necessary to activate this element

⁺ This was complemented by active monitoring of official web-sites for announcements of official deaths.[see Mortality attributable to influenza and disease burden, below] Source: ECDC. [57]

Sentinel syndromic surveillance of influenza-like illness (ILI) and/or acute respiratory infection (ARI) is carried out by nationally organised sentinel networks of physicians—mostly general practitioners*—covering at least 1–5% of the population in their countries. Every sentinel physician then reports the aggregated weekly number of patients seen with ILI, ARI or both (depending on the country's choice) to a nominated national focal point who subsequently validates the data and then uploads the data to TESSy for reporting in the WISO (see examples in Figures 2a-d).

In addition to these ILI/ARI rates, semi-quantitative and only partly standardised indicators of intensity, **geographic spread and trend of influenza activity** are reported. The intensity is assessed by comparing current ILI/ARI rates with country-specific baseline rates outside of the influenza season and with historical values and other factors like absenteeism. The geographic spread can range from no activity to sporadic, local, regional and widespread activity, taking into account laboratory confirmation. The trend is assessed by comparing current influenza activity with previous weeks and can be described as increasing, decreasing or stable.

Virological surveillance and monitoring antiviral susceptibility includes laboratory data on the type and subtype of virus, the antigenic and genetic characteristics, the predominant strains and their anti-viral susceptibility. Sentinel physicians take nasal or pharyngeal swabs from a subset of their ILI/ARI patients that are then sent to the respective country's collaborating reference laboratory (members of the ECDC-funded Community Network of Reference Laboratories (CNRL)) for virus detection, (sub-) typing, antigenic and/or genetic characterisation and antiviral susceptibility testing. Some laboratories also test these specimens for the presence of respiratory syncytial virus (RSV) and report the data on these to WISO. Samples referred to the reference laboratories from non-sentinel physicians are also reported and are especially useful in the case of viruses derived from hospitalised severe cases.

New system: Hospital-based sentinel surveillance of severe acute respiratory infection data were introduced in 2009. The concept arose to respond to the fact that there had been little data on people severely affected. Sentinel surveillance of severe acute respiratory infection (SARI) includes data on any patients with sudden onset of fever of >38°C and cough or sore throat in the absence of other diagnoses, and shortness of breath or difficulty breathing requiring hospital admission (this includes any healthcare-acquired influenza infections). These case-based data are recommended to be collected from selected sentinel acute-care hospitals that are willing to participate and have the capacity to do so, although this was not always the case in the first year of data collection. The hospitals should have clearly defined catchment populations to facilitate the determination of comparable rates. Deaths recorded in a person with SARI are also reported. Most countries, at least initially, only reported hospitalised patients with confirmed pandemic influenza.

* In certain countries, where paediatricians provide primary care for children, they are included.

Figure 2a: Distribution of sentinel ILI notification rates in Portugal, last two seasons

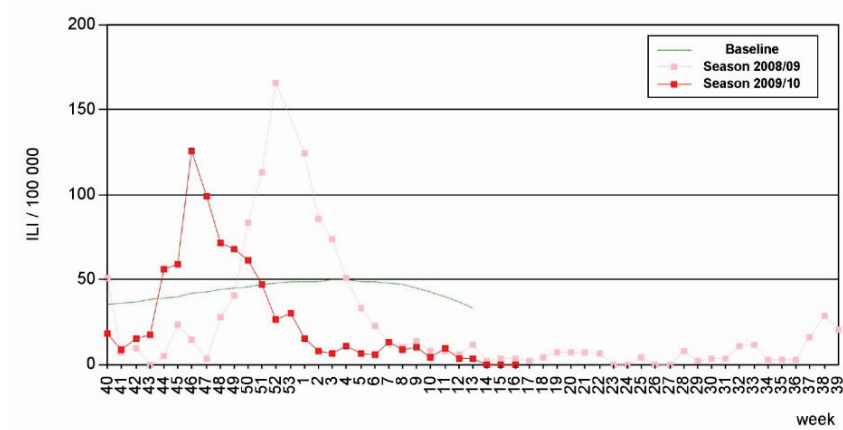


Figure 2c: Distribution of sentinel ARI notification rates, last two seasons in France

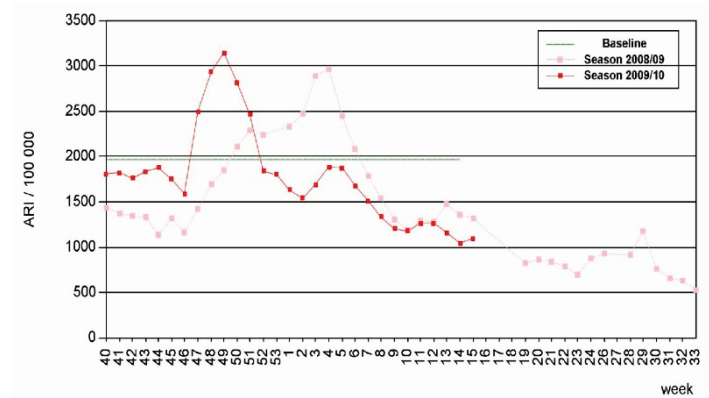


Figure 2b: Distribution of sentinel ARI notification rates by age group in Bulgaria, week 40/2009 to week 21/2010

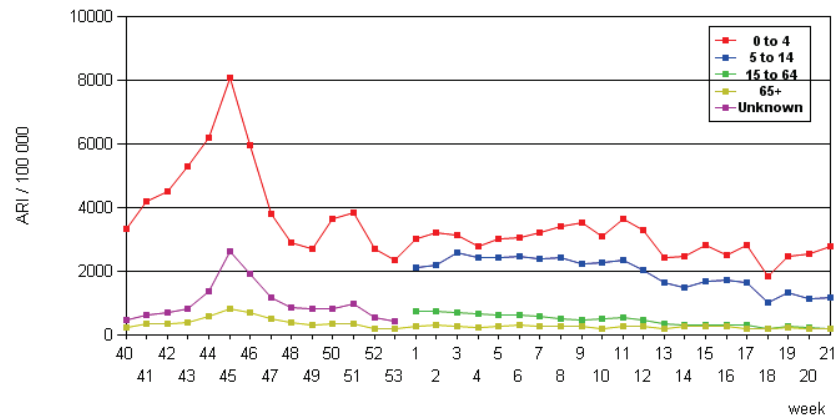
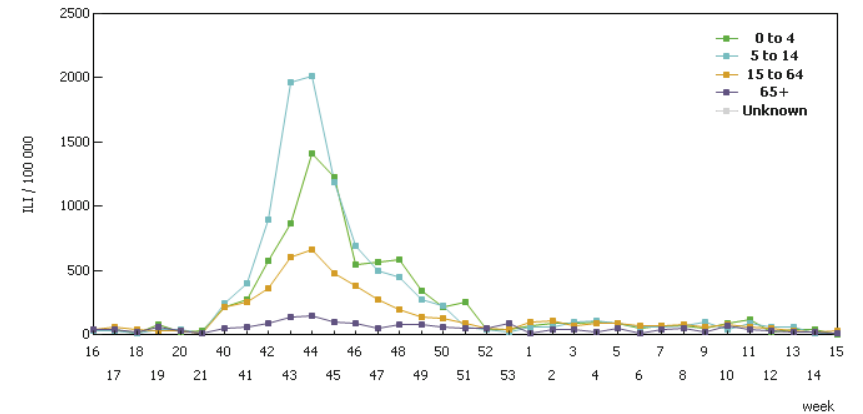


Figure 2d: Distribution of sentinel ILI notification rates by age group in Belgium, week 16/2009 to week 16/2010



New system: Reports of influenza deaths were collected in 2009 following the adoption of a common EU case definition for a death due to influenza [57]. European Union and European Economic Area countries reported aggregated data on cases and deaths by age group on a weekly basis to TESSy. This data was augmented with the data on deaths from influenza as announced by the various Ministries of Health or Public Health Institutes, usually on their websites that were collected by ECDC through its epidemic intelligence activities. The data on all deaths officially recognised and reported as pandemic A(H1N1) were therefore collected by ECDC from two sources (Figures 13 and 14).

Qualitative data reporting aims to provide a relatively reliable and quick view of the situation. It is relatively easy to maintain and may prove to be the main source of information when a severe epidemic/pandemic has overwhelmed the country's surveillance system resources rendering them unable to reliably generate the data requested. It includes the same subjective assessment indicators of geographic spread, trend and intensity as described under the ILI/ARI surveillance. It also includes an attempt to describe the impact* of the pandemic, defined as the degree of disruption of healthcare services as a result of acute respiratory disease [12].

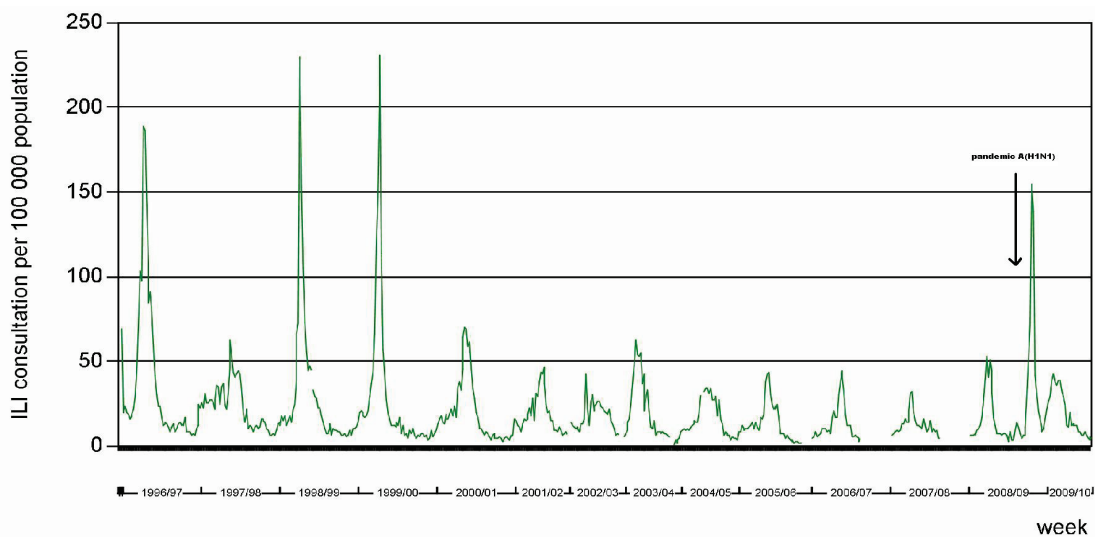
* The discussion on impact did not reach any consensus between the Member States on whether or not to include it for monitoring the pandemic's impact on healthcare systems. Many cited fears of the political and negative social implications of a country's official source describing their own healthcare services as being overwhelmed by the pandemic.

3 Results

3.1 Epidemiology and virology of the recent interpandemic flu in European Union and European Economic Area countries

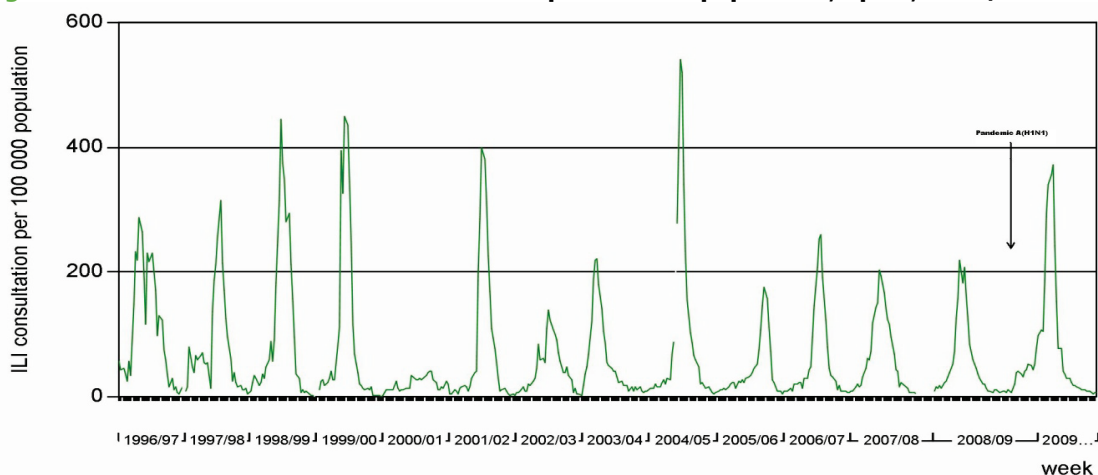
Traditionally in the EU/EEA countries, the influenza surveillance season starts during week 40 of a year and continues to week 20 the following year*. This is an arbitrarily period and the influenza virus does not confine its activity to just these weeks. There is known to be low level transmission outside that period, sometimes due to introduction by returning travellers from moderate and Southern Hemisphere regions, and the phase of more intense transmission within it is quite variable (Figures 3a and 3b), with somewhat separate waves for the influenza A and B viruses. Nevertheless, several countries maintain a year-round reporting system based on sentinel networks of physicians who report their aggregated weekly number of patients seen with ILI/ARI. As a minimum they also routinely report on the degree of geographic spread (Figure 4) and intensity of illness.

Figure 3a: Trends of the ILI consultation rates per 100 000 population; UK (England), 1996/97 to 2009/2010



Source: WISO reports based on EISN data in TESSy.

Figure 3b: Trends of the ILI consultation rates per 100 000 population, Spain, 1996/97 to 2009/2010



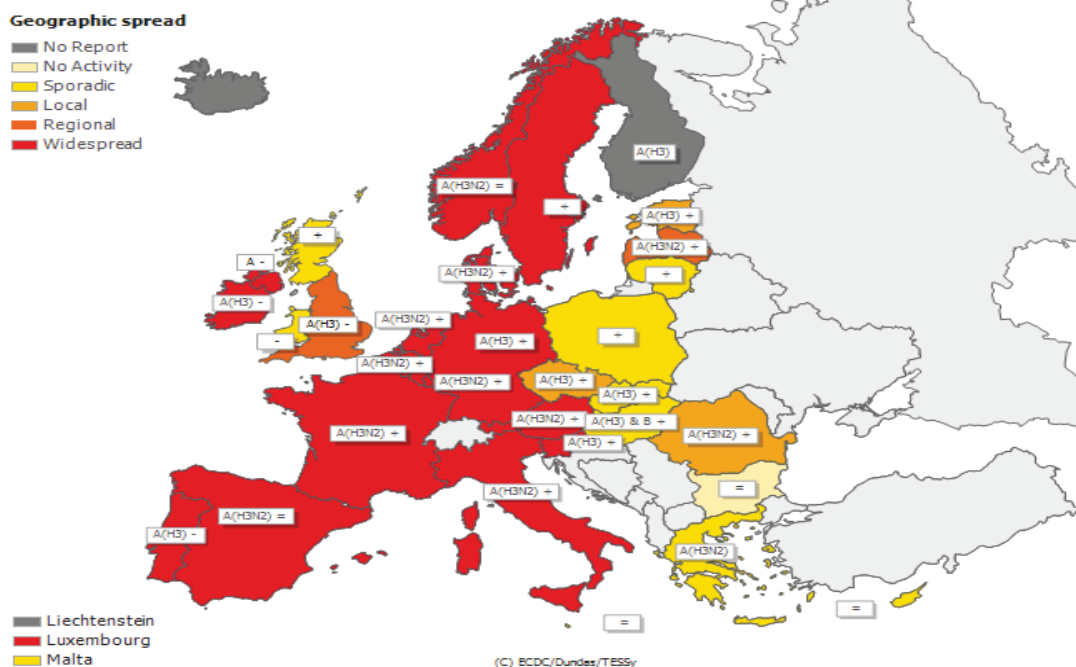
Source: WISO reports based on EISN data in TESSy.

* Many countries fund their sentinel networks and resource their reference labs to cover the patients seen and those samples collected over this period only.

The 2008/2009 season in the EU/EEA countries is described in greater detail elsewhere [58], but in summary, significant ILI/ARI clinical activity—caused predominantly by influenza A strain of A(H3N2)—started earlier than in preceding years, around week 48/2008, and peaked around weeks 51/2008 to 3/2009. A secondary wave of influenza B appeared towards the end of the winter in March 2009, reaching a peak around week 12/2009 [58].

Intensity of transmission, geographic spread and pressure on services was high enough (Figure 4) for ECDC to issue a warning and encouragement in January 2009 to prolong the vaccination campaign targeting risk groups [58].

Figure 4: Geographic spread of influenza in Europe in week 3/2009 [58]



Source: *EISS Weekly Electronic Bulletin*

Ad hoc estimates of the number of excess deaths recorded suggest that these were higher than in some recent years, but as expected occurred mainly in older individuals (persons age 65 and over) [34, 59].

As has been described for several previous seasons [28–32], the peak intensity of clinical influenza activity by week progressed across the continent from west to east.

The antigenic characteristics of the 2008/2009 influenza viruses were similar to those of the A(H1N1) and A(H3N2) components included in the 2008/2009 Northern Hemisphere influenza vaccine. There was a mismatch between the two antigenically distinct lineages of the B/Victoria/2/87 virus that made up most of the B viruses this season and the B/Yamagata component of the vaccine, but this is unlikely to have been of any public health significance given the relatively low prevalence of B viruses observed during this season [58].

The virological picture in the EU contrasted with that in the USA where the 2008/2009 season was dominated by oseltamivir-resistant influenza A(H1N1) virus [60], that was the case in the EU/EEA countries the previous year [19].

As a point of interest during this same season (2008/2009), there was an isolated case reported in Spain of a 50-year-old woman who, on 8 November 2008, developed fever, cough, extreme tiredness, myalgia, irritation of the nasal/oral mucosae and shivers of sudden onset. A throat swab sample revealed swine influenza A (H1N1), at this stage, was not the pandemic variety but the 'true' or 'classical' swine flu virus. The patient revealed no history of recent travel but did work on the family's swine farm where she had direct contact with pigs. No other family member or co-worker reported flu-like symptoms before or after this case and no symptoms were observed in pigs. The patient did not need specific treatment or hospitalisation and recovered fully [61]. The case only came to light retrospectively because the case doctor happened to be part of a surveillance scheme and the swab was referred centrally as untypable. This example highlighted how little is understood about the interface between swine influenza in pigs and humans in EU/EEA [62].

3.2 Epidemiology of the 2009 pandemic

Soon after the declaration of a public health emergency of international concern by WHO, and the ECDC raising their emergency response level*, cases of 2009 pandemic influenza A(H1N1) started to be more frequently recognised in the EU/EEA. The first cases were seen (but not reported) around week 16/2009 (mid-April) mainly in travellers returning from Mexico, or their direct contacts. On 27 April 2009, Spain officially reported the first laboratory-confirmed case of the new influenza A(H1N1) virus infection in EU/EEA, in a traveller returning from Mexico [63]. Later that same day, the first two confirmed United Kingdom cases of new influenza A(H1N1) virus infection were reported in Scotland in a couple also returning from visiting Mexico† [64].

Following these initial cases coming from North America into Europe, a spring/summer wave of local transmission was apparent, affecting most EU/EEA countries, but mainly the UK. The rate of transmission appeared to briefly subside as the summer progressed but then accelerated again as autumn set in, this time in all countries (Figure 5) following a not unusual west to east progression. For the entire official pandemic period of 68 weeks (week 18/2009 to week 35/2010), 925 861 cases of ILI (27 reporting countries) and 7 202 014 cases of ARI were reported by EISN.

Due to the inter-country variability in data collection, the ILI data cannot be directly compared or cumulated. One way of using this data to demonstrate the overall trend is proposed in Figure 5. This figure was compiled by taking each country's total caseload that was reported throughout the whole time period as the denominator. Then, assuming that country's network's sentinel reporting practices are constant throughout the whole period (which is not the case as in times of heavy duress, the completeness of reporting tends to suffer, counterbalanced by some over diagnosis in the season), and also that the sentinel catchment area remains constant throughout the period, the actual number of cases reported each week was used as the numerator to estimate a percentage weekly reported ILI caseload. This is then estimated for each country and for all the weeks under study, and individual trends were produced. Since this percentage of the weekly caseload is a surrogate measure of the degree of strain that each country's sentinel networks were under each week, it should be possible to cumulate all MS's weekly proportionate caseloads to obtain an idea of the overall degree of weekly strain throughout the whole EU/EEA (Figure 5). This represents the overall ILI trend and shows the relatively small spring/summer wave that persisted until the temperatures started to drop in autumn when a much taller autumn/winter wave occurred, peaking around week 48/2009.

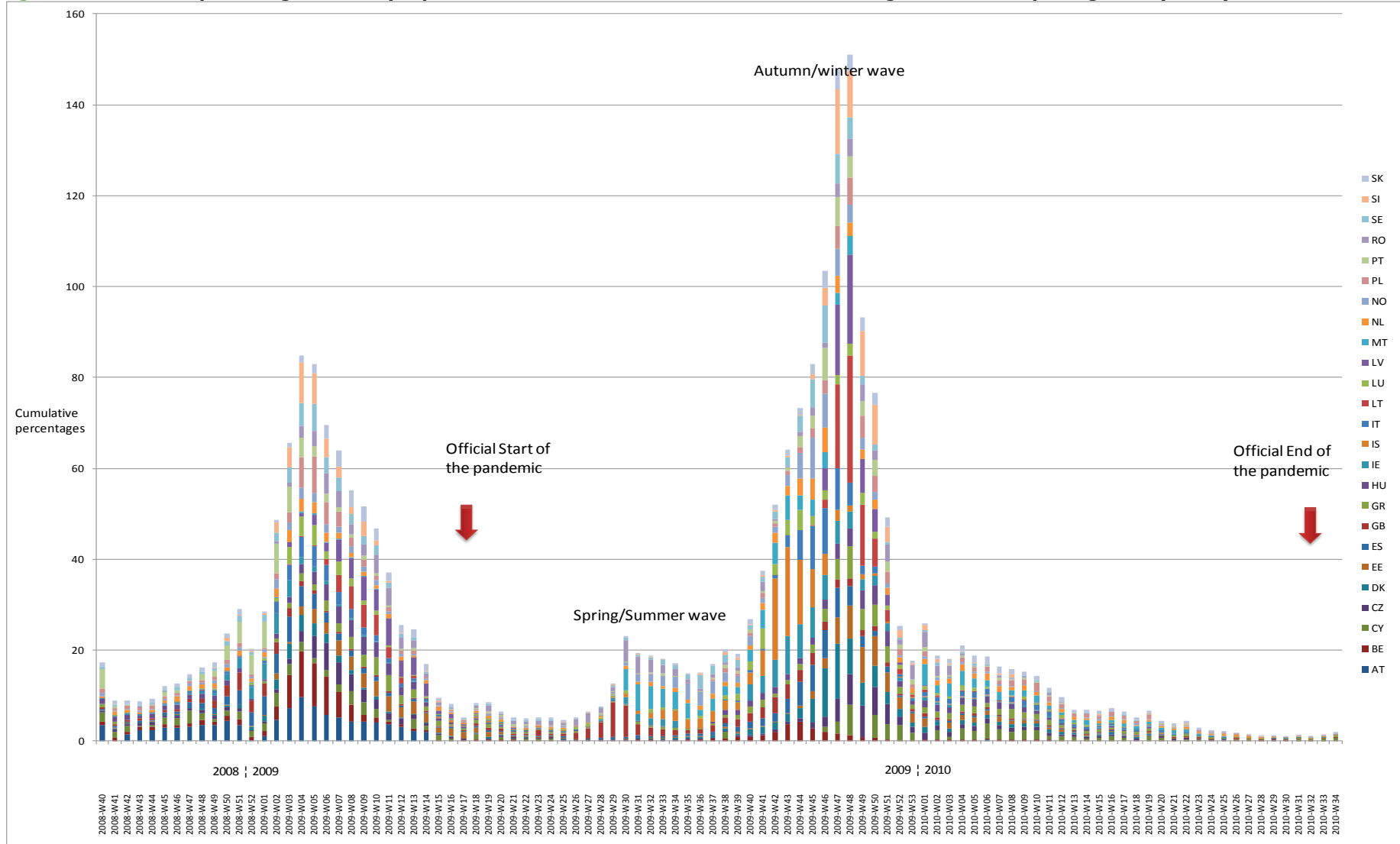
As for the previous year, more western EU countries appeared to have been affected earlier than the eastern parts of the EU, so accumulating the weekly percentages of distinct geographic groups of countries would again demonstrate the overall progression from west to east of the 2009 pandemic A(H1N1).

* For more information, click here:

http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

† ibid

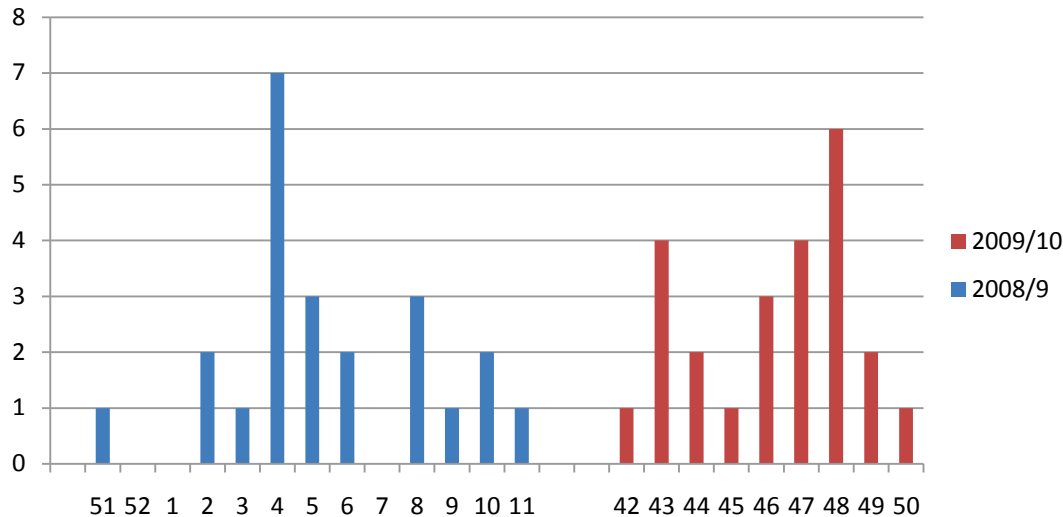
Figure 5: Cumulative percentage of weekly reported sentinel ILI caseload for 25 MS and showing the relative reporting weekly load (wk 40/2008–15/2010)



Source: EISN reports to TESSy

It is difficult to say with any precision when the pandemic A(H1N1) was really severe in Europe in the autumn/winter of 2009-2010. The modal peak week for the 24 countries consistently reporting their sentinel ILI consultations was week 48/2009 (six MS), as opposed to week 4/2010 (seven MS) for the previous season. By the end of week 50/2009, all the MS had reached or passed the peak of their pandemic curve (Figure 6).

Figure 6: Frequency of countries reporting their peak sentinel ILI consultations in the autumn/winter waves by week, seasons 2008/2009 (n= 23 ILI reporting countries) and 2009/2010 (n= 24 ILI reporting countries)

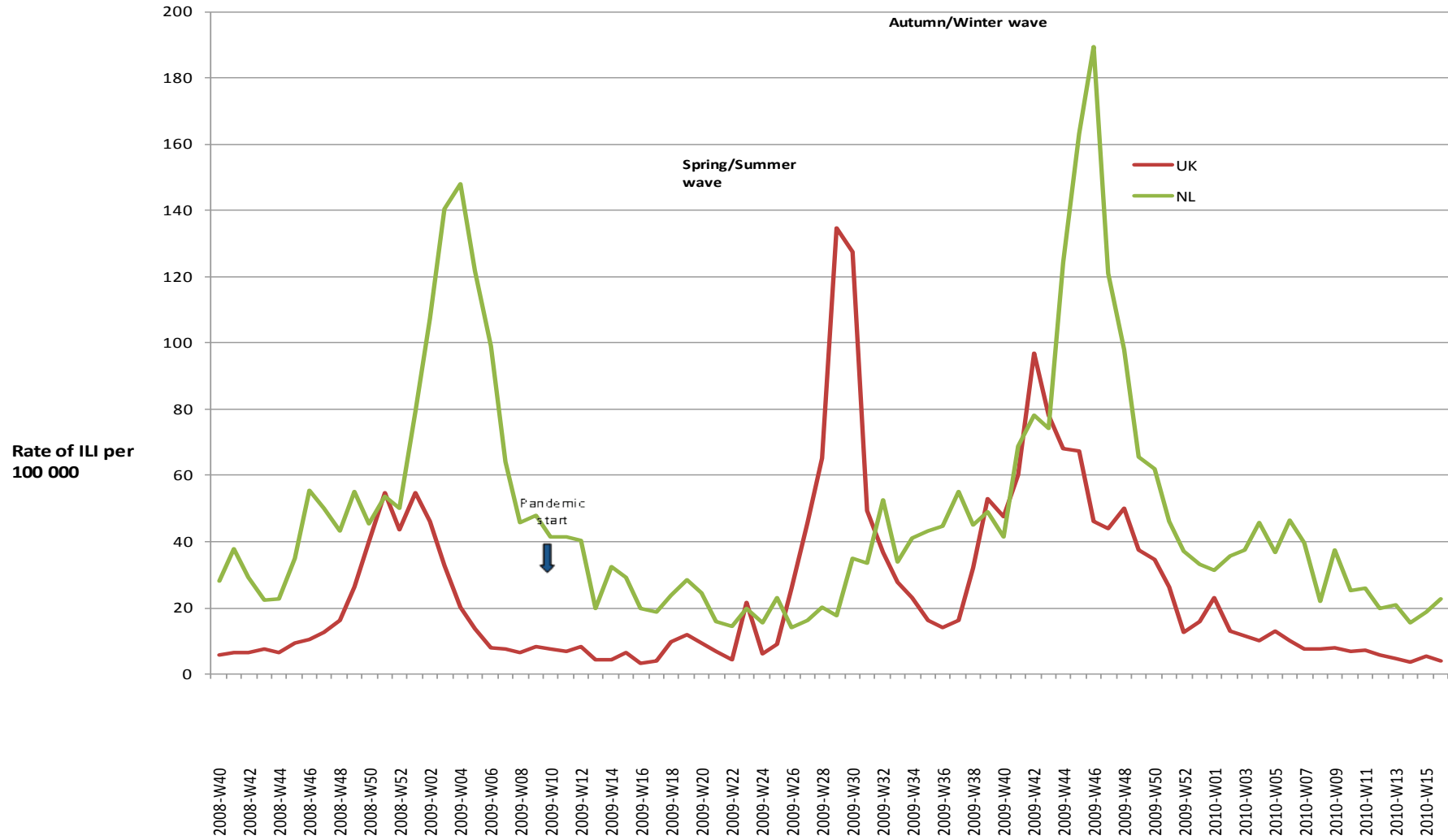


Source: EISN data in TESSy

Individual downloadable epidemic curves for each country are available on the ECDC pandemic website*. Influenza-like illness and acute respiratory infection curves generally follow the classical epidemic curve reminiscent of the 1957 pandemic (apart from their being no follow-up year extension yet) with a duration of around 14–16 weeks [24, 65]. An interesting exception is the curve for the UK (England). Compared with a more typical trend seen in the Netherlands (Figure 7), there is a clear and atypical spring/summer wave followed by an unexpectedly smaller autumn/winter wave that appears to be stunted in comparison. This is possibly a result of the UK authorities introducing telephone access to medical services and advising potential flu sufferers from not attending primary care services, perhaps also an outcome of the liberal use of antivirals over the previous summer.

* Available from: http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=526

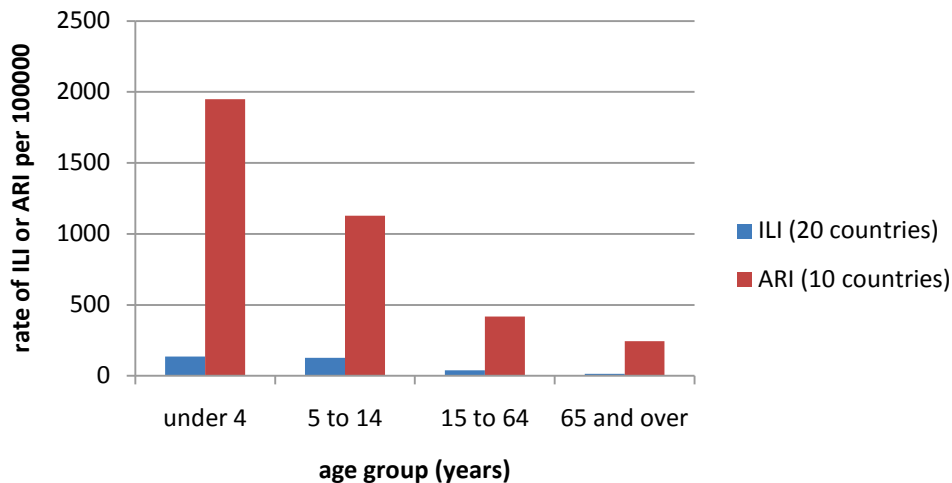
Figure 7: Comparison of the distribution of sentinel ILI notification rates between the UK and the Netherlands (seasons 2008/2009 and 2009/2010)



Source: EISN data in TESSy

Sentinel ILI and ARI networks also provide data on broad age groups (younger than 4 years, 5 to 14 years, 15 to 64 years and over 65 years; see also Figures 2b and 2d) but not on gender. All country distributions showed a consistent pattern by age group similar to that seen in Figure 8. The main age group affected was children younger than 14. This was validated when matched with the case-based data collected in the early stages of the pandemic (see section 3.3 Detailed analyses of the initial cases).

Figure 8: Distribution of EU/EEA sentinel ILI (n=724 038, 20 countries) and ARI (n=5 831 365, 10 countries) notification rates per 100 000, by age group, wk16/2009 to wk16/2010



Source: EISN data in TESSy

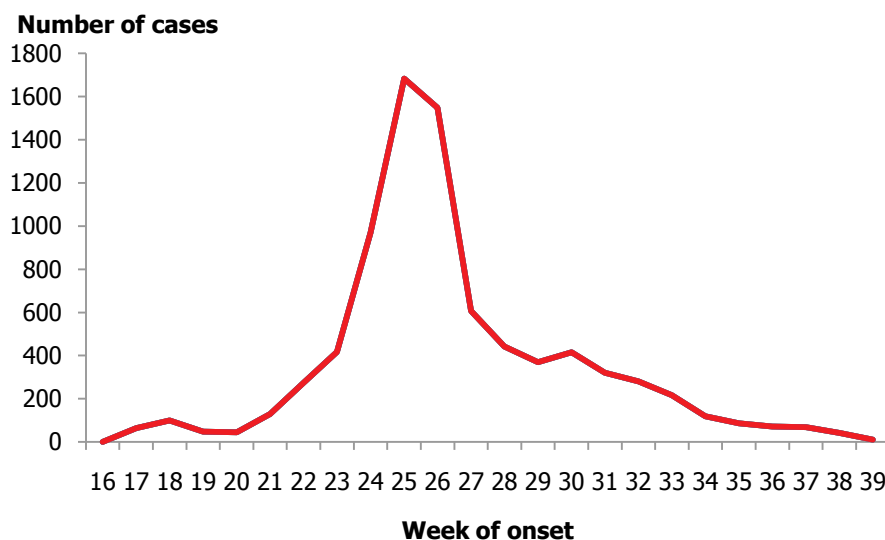
3.3 Detailed analyses of the initial cases

European Union/European Economic Area countries submitted the first case-based reports to the ECDC using the EWRS ad hoc database in May 2009, with the earliest validated date of onset of these cases being on 19 April 2009. By the time it was agreed that ECDC would stop collecting case-based data (after week 39 of 2009) the database contained 11 275 individual records (11 207 of which were laboratory-confirmed) submitted by 28 EU/EEA countries. When analysing this data, it should be remembered that there were two broad categories of cases: The earlier cases were mainly travellers returning from infected areas so their basic descriptive variables, such as age and gender, reflected characteristics common to the average traveller; in contrast, the later cases resulted more from in-country, person-to-person transmission and reflected characteristics more representative of the active general population. Also, the cases reported may have been subject to some bias as many of them reflected the results of intense case-finding carried out in several countries or the results from investigation of outbreaks, notably in schools.

A more detailed analysis of this data is available elsewhere [58, 66] but, in summary, 8328 cases include reliable information on the date of onset of disease. The distribution of these cases indicates that the peak onset of disease in the spring/summer wave was reached in week 25 when up to 344 persons were reported to have fallen ill in one day and 1684 during that week (Figure 9). Evidence later emerged that suggested that throughout this period there was also a high incidence of asymptomatic or mild infections which would not have been picked up by the surveillance schemes in place [67], so a high proportion of infections were most likely not reported [68].

From week 16/2009 to week 27/2009, cases of pandemic influenza reported by the UK accounted for 66% of all the cases reported in EU/EEA countries. The shape of the epidemic curve after week 27/2009 was heavily influenced by the decision taken by the UK (and subsequently other governments) to stop generalised laboratory confirmatory testing for suspected pandemic influenza cases.

Figure 9: Reported laboratory confirmed cases of the 2009 pandemic influenza in EU/EEA by week of onset of disease, from week 16/2009 to week 39/2009 (n=8328) [66]



Source: Country reports to EWRS ad hoc database.

Note: This data omits any estimate of under-reporting or missed cases, even though it is understood that there most likely was a significant number of cases that must have been oligo- or asymptomatic and therefore would not have approached any clinical services.

The median age reported for these spring/summer cases was 19 years, with 78% of the reported cases younger than 30 years of age. Children from 5 to 19 years of age accounted for 46.5%. There was no difference in the overall male to female ratio, but among cases under 30 years of age, there were 20% more males than females. Of the 11 207 confirmed cases that included some clinical information, only 404 cases (3.6%) were reported to suffer from 489 underlying conditions. As expected, the most frequently reported condition was chronic lung disease (120 patients) [58].

Sixty-four (0.57%) of the 11 207 cases developed pneumonia as a complication, and three of the 11 045 confirmed cases with information on survival status were reported to have died (case fatality ratio of this series: 0.03%). Ten thousand nine hundred and ninety cases had information on their hospitalisation status with 1443 (13.1%) of confirmed cases reported to have been hospitalised. Caution is required when interpreting this data as the hospitalisation policies in place for the earlier cases were not necessarily linked to the severity of the disease but were influenced by the attempts of several countries to contain the transmission, sometimes by hospitalising patients whose clinical condition did not require hospital care [69].

Of the 10 759 cases in this database with information on probable country of infection, 3599 (33.5%) were reported to have imported the infection. Returning travellers from the USA, Spain, the UK and Mexico (n=2348) accounted for 65.2% of the travel destinations. This proportion is much higher if only the first few weeks of the cases are considered as the denominator.

The age-specific patterns represented by these overall figures compare well with the early data on the first patients in national reports by several countries [63, 64]. The heavy influence of the UK on the overall database is a result of it having experienced the majority of the spring/summer transmission that took place in the EU/EEA and to have a relatively good surveillance data collection system in place. The heavy spring/summer load on the UK is likely to have been a result of the close travel links with North America and perhaps the relatively late date of closure of the UK schools for summer holidays [70].

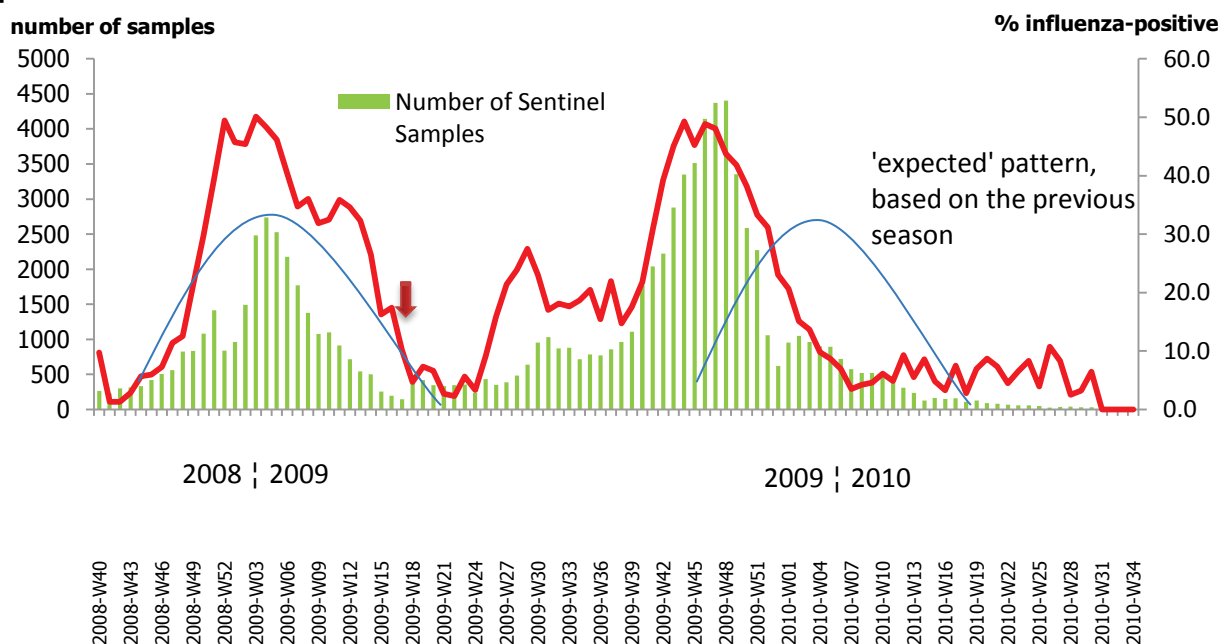
The general results of the EWRS case based database also compares well with the early data from the USA. One early summary report (issued in January 2010) on the first 99 patients with laboratory confirmed H1N1 admitted to New York City hospitals, showed that approximately 60% of admitted patients were younger than 18 years of age. The most common age group was the 5–17 year olds (n= 39 (39%)) and 55% (54 cases) were in males. The most commonly documented underlying condition in these 99 hospitalised cases was asthma, observed among 50% of patients younger than 18 years and 46% of adult patients. Multiple underlying conditions were observed in 17% of patients (12% of children, 24% of adults) [71].

3.4 Virology of the novel virus

The novel virus contained a combination of eight gene segments never reported before in the Americas or elsewhere. The new A(H1N1) genome contained six gene segments similar to ones in triple-reassortant swine influenza viruses circulating in pigs in North America. Another gene appeared to be derived from avian influenza viruses from the North American lineage, while the last gene came from human influenza A viruses. The swine influenza H1N1 gene components of the 2009 virus can be traced back to the 1918 A(H1N1) pandemic strain (Spanish influenza). It is widely believed that, around that time, a presumably new influenza virus with a novel set of eight influenza gene segments—probably derived from an existing avian virus—became adapted to mammals. This new A(H1N1) virus went on to cause the historic 1918 pandemic, during which humans also transmitted the virus back to pigs, and where its progeny remain in circulation today. Since then the virus evolved on separate tracks in the two hosts—evolving more slowly in pigs—in which it reassorted to form the North American triple swine flu reassortant [72]. Since 1918, the swine H and N surface proteins have changed much less than in the human H1N1 virus. Therefore, even though the current human interpandemic A(H1N1) and the 2009 pandemic A(H1N1) have the same 'H' and 'N' nomenclature they are actually very different, so that it can be assumed that most humans have little immunity against the 2009 pandemic strain. So, although the 2009 H1N1 pandemic virus is a new subtype for humans, it represents yet another genetic line of the same 1918 virus [6]. This is supported by the observation that people who had some protection against the 2009 pandemic virus were older people who most likely benefited from their encounters with old A(H1N1) viruses (virus progeny closer to the 1918 pandemic strain), before this group was supplanted by A(H2N2) in 1957 [67].

Over the 2008/2009 influenza surveillance season (i.e., from week 40/ 2008 to week 20/ 2009), sentinel physicians in the EU/EEA had submitted 41 064 respiratory specimens of which 12 244 (29.8%) tested positive for influenza virus (Figure 10).

Figure 10: Distribution of the number of sentinel samples submitted and the percentage found positive for influenza, seasons 2008/09 to 2009/10, in 28 EU/EEA countries. (Arrow denotes the probable start of the pandemic)

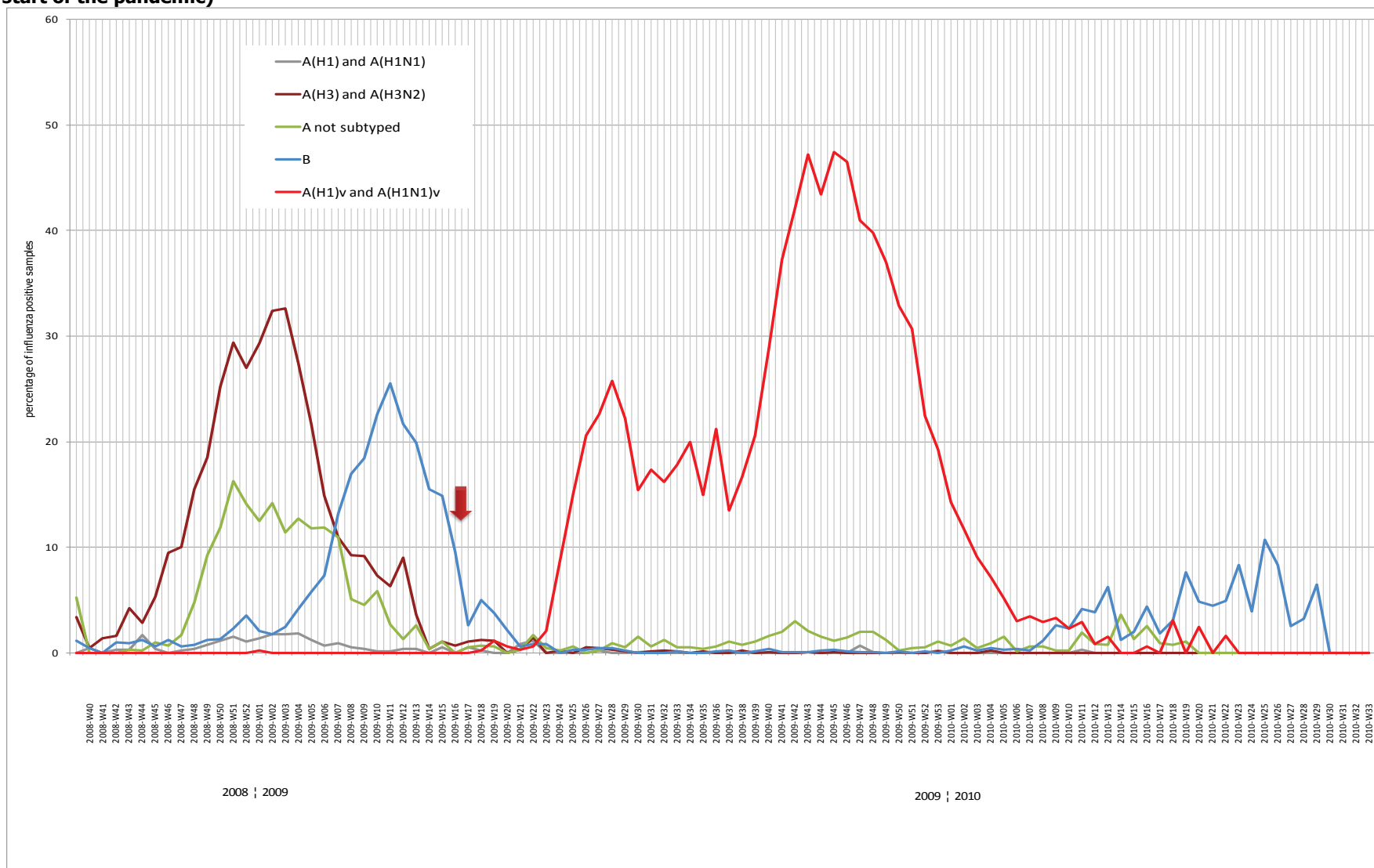


Source: EISN reports.

Source: EISN data in TESSy. (note the blue arrow denotes the probable week of entry of the pandemic strain in the EU/EEA countries).

Of those interpandemic (2008/2009) samples found positive for influenza virus, 84% were found to be type A (predominantly H3 and H3N2), and 16% were type B (Figure 11). Of the 6658 antigenically and/or genetically characterised influenza viruses, 4615 (69.3%) were found to be A/Brisbane/10/2007 (H3N2)-like, 250 (3.7%) were A/Brisbane/59/2007 (H1N1)-like, 357 (5.4%) were A /California/7/2009 (H1N1)v -like, 1379 (20.7%) were B/Malaysia/2506/2004-like or B/Brisbane/60/2008-like (B/Victoria/2/87 lineage) and 57 (0.9%) were B/Florida/4/2006-like (B/Yamagata/16/88 lineage).

Figure 11: Distribution of virus types detected from sentinel samples, seasons 2008/2009 and 2009/2010 in 28 EU/EEA countries. (Arrow denotes the probable start of the pandemic)



Source: EISN reports.

As the normal 2008/2009 season tailed off into the start of the pandemic in the spring/summer of 2009, there was a massive demand for the subtype-specific, real-time polymerase chain reaction (RT-PCR) developed for the new A(H1N1) sub-type, usually denoted at this point as A(H1N1)v. This was made available on the last week of April 2009 and was more or less in common use throughout EU/EEA about two weeks later. This may have slightly delayed the increase in the proportion of positive influenza results in the samples of suspected pandemic influenza cases submitted for testing. Alternatively, many of these early test results were listed either as 'A unsubtypeable' or just 'influenza A' due to the availability at the time of unspecific H1N1 probes; therefore the proportion of confirmed A(H1N1)v should be even higher. Nevertheless, from week 21/2009 to week 32 of 2010 (the official end of the pandemic), there were 61 086 samples submitted by the sentinel practices, of which 31.5% were found positive, mainly with A(H1N1)v.

Viruses collected in EU/EEA countries are characterised by national reference laboratories, and for international comparison a subset is characterised by the London-based WHO Collaborating Centre (WHO CC) for Reference and Research on Influenza. This centre is an established contributor to the WHO recommendation on the composition of influenza vaccines [73]. During the spring/summer wave, the positivity rate for pandemic A(H1N1) virus among sentinel samples rose to a more or less steady 20% where it persisted. In early autumn, especially from week 43/2009 to 49/2009, more than 3000 samples per week were submitted, (peaking at 4405 in week 48). The overall positivity rate rose sharply to remain just below 50% for the remaining weeks of the year and only started to drop around the time schools closed for the festive season. Almost 100% of the samples submitted by sentinel cases and found positive were identified as the 2009 pandemic A(H1N1) virus during this period.

All viruses characterised by the WHO CC in London from samples collected in EU/EEA countries between January and March 2010 were found to be 2009 pandemic A(H1N1). A minority of the viruses show a four-fold reduction in titre with the antiserum raised against the vaccine virus A/California/7/2009, but these are not considered epidemiologically or antigenically significant. Gene sequence analysis of a subset of recent viruses and clinical specimens shows that circulating viruses continue to remain genetically similar to the prototype and vaccine viruses [74].

An interesting observation in Figure 11 above is that influenza B viruses emerged quite prominently towards the end of 2008/2009 season, as expected in a normal season. Despite the arrival of the pandemic A(H1N1) and its total dominance over the other strains, influenza B still managed to make an appearance.

3.5 Antiviral susceptibility

The antiviral resistance profile of the pre-pandemic strains together with the 2009 pandemic A(H1N1) is summarised in Table 2.

This table compares the profiles of the virus circulating during the pandemic (sampled week 40/2009 to week 18/2010) with that of the previous year (sampled week 40/2008 to week 39/2009).

Of the 1453 samples with the pandemic virus A(H1N1)v from nine countries collected from week 40/2009 to week 18/2010, 37 (2.5%) were found to be resistant to oseltamivir with the H275Y mutation in the neuraminidase gene and, of 1447 viruses tested during the same period, none were resistant to zanamivir (Table 2). All the samples of the pandemic virus were found to be resistant to M2 inhibitors, the adamantanes. The Netherlands reported a single isolate with reduced sensitivity against oseltamivir as well as zanamivir in week 14/2010 [75]. Following investigation, most of the cases of oseltamivir resistance were in persons with altered immunological competence who had been treated with oseltamivir. There were reports of occasional person-to-person transmission of oseltamivir-resistant viruses, but these were very few and unlikely to be of any significance. The pandemic strain does not appear to have developed the capability to transmit as efficiently as in inter-pandemic influenza A(H1N1) with the H275Y mutation [27].

Table 2: Antiviral resistance by influenza virus type and subtype, over the last two seasons (weeks 40/2008–18/2010) in samples collected by primary care sentinel networks in the EU/EEA

Virus type and subtype	Resistance to neuraminidase inhibitors								Resistance to M2 inhibitors			
	Oseltamivir				Zanamivir				Isolates tested	Resistant	Isolates tested	Resistant
	Isolates tested	Resistant	Isolates tested	Resistant	Isolates tested	Resistant	Isolates tested	Resistant		n (%)		n (%)
		n (%)		n (%)		n (%)		n (%)	n (%)	n (%)		
wk 40/08 to wk 39/09		wk 40/09 to wk 18/10		wk 40/08 to wk 39/09		wk 40/09 to wk 18/10		wk 40/08 to wk 39/09		wk 40/09 to wk 18/10		
A(H3N2)	653	0	0	0	612	0	0	0	644	644 (100)	0	0
A(H1N1)	260	256 (98)	0	0	260	0	0	0	124	1 (1)	0	0
A(H1N1)v	424	0	1453	37 (2.5%)	415	0	1447	0	56	56 (100)	205	205(100%)
B	117	0	0	0	113	0	0	0	NA*	NA*	NA*	NA*

* NA - not applicable, as M2 inhibitors do not act against influenza B viruses

Source: EISN and CNRL data in TESSy.

3.6 Variants, severe disease and D222G substitution

Towards the start of the pandemic, a specific mutation was observed in samples taken from a few patients with severe disease. On retrospective analysis, this mutation had very likely already occurred as early as spring 2009 in Mexico, but was best described in samples collected from May 2009 to January 2010 in a study of severe disease in Norway [76]. Here they described the occurrence of an amino acid substitution, aspartic acid to glycine in position 222 (D222G) in the HA1 subunit of the viral haemagglutinin. The mutation was observed with significantly higher frequency in clinical cases that resulted in severe or fatal infections in Norway [76], Hong Kong [77], India [78] and all together from at least 20 countries across the world [79]. The mutation was not found in a series studying several hundred mild cases [76, 77]. The substitution has been associated sometimes with nucleotide mutations occurring during isolation of the virus and which have not been seen in the original clinical specimen [79]. However, some mixed populations of D222G mutation and wild-type have also been detected [76, 77]. The D222G substitution viruses do not form a genetically distinct cluster and have not been reported to be associated with antigenic changes. Experiments with ferrets have not supported a causal link of D222G substitution with higher virulence [79]. Based on the currently available virological, epidemiological and clinical information, the substitution does not appear to pose a major public health concern [80].

3.7 Pandemic influenza and interpandemic influenza—similarities and differences

There are both distinct similarities and significant differences between the 'old' (1999–2009) interpandemic influenza and the 2009 A(H1N1) pandemic influenza. The similarities are a result of some common features. First, the modes of transmission (droplet, direct and indirect contact), incubation period and serial interval were similar [81]. Also, patients in both infections seemed to be most infectious when they had their initial symptoms. The general clinical presentation and case definition are similar, except that there are reports of more cases with diarrhoea with the pandemic infection than is usual with seasonal flu [82]. It appears that the personal hygiene measures (frequent handwashing, using tissues properly, staying at home when ill) are likely to have been effective for both types of influenza [83, 84] and that in temperate zones, such as Europe, transmission tended to decline for both in the spring and summer, though this effect was far more pronounced for interpandemic influenza than 2009 pandemic influenza. Also similar was a higher level of transmission detected in children in both interpandemic and this pandemic influenza.

Regarding the differences between the interpandemic and 2009 pandemic influenza, the timing of the pandemic was different, starting 'out of season' for Europe with a spring/summer initial wave followed by an early autumn/winter wave (Figures 5 and 10). The new virus almost entirely displaced the preceding duo of circulating influenza A viruses—A(H1N1) and A(H3N2)—and co-existed with only some influenza B viruses that came late in the 2009/2010 winter season. The setting for transmission of interpandemic influenza is known to be any setting where people gather; however, for the 2009 pandemic, schools [85] and households [86] were especially important. The intensity of interpandemic influenza transmission in the general population is variable year to year, but it is estimated that between 5 and 10% of the population become infected. However, in the case of the 2009 pandemic, the prevalence of infection in any local cluster was considerably over 15%, as demonstrated by serological studies [85]. Equally, serology and clinical observations are consistent with an infection with a higher proportion of asymptomatic and mild infections than usual; so much so that the clinical CFR could not be calculated as the true denominator could not be reliably estimated [70].

The most profound difference was in who was becoming sick. During interpandemic influenza, those who experience severe disease are normally those in specified clinical risk groups and older people [33], with around 90% of interpandemic influenza deaths occurring in those aged 65 years or older [87]. However, based on the reports of confirmed deaths to ECDC during the 2009 pandemic, the opposite was the case for this pandemic, with around 80% of these deaths under the age of 65 years. This is consistent with the findings reported in several national reports [34, 88].

In national studies, around 25 to 30% of deaths attributed to the pandemic were in entirely healthy young adults and outside the traditional risk groups. Pregnant women and the obese were uniformly reported to have been at special risk. While young children (younger than five years) experienced high rates of admission to hospital, deaths in this age group were uncommon unless they had a serious underlying condition. One explanation for this age predilection is that many people born before the mid-1950's were shown to have some immunity to the 2009 pandemic as a result of exposure to an earlier influenza with antigenic similarities to the 2009 pandemic strain [89]. Finally, there were some differences in the clinical presentation of severe cases, with the appearance in pandemic cases of viral pneumonia and ARDS, even in young and fit adults. Acute respiratory distress syndrome is seen very rarely in people infected with interpandemic influenza, but in the 2009 pandemic there were several reports from many intensive care units of untreatable or very difficult ARDS cases [82].

3.8 Severity of the pandemic

This was the first pandemic where WHO applied a severity measure. In preparing the pandemic guidance that emerged as the 2009 pandemic plan, WHO was encouraged by experts from EU/EEA countries to develop a severity scale. It produced a three point scale—mild, intermediate and severe—and left the definition of these as a matter of judgement. When Phase 6 was declared and, following expert consultation, the Director General stated this was a moderate pandemic*.

The severity of any pandemic is difficult to define as the term means different things to different people and there is no agreed upon objective scale. An earlier attempt by the USA produced a five-point scale based on measured case fatality rates [90]. However in this pandemic, it proved impossible to measure the CFR quickly and accurately; in fact, this scale was never used for this pandemic. Some candidate categories are suggested in a separate document†.

An overall impression of severity is difficult to provide as the distribution of influenza is notoriously heterogeneous. This was certainly the case in this pandemic. Transmission could be intense in one locality, but much less nearby. This pandemic proved to be burdensome for primary care and at times extremely so for paediatricians in some hospitals, particularly in their intensive care units. In contrast, for those who had been preparing the non-health sectors for significant proportions of essential staff being off work, no real challenge materialised. In general, severity was judged by EU policy makers to be not serious enough to justify applying disruptive public health measures, such as widespread proactive school closures or cancelling mass gatherings [91–93]. However, this pandemic has been sensitive to targeted school closures [70]. An only slightly more severe pandemic would have justified the widespread use of this measure, even if it served mainly to smooth out the intense local peaks of transmission and reduce pressure on hospitals. The two main epidemiological measures of severity are provided by the data collected on the hospitalised cases and on those dying from influenza.

3.9 Hospital sentinel surveillance of severe acute respiratory infection cases

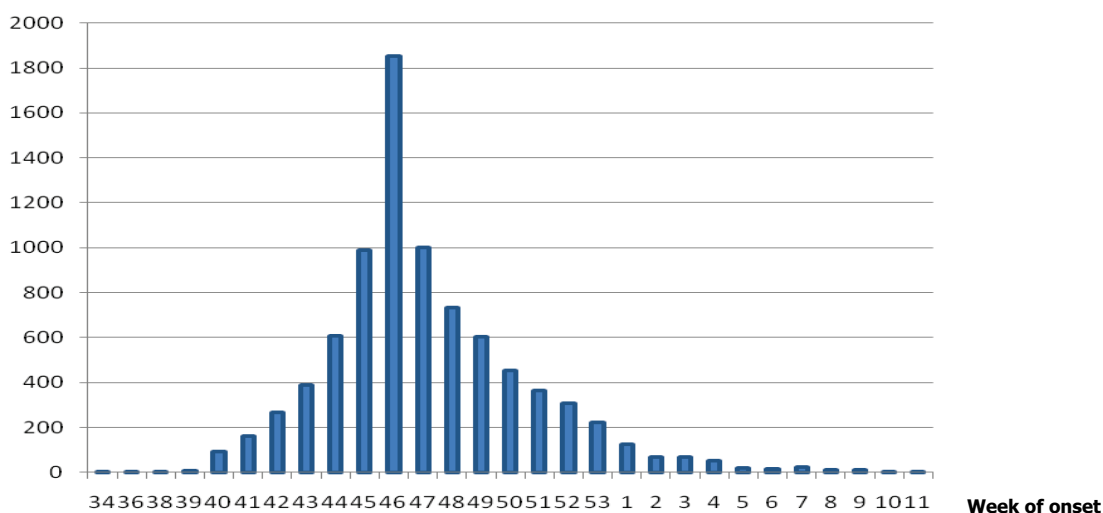
The routine pre-pandemic influenza surveillance systems did not collect data on the more severe cases or deaths. An attempt to collect the first SARI cases, set up in the early stages of the pandemic, met with limited success [94]. During the autumn/winter wave— week 36/2009 to 20/2010—11 904 SARI cases and 586 related fatalities were reported to ECDC by eleven EU countries‡. Using the date of onset of disease, 8443 SARI cases were reported by nine countries that used this parameter (Figure 12).

* See at: <http://www.who.int/csr/disease/influenza/pipguidance2009/en/index.html> and http://www.who.int/mediacentre/news/statements/2009/h1n1_pandemic_phase6_20090611/en/index.html

† For more information, click here:

http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/100505_pandemic_severity_of_pandemics_december_2009.pdf

‡ Austria, Belgium, Cyprus, Finland, France, United Kingdom, Ireland, Malta, the Netherlands, Romania and Slovakia. (France only reported 2009 pandemic influenza A(H1N1) cases admitted to ICU)

Figure 12: Number of SARI cases by week of onset in nine EU countries, season 2009/2010 (n=8443)

Source: WISO reports based on EISN data from 9 countries: Austria, Cyprus, Finland, France, United Kingdom, Malta, the Netherlands, Romania and Slovakia.

Of the 10 014 reported SARI cases with this information, 95.0% were laboratory confirmed for the 2009 pandemic influenza A(H1N1) virus. The median age of these cases was 25 years and the overall male-to-female sex ratio was 1.1. The population, age-specific notification rate was seen to decrease with age, from 21.9/100 000 in children younger than one year old to 1.9/100 000 in those older than 75 years old. Among SARI patients for whom vaccination status against the pandemic virus was known (n=3985), 63.3% of these cases were not vaccinated while 28.7 % received immunisation against interpandemic influenza, and 8.0 % were reported to have received immunisation against the 2009 pandemic influenza A(H1N1) virus (some in addition to the seasonal trivalent vaccine).

In the 4873 SARI cases with the information, at least one documented underlying condition was identified in 73.7% of cases (37.7% had more than one). As expected, the majority of underlying chronic conditions were lung and heart diseases and diabetes; all together, these diseases represented half of all reported conditions.

Five countries (Ireland, Malta, the Netherlands, Romania and Slovakia) reported data on the type of hospitalisation (ICU vs in-patients) and one country (France) changed its strategy from week 45/2009 to report only SARI cases admitted in ICU. One thousand seven hundred and nine of the SARI cases were admitted to intensive care units (ICUs) with complications. These patients were older (median age 44 years old) than patients with less severe disease, but contrary to what is expected in interpandemic flu, the majority (88.6%) of SARI cases admitted to ICU were under 65 years of age. Of the 1508 SARI patients in ICU with available information, 68.4% needed ventilation and 27.6% just needed oxygen support. Of the 1133 SARI patients in ICU with documented complications, 58.9% presented an ARDS and 39.8% with pneumonia with secondary bacterial infection. The mortality rate in the 612 ARDS patients was 24.5% (n=282), while it was 20.3% of the 414 patients with a bacterial pneumonia. Of all the 1670 SARI patients admitted to ICU, 17.2% died. The case fatality ratio (CFR in ICU patients steadily increased with age, from 4.0% in infants to 39.7% in those older than 75 years old.

In previous pandemics, pregnancy had been recognised to be a risk factor associated with complications, especially late pregnancy, and this had also been observed in North America at an early stage for this pandemic [89]. In total, 202 pregnant women were hospitalised with SARI, with no fatalities. Of these, 67.3% had no underlying conditions.

The crude CFR among all SARI cases for which this information was available (n=9586) was 6.5% overall. Aside from the presence of underlying conditions that affected the prognosis, age was also an important determinant. The median age of SARI patients who died was 50 years but 77.5% of deaths occurred in patients younger than the age of 65 years [94], slightly higher in males (males to females ration: 1.42). The CFR remained low with those younger than the age of 24, and then increased steadily up to 27.1% in persons aged 75 years and older.

3.10 Mortality attributable to influenza and disease burden

The true total number of annual deaths caused by influenza virus infection cannot be determined without special studies and even then this can only be an estimate [95]. This is because influenza symptoms are not specific, laboratory testing is usually uncommon and deaths are rarely coded as influenza in death certificates [34]. Most (around 90%) of the deaths caused by interpandemic influenza occur in people older than 64 years of age who also suffer from one or more chronic underlying medical condition. In such cases acute influenza may contribute

significantly to death but testing for influenza viruses is rarely done, so the deaths will most likely be attributed to the underlying medical condition, exacerbations of chronic obstructive pulmonary disease (COPD), pneumonia or cardiovascular complications [35].

Nevertheless, some relatively reliable estimates of the number of influenza associated deaths have been produced for various seasons and settings. These consistently showed that a substantial proportion of the excess deaths occurring during the periods of influenza circulation each year can be attributed to influenza [96, 97, 98]. The most commonly applied method uses statistical models designed to calculate excess mortality that occurs during the period when influenza viruses are circulating widely in a given population [95]. The models use official data on causes of deaths from vital registries and compare the number of deaths during epidemics of interpandemic influenza with a baseline number of deaths expected in the same period if there was no influenza circulation, estimated using historical data. Excesses can be calculated for all causes of deaths or for specific causes that can be related to influenza infection such as pneumonia, influenza and cardiovascular causes. This accounts for the fact that many deaths are not coded as influenza, so including only deaths when influenza is mentioned in the death certificates would lead to severe underestimations of the true influenza attributable deaths [99].

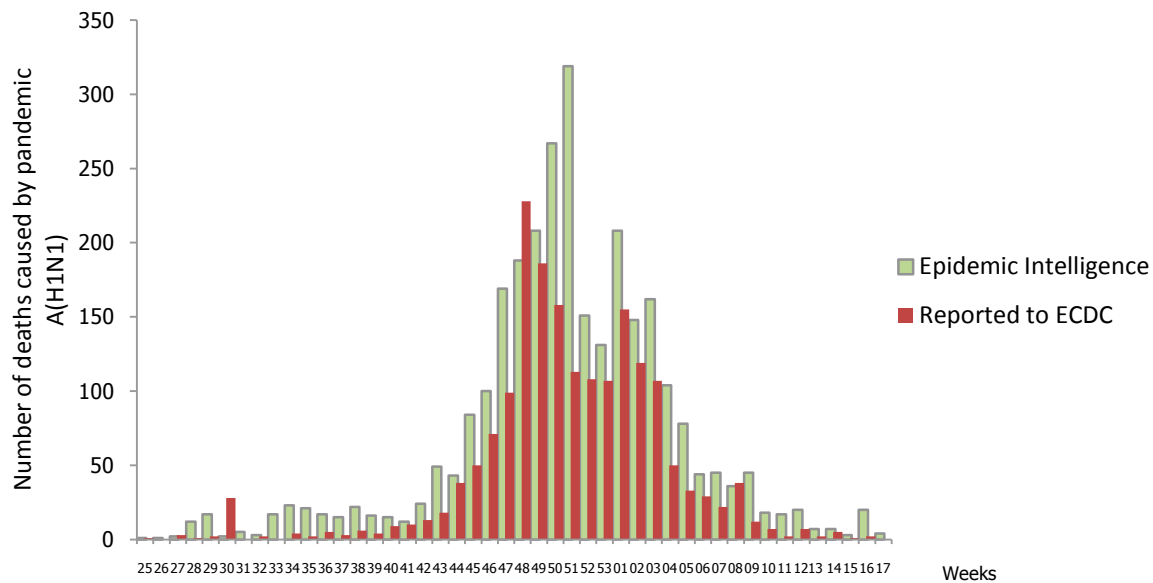
In the first year of the pandemic, 1975 laboratory-confirmed deaths (not estimates) were reported to the ECDC; very few deaths were reported after April 2010. As for all forms of influenza, these are known to be a considerable underestimate of the true picture of mortality during the pandemic [100]. A study attempting to estimate the true mortality burden and the degree of error in these figures showed that in the first few months of the pandemic, up to 23 July 2009, although 302 deaths were officially reported in the USA, the median estimated number of deaths attributed to the pandemic was 800 (90% range 550 to 1300) [68]. In another study in the USA using the same method, the estimated deaths caused by the pandemic from April 2009 to 13th February 2010 were 12 000 (range 8520–17 620), as opposed to the approximately 2500 officially reported deaths [101]. The CDC's Emerging Infections Programme has come up with an estimate of about four actual deaths for every confirmed reported death when compared to formal death reporting through the Aggregate Hospitalisations and Deaths Reporting Activity (AHDRA) system [102, 103]. Such a simple formula should not be applied to Europe, but it makes the point that reported and announced deaths will be a significant underestimate, as is the case for interpandemic influenza [34].

Another American study applied the method normally used to calculate the excess mortality for interpandemic influenza seasons to the pandemic. Using data from 122 US cities, they estimated that between 7500 and 44100 deaths were attributable to the A(H1N1) pandemic virus in the US, during May-December 2009. As the mean age of reported pandemic deaths was 37 years, they applied the 'Years of Life Lost' (YLL) measure of burden of disease and found that between 334 000 and 1 973 000 years of life were lost as a result of the 2009 H1N1 pandemic during this period. This range touches, at its lower end, the burden of an average seasonal epidemic caused by A(H3N2)—the most virulent interpandemic virus subtype of the last three decades—while the upper range of these YLL estimates for the 2009 pandemic exceeded the burden of the 1968 pandemic, adjusted to the year 2000 population [25].

One study from the UK on the mortality burden from the 2009 pandemic A(H1N1) used data on cases from acute and primary care hospitals whose confirmed cause of death was reported as pandemic A(H1N1). For the 138 reported deaths, they established a CFR of 26 (range 11–66) per 100 000. It was lowest for children aged 5–14 at a rate of 11 (range 3–36) per 100 000, and highest for those older than 64 at 980 (range 300–3200) per 100 000. The median age was 39 (interquartile range 17–57). Fifty (36%) had no, or only mild, pre-existing illness. The age group older than 65 years of age had the lowest estimated incidence rate but the highest CFR. Conversely, those aged 5–14 and 15–24 had the highest estimated incidence rates and the lowest estimated CFR [34, 88]. This further confirmed the protective mechanism against infection in older people due to residual immunity from antigenically similar A(H1N1) strains circulating in the early part of the 20th century [67, 104]. Most patients (n=108, 78%) had been prescribed antiviral drugs, but of these, 82 (76%) did not receive them within the first 48 hours of illness [88]. In the same study, the overall estimated CFR of 26 (range 11–66) per 100 000 was described as 'comparing favourably' with the other twentieth century influenza pandemics [88].

As mentioned previously, EU/EEA countries' surveillance data on deaths officially recognised and reported as due to the 2009 pandemic A(H1N1) were collected from two sources: aggregated data on deaths by age group reported on a weekly basis to TESSy, and through epidemic intelligence (EI) activities. Deaths from influenza were announced by the various Ministries of Health or Public Health Institutes, usually on their websites (Figure 13).

Figure 13: Officially announced and reported deaths due to 2009 pandemic A(H1N1) in the EU/EEA, by week of report, season 2009/2010



Source: EISN reports and ECDC epidemic intelligence data collected from official national websites.

The resultant distribution of reported deaths by week of report from these two data sources (Figure 13) showed a significant difference between the two, with the mean weekly deaths reported by the national websites (63.04) being significantly higher ($p=0.00013$, by paired t-test, with two-tailed distribution) than those reported at the European level (41.33). Also, although the deaths reported to the ECDC appeared to have peaked in week 48, three weeks before those detected by EI, this could be due to reporting fatigue setting in during the peak of the pandemic autumn/winter wave. It is also likely that during the traditional holiday period of weeks 51 and 52, the reporting delay will most likely tend to be longer than usual and deaths notified during those weeks would then be registered later in weeks 1 and 2 of the following year.

At the EU level, mortality data were also monitored in terms of 'all causes excess deaths' through a European project known as the European Monitoring of Excess Mortality (EuroMOMO). This analysed weekly fluctuations of all-cause mortality reported by eight European countries during the period between week 27/2009 and 51/2009 in comparison with three previous years. The aim of EuroMOMO is to provide near to real time monitoring of excess mortality; however, delays in reporting are inevitable and vary between countries and possibly age groups. By pooling data from eight countries, their preliminary results show that the mortality data reported during the 2009 influenza pandemic did not reach levels normally seen during inter-pandemic influenza epidemics. However, they did detect excess mortality in the 5–14 year-old age group compared with excess levels of the previous three years. This estimate is probably conservative due to delays in reporting [105]. However, given the significant background rate of deaths in the EU, substantial numbers of deaths may not be detectable by excess death monitoring, especially if the pandemic coincided with a fall in background rate for any reason.

3.11 Epidemiologic parameters of the pandemic for modelling and forecasting

Expert networks of modellers have been formed globally by WHO, and for the specific picture in Europe by ECDC. Great efforts have been made to ensure no duplication of effort while facilitating sharing of views and data. In particular, these networks collaborated to produce agreed tables of empirically based estimates of parameters, such as those relating to transmission dynamics (reproductive number (R_0)^{*} and serial interval[†]) and severity [81].

Estimates of the attack rates, R_0 and serial interval vary according to the specific conditions (season of year, if from an outbreak investigation, access to care, availability of confirmatory testing, hospital admission practices, etc.) under which they were estimated. In the EU/EEA, the R_0 is likely to have been from 1.1 to 1.4 (95% confidence interval) [81], the serial interval probably 2.2 to 2.3 days [106], the mean generation time between 2.5 and 3 days

* The basic reproduction number (sometimes called basic reproductive rate or basic reproductive ratio) of an infection is the mean number of secondary cases a typical single infected case will cause in a population with no immunity to the disease in the absence of interventions to control the infection.

† The serial interval refers to the time between successive cases in a chain of transmission.

[81] and the mean incubation period from 1.5 to 2 days which is similar to previously circulating influenza strains [81].

3.12 Clinical attack rates, case fatality rates and planning projections

Clinical attack rates, meaning the proportion of the exposed population that were experiencing illness, were especially difficult to determine because of the high numbers of mild and asymptomatic cases. A classical application of an influenza-like illness definition could result in very low attack rates, while more sensitive case definitions pushed the rates up considerably. Eventually, careful serological studies showed the higher rates were closer to the true situation, especially in children [67]. The same applied for estimations of the CFR. Through working with EU/EEA countries, ECDC produced planning projections in July 2009 for the autumn/winter wave in September of that year and then revised these as more information became available in November 2009* (Table 3). Experience in the first infected countries, notably in the Southern Hemisphere, suggested that a simple single curve should be assumed for European MS autumn/winter wave and that it was reasonable to apply a standard 15–16 week curve. This proved to be the case.

Table 3: Planning projections—summary of impact to prepare for a reasonable worst case over the course of the first year of the pandemic. (ECDC and EU/EEA countries, November 2009) [15]

Clinical attack rates:	Up to 20%*
Mortality rates:	Up to 3 per 10 ⁵ of population
Hospitalisation rates:	Up to 100 per 10 ⁵ of population
Absenteeism	No different from a severe normal winter

* An "expected" clinical attack rate is expected to be 5–20%. The number 20% indicates thus, as earlier mentioned, the reasonable worst case scenario.

Note: These are not predictions. These estimates are for planning purposes and represent the reasonable worst case for a country or region where there has been no prior wave. Countries and regions where there has been a sizable first wave could expect a lesser future epidemic wave.

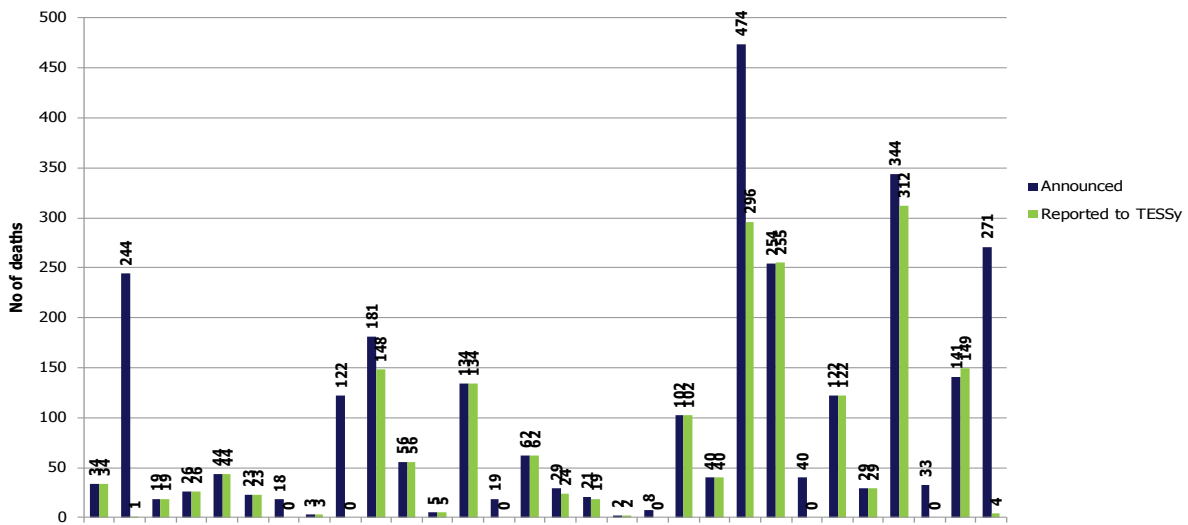
3.13 Performance of the influenza surveillance systems during the pandemic

Overall, the pre-existing surveillance systems managed to hold up well despite the workload, and data kept being collected from clinical care services even during the times of stress. By week 37/2009, the EU/EEA countries had started to report regularly to the new system (WISO) based in TESSy at ECDC. The first WISO report was published on 15 September 2009, covering the data of week 36/2009. Initially, the EU/EEA countries were asked to report through two systems (ECDC and WHO Regional office to Europe), but this was resolved sometime later by applying a technical solution to enable single data entry that supplied both systems. For the most part the new systems worked well, even though they suffered from minor problems that resulted from starting new systems half way through a crisis. Only 11 countries managed to report some SARI data on hospitalised patients (see 3.9), but this at least indicated that such systems were feasible.

Similarly, comparison of the reported and announced deaths suggests considerable reporting delay and under-reporting (Figure 14). Only 15 of the 29 EU/EEA MS reported all the deaths published on their home websites to the ECDC. Of the remaining 14 countries, two countries reported a few more deaths to ECDC than they had announced. On the other hand, two countries reported less than 10% of their announced deaths, while eight MS reported either minimal (such as 1 out of 244) or no deaths at all to ECDC, despite having the data on deaths available and published on their own official websites.

* Available from: http://www.ecdc.europa.eu/en/healthtopics/H1N1/Pages/pandemic_preparedness.aspx

Figure 14: Cumulative confirmed fatal 2009 pandemic influenza A(H1N1) cases (announced and reported deaths), by reporting EU/EEA Member State, as of week 17/2010



Source: EISN reports and ECDC epidemic intelligence data collected from official national websites.

Note: each space on the x-axis represents an EU/EEA MS (anonymised), and the order has been randomised so as not to follow alphabetical order.

Therefore, when it came to information on the severity of the pandemic, much of the important and basic data had to be extracted from epidemic intelligence and targeted science-watch activities.

4 Discussion: European preparation and response

The European Commission and the WHO Regional Office for Europe (WHO-Europe) held a joint meeting in 2005 that was followed by the issuing of new guidance by WHO and a communication from the Commission [107]. Subsequently, ECDC made pandemic preparedness activities one of its top priorities. The pandemic response in the EU/EEA was mainly the responsibility of the EU/EEA countries with the European Commission mandated to coordinate management efforts within the EU.

Therefore an extensive programme was undertaken to varying extents by all MS over the first four years. This was supported by the ECDC's structured mechanism (applied in collaboration with the European Commission and WHO) for the self-assessment of their preparedness plans for a pandemic, applied in all 29 MS. All MS were far more prepared in 2009 than they were in 2005.

The 2009 pandemic was the first full-scale test of ECDC's capacities in a sustained major global outbreak of communicable disease. The young and still growing organisation mobilised all its resources to deal with this challenge, activating pre-planned crisis management structures and procedures. Externally, ECDC support included providing initial threat assessments, a variety of direct technical support, scientific guidance and advice, and communications support and response activities*. Technical support to key stakeholders (European Commission and the EU MS) was also provided, and these measures included the following: developing common case definitions, providing a platform for European surveillance of virology, morbidity (cases and ILI/ARI) and mortality, as well as supporting the health security council in developing EU statements on school closures, travel advice and target groups for vaccinations. Scientific advice took the form of risk assessments, collating and coordinating scientific studies, and coordinating modelling work.

4.1 Adjusting the prepared responses

A major issue that emerged early on was that after the initial uncertainty of the first two months, it quickly became apparent that this was not the major pandemic that countries had prepared for; it was neither A(H5N1) nor a 1918–2019 pandemic-like virus. This posed some difficulty because the pandemic preparedness plans that were already activated by this time had been prepared to respond to a more severe—or worse case scenario—and it took a lot of effort from the EU/EEA countries' advisors to modify their relatively inflexible plans, while dealing with the day-to-day issues brought up by the pandemic.

4.2 Personal measures

Most EU/EEA countries recommended to their citizens to adopt the simple public health measures of respiratory hygiene, handwashing and early self-isolation for those developing illness. This was consistent with what ECDC and WHO recommended [108]. No Member State is known to have recommended mask-wearing outside of health care settings.

4.3 Containment and mitigation

Though containment was not a main strategy of any national plan, once Phase 6 was reached a number of EU countries still attempted to contain or delay the pandemic at national level by implementing such policies as travel restriction and later with a resource-intensive mix of case detection, case isolation, contact tracing and anti-viral treatment of all cases identified. This was quite vigorously applied for example in parts of the UK, the most affected EU country in the spring and early summer. However by late June 2009, it had become clear that, as WHO had advised in April, domestic transmission was inevitable in all countries. This meant that for surveillance purposes, systematic laboratory testing of suspect cases could only be justified for the first few hundred domestic cases in each country and after that only for an occasional sample of cases (for surveillance and for unusual cases). The EU Swedish Presidency took the lead to have this issue discussed by technical specialists and then ministers at a meeting and an informal council respectively in Jönköping in early July†. There the testimony of the experience in the UK and New York City was especially valuable and it was agreed that a move from containment to mitigation

* See at: <http://ecdc.europa.eu/en/healthtopics/H1N1/Pages/home.aspx>

† See Swedish Presidency of the European Union. Press Release July 6th 2009. Available from:

http://www.se2009.eu/en/meetings_news/2009/7/6/press_release_important_steps_towards_an_eu_strategy_for_pandemic_preparedness

should be adopted by EU/EEA countries at a pace they would determine individually* [69]. It is too early to make a final assessment of the true impact, if any, of these containment policies.

Recommendations on antiviral use and practices were not formally monitored, but were seen to vary between countries. The World Health Organization produced evidence-based recommendations on their use [109] while, as befits its mandate, ECDC only produced guidance† dealing with the pros and cons of antiviral use and scientific evidence when questions arose over effectiveness [110]. Most countries seemed to have managed to keep antivirals restricted to prescription only by individual doctors (i.e., avoided changing policies from seasonal usage) but others were more liberal, allowing telephone triage and antiviral advice by trained persons (the UK) or providing pharmacists the temporary right to issue prescriptions, so patients could get a prescription from their doctor or from the pharmacy (Norway). Many countries debated the decision on whether to offer antivirals to all those with symptoms or only to those in risk groups. What is unclear is the extent to which practices followed policies, especially since most primary care doctors in Europe rarely used antivirals for interpandemic influenza [111]. It is however remarkable, from studies of hospitalised influenza patients, how infrequently the use of antivirals prior to reaching hospital was reported [66]. One important influence on the policy chosen was the size of the national stockpile of antiviral treatment prior to the pandemic.

4.4 Effectiveness of interpandemic vaccines against the pandemic virus

Laboratory studies indicated it was unlikely that the interpandemic influenza H1N1 strain vaccine would provide protection against the new strain of A/California/04/2009 H1N1 [11, 112, 113]. This was later confirmed by a series of epidemiological studies and one Canadian series of studies even suggested that prior immunisation with interpandemic influenza increased the risk of laboratory confirmed 2009 pandemic influenza in people seeking medical care [114]. An ad hoc monovalent vaccine that was being developed following the declaration of Phase 6 needed to be produced, tested and distributed in time to protect the population from the 2009 pandemic virus.

Vaccination policies were more standardised despite some initial uncertainty on the one or two dose schedule. This owes much to the advice by the WHO SAGE committee and to a decision by the EU's Health Security Committee (HSC), informed by guidance prepared by the Commission and ECDC [115]. However, the recommendations on 'Risk and Other Target Groups' by the HSC (pregnant women, those older than six months with chronic ill health and healthcare workers) represented a minimum to which all countries could agree. A number of countries went further, from aiming to immunise some children to the entire population. The policies adopted, practices and coverage are now the subject of a Vaccine European New Integrated Collaboration Effort (VENICE) survey undertaken by ECDC for MS and WHO. As before, the policy selected was likely also influenced by that country's availability of the vaccine (pre-ordered).

The European Medicines Agency (EMA) recommended marketing authorisation of two adjuvanted pandemic vaccines—Focetria and Pandemrix—on 25 September 2009 and this was granted five days later by the European Commission. Shortly after that, another non-adjuvanted vaccine, Celvapan, was authorised for marketing in the EU. These vaccines were originally authorised using the mock-up procedure, which allowed fast-tracking of the assessment procedures and then in April 2010 full authorisation was granted, following assessment of additional data from clinical studies [116]. Two doses were recommended in the original opinion on these vaccines by EMA. Already at that stage, however, there were indications that one dose would provide sufficient immunogenicity in most formulations [117]. In addition, in early 2010, Arepanrix and Humenza were also approved centrally for the EU. Despite the rapid central authorisation of these vaccines, Hungary was the first EU country able to start vaccination programs (during week 40) by using national authorisation procedures for the domestically produced vaccine Fluval P. After Hungary, several other pandemic vaccines were authorised within the EU by national authorities: Cantagrip in Romania, Panenza in France, Belgium, Germany, Italy, Luxembourg and Spain, PanVaxH1N1 in Germany, and finally Celtura by Switzerland and Germany.

Conscious of the American experience of cancelling an H1N1 mass vaccination campaign in 1976 after reports of Guillain-Barré Syndrome (GBS) developing in vaccines [118], very close monitoring of adverse events was paid from the very beginning of the 2009 pandemic mass vaccination campaigns in Europe. This resulted in the most sophisticated system of monitoring adverse events introduced in Europe so far. Reporting of adverse events following immunisations (AEFI) are normally the responsibility of manufacturers and national medicines agencies and are monitored at the EU level through EMA's EudraVigilance database. However, due to the special nature of a mass vaccination campaign EMA, ECDC and the heads of national medicines agencies issued a document entitled 'European Strategy for Influenza A/H1N1 Vaccine Benefit-Risk Monitoring'‡ that proposed to establish an information exchange between the main stakeholders—national competent authorities (NCA), public health

* More at: http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

† Various technical guidance reports are available at: <http://www.ecdc.europa.eu/en/healthtopics/H1N1/Pages/antivirals.aspx>

‡ Available from http://www.ema.europa.eu/pdfs/human/pandemicinfluenza/european_strategy.pdf

institutions, the EMA and the ECDC—in order to strengthen the monitoring of the benefits and risks of pandemic vaccines. Two European collaborative projects, Influenza Monitoring of Vaccine Effectiveness (I-MOVE) and Vaccine Averse Events Surveillance and Communication (VAESCO) focussed on monitoring vaccine effectiveness and safety, respectively. These projects are still ongoing.

As of 19 July 2010 in the EU/EEA, at least 38.6 million people had been vaccinated with one of the three centrally authorised vaccines. Adding those vaccinated with the nationally authorised vaccines, the total rises to at least 46.2 million people or about 9% of the total population. As of 11 July 2010, a total of 15 376 reports on adverse events had been received (the majority of which were minor events) and the EMA issued 21 safety updates in all the EU languages [119]. Several severe events have been reported including GBS, myocardial infarctions and deaths, but the rates were considered not to differ from the expected background rates in the unvaccinated population.

The WHO Europe office in Copenhagen was involved in all the important meetings with the policy makers. They were instrumental in providing the test kits early and then helped coordinate the provision of antivirals and vaccines from the WHO stockpiles to a number of European countries. As of 3 May 2010, WHO global office had delivered more than 20 million doses of vaccine to 39 out of the 99 countries that had requested donations*. To assist the vaccination programs, WHO developed deployment guidelines and communication packages. A survey was done to inform the distribution policies for the global stockpile. In addition, several countries received laboratory support, training and support in implementing pandemic preparedness plans.

4.5 Limitations of the data

The data presented and analysed here are subject to certain limitations and some of the results should be interpreted with a degree of caution.

The influenza-like illness or acute respiratory infection surveillance data reported are not entirely comparable between countries as there is quite some variability in the data sources. These include the following: different choices of type of physician making up the sentinel networks (also affected by differences in the healthcare systems' organisation and their accessibility); variability in the size and representativeness of the sentinel networks; the accuracy of the estimate of their catchment populations used to estimate the rates varies; differences in the discipline with which the case definitions are applied; differences between countries in the rigour and resources devoted to collecting and validating this data and also to the degree of epidemiologic investigation and systems to report back to the participants (hence indirectly influencing the reporter's enthusiasm, with implications on the completeness of data). As such, the height of the curves from individual countries cannot be compared; neither can they be considered as a true measure of either attack rates or comparative severity between the countries. The ILI/ARI epidemic curves were also distorted during the pandemic and therefore did not necessarily reflect the true course of events. This was partly due to several countries, at different points in time, actively recommending that anyone with influenza-like symptoms stay at home and not approach their primary care provider (unlike what they would do in a normal flu season), thus excluding them from the possibility of being reported. Also, it is well known that influenza, including the pandemic variety, always shows a wide range of morbidity, with the majority of infections so mild that the individual does not usually seek medical attention, although this healthcare seeking behaviour is known to vary widely between countries. The surveillance data presented here omits any estimate of this sizable underestimate of these infections. In times of heavy workload, it is likely that a few of the primary care providers responsible for reporting to the sentinel networks will have less time to devote to administrative matters such as notifications, so the number of reported ILI or ARI cases at this time may be slightly less. Opposing this, in the middle of a season, the majority of respiratory cases are diagnoses as ILI leading to some over-reporting. Finally, early on in the development of the sentinel ILI/ARI surveillance and in the interest of keeping reporting as simple as possible (hence facilitating the implementation and the sustainability) capturing gender as a variable did not occur and the data only included four very broad age groups (not appropriate for the 2009 pandemic). For basic monitoring and planning purposes of seasonal flu, these omissions were probably acceptable; however, for monitoring in a pandemic, the limited variables are quite inadequate.

The qualitative data (mainly intensity and geographic spread) collected was originally intended to provide a quick picture of the situation throughout the EU during the previous week of report. These estimates of intensity, geographic spread and trend of influenza activity in any particular country are only partly standardised indicators. The intensity scale is based on comparing current ILI/ARI rates within any country with the country-specific baseline rates outside of the influenza season and with historical values as well as additional sources of information like school absenteeism. However, these baseline rates are known to be estimated using different methods and with varying accuracy, and the recommended scale method is known not to be applied with uneven discipline between countries. The countries that do apply this baseline correctly are still faced with the problem of comparing

* see at: http://www.who.int/csr/disease/swineflu/action/h1n1_vaccine_deployment_update20100503.pdf

the epidemic curve of a pandemic virus with a baseline that was estimated using the data generated by a variety of interpandemic virus epidemics (mainly A(H1) and A(H3) but also B).

The scale of geographic spread is perhaps a simpler, but possibly more subjective, measure and for many countries depends greatly on the opinion of the country expert compiling the data that day (some countries do not even have a regional level as they are too small). The trend estimate is perhaps a little more accurate as it is based on comparing current influenza activity with previous weeks; still, in some countries when the data is minimal or borderline, the interpretation of increasing, decreasing or stable trends finally rests on the opinion of the country expert.

Virological data are derived from samples sent for laboratory testing and confirmation. This represents only a selected subpopulation of the cases, usually the more severely affected cases that go to visit a general practitioner (GP) or hospitalised patients. The sentinel samples are representative of patients attending GP practices, while the non-sentinel derive from a varying mix of GP diagnostics not included in the sentinel system and more seriously affected cases that are admitted to hospital; so the non-sentinel data is really a mix of mild and severe cases, which can differ by country. The representativeness of laboratory tested samples is also biased by the varying availability of laboratory services across the countries and the different clinical norms and practices applied to taking swabs. In addition only small subsets of these samples, not selected randomly and therefore not necessarily representative of the country, are sent for central antiviral, antigenic and genetic characterisation to WHO-CC and/or HPA, London. In the 2008/2009 influenza season, twenty-one countries carried out antiviral resistance testing and most reported their results; however in 2009/2010, only seven countries reported antiviral data to TESSy.

One important aspect of laboratory-based surveillance that was missing at the European level was serological surveillance. Although a few countries did carry out local studies that provided valuable information [67, 120], this analysis was not carried out in a standardised and comparable manner early on in the pandemic. Also the results were mainly available rather late and it was not clear if the information they provided could be extrapolated to other countries.

The systems for collecting data on the more severe cases (SARI) or deaths were introduced in response to the emergency, after the pandemic had already spread to all the EU/EEA countries. This was a less than ideal time to introduce a new system, as the countries' surveillance systems had to adapt or introduce new processes at a time when their resources were very stretched. Also, the coordinating centre for this data (ECDC/EISN) could not devote sufficient resources to support the country's data collection systems or to help them correctly apply or comply with the guidelines published [57]. As a result, a sizable portion of the data submitted as SARI is known to really represent just those hospitalised cases that were confirmed as having a positive result to the swab for the pandemic virus. The cases from these hospitals were supposed to be reported with some estimate of the capture population of that hospital; however, it is understood that several countries did not have reliable estimates of these denominators, shedding some doubt on the estimated rates. Similarly, the concept of SARI being a sentinel system where the intention is to include only a selection of reliable and representative hospitals (with well-defined capture populations) in the data collection process was not really given enough attention. This resulted in quite some variability in the quality of the data between the countries, and in its completeness and representativeness. Another general limitation with these data is that, even if correctly collected, it will always miss a proportion of cases, so the total number of reported SARI or its rate should be seen as just an indication of the situation and probably best used to monitor trends and perhaps define some major characteristics. This data should not be seen as an accurate measure of the more severe morbidity caused by the pandemic. One study (not on the EISN data) tried to estimate the degree of missed cases, and found that there were probably 2.7 times as many true hospitalised cases due to the pandemic as reported [68].

It is likely that these known problems with the data may have served to put off some countries from reporting their severe cases. Also, as the system was hurriedly introduced in the middle of a crisis, some countries may not have felt confident enough in the quality of their SARI data to share these in an official EU report. This resulted in the SARI data being limited to data submitted from only 11 out of the 29 EU/EEA countries normally reporting, representing just over 40% of the total EU/EEA population. These 11 reporting countries are known to have collected their data in a variety of ways, ranging from a mix of true sentinel hospitals (i.e., well defined, with known served population denominators and standardised reporting practices) to an opportunistic sample of hospitals or even, in the smaller countries, from all their main acute hospitals. In addition, although the majority did try to apply the recommended case definition for SARI [57], it is known that others tended to include all hospitalised laboratory confirmed influenza cases or even all pneumonias notified by clinicians. Another limitation relates to the variability in the resources available and dedicated by the national surveillance authorities to ensure that as high a completeness rate as possible is achieved in these data. It is understood that during a pandemic, the resources devoted to national influenza surveillance will be very stretched— in some countries more than others— and this is not conducive to providing much opportunity for follow-up validation of cases or to systematically collect missing variables. Finally, the shape of most epidemiological curves depicting severe cases in a pandemic is heavily influenced by changes throughout this period in the testing and control policies, especially in bigger locales, like the UK. The steep decline in cases, as was the case after the peak in week 25/2009, can be partly explained by

changing testing policies with a general move away from intense contact tracing and to limit laboratory testing to more severe cases.

Just as reported cases are an underestimate, so is the data on deaths due to the 2009 pandemic influenza. As stated previously, a large proportion of deaths caused by influenza usually occur in the elderly or those who often suffer from one or more chronic underlying medical condition. The impact of an acute episode of influenza will, in many cases, be the last episode that triggers the final deterioration in the general condition of these patients and eventually lead to their death. The death is not necessarily immediate, and some patients may struggle for a few weeks before they finally succumb to a variety of complications, long past the acute episode of influenza. Testing for influenza viruses is not systematically carried out in persons with serious chronic conditions, as most of the clinical attention will be devoted to dealing with stabilising the patient rather than finding out the original cause of their current poor condition. Even so, the availability and level of sophistication of laboratory tests varies throughout the EU/EEA. These factors all contribute to the deaths directly caused by influenza being officially registered as and attributed to the known chronic medical condition, or the complication that arose (like secondary bacterial pneumonia or renal failure), rather than to the true cause. All these factors indicate that official death figures represent a major underestimate of the true picture of mortality during both an epidemic but especially so during a pandemic, and presently only special study can attempt to determine estimated mortality more accurately [100].

5 Conclusions and lessons learned

5.1 Main conclusions

In order to tackle any new threat to health in the EU/EEA countries, decision-makers have to take adequate measures based on scientifically based information. The surveillance systems have managed to describe the main features of the first year of this 2009 influenza pandemic in the EU/EEA.

The most severe period of the pandemic occurred in the second autumn/winter wave starting around week 43/2009. This was the period with the most geographic spread, intensity and hospitalised SARI. The peak of reported mortality was either week 48 (officially reported deaths to ECDC) or week 51 (deaths identified by EI). The risk groups affected by the pandemic were different to those normally affected by the interpandemic flu; while both mainly affected those with chronic medical conditions, the pandemic seems to have targeted more pregnant women and the obese than the interpandemic flu. It resulted in an unusually high number of serious cases and deaths occurring among young people, including the previously healthy, than the interpandemic flu which usually targets the elderly. Pregnant women, including the previously healthy, who contracted pandemic flu were reported to have become more seriously ill and have a much higher risk of dying than in the interpandemic flu [121, 122, 123].

The virological data presented here suggest that the 2009 pandemic A(H1N1) wiped out all signs of any other A strains in the EU/EEA in 2010. The B strains were less affected and made an appearance late in the season. It remains to be seen if these strains will re-emerge after this virus converts into an interpandemic strain, but it is likely that the next season will contain a mix of H3N2, H1N1 2009 and B viruses. The EISN virological surveillance was quick to pick up the first 2009 pandemic influenza viruses, initially through the non-sentinel samples collected from the hospitalised cases—approximately one week after the first official cases in EU/EEA had fallen ill—then through the sentinel networks about two weeks later.

The interpandemic vaccine used in season 2008/2009 did not appear to impart any immunity against the new pandemic strain, but evidence quickly accumulated showing that the specific pandemic vaccines showed a good immune response with an acceptable safety profile [117]. Oseltamivir was used to good effect for prophylaxis as well as for treatment of the infection [110]. To date, only a small proportion of anti-viral resistance has appeared, and this will need to continue to be monitored closely [124].

This information was made available primarily by the surveillance systems established prior to the pandemic. Maintaining strong and well resourced public health authorities and institutes is vital to better prepare and react to the next crisis. In particular, strong microbiology laboratories and epidemiological systems are critical. However, certain gaps exist and these were discussed at the Belgian EU Presidency's Conference on lessons learned from the influenza pandemic A(H1N1)2009 in July 2010*. The surveillance gaps that need further work include the following:

- surveillance of severe disease (surveillance in hospitals) and deaths;
- agreed definitions of severity of a pandemic (but be wary of simplistic solutions here);
- timely information on who has been infected (supported by seroepidemiology); and
- rapid sharing of analyses between member states, even in a crisis.

This implies the need of investment between pandemics to decrease the future level of uncertainty and to improve knowledge quality, extent and timeliness. This should also ensure the ready ability to assess a health threat and to predict its severity is sustained.

From a European perspective, there were many positive general features of the 2009 A(H1N1) pandemic (Table 4).

* For more information: <http://www.influenza.eutrio.be/agenda.html>

Table 4: What was positive about the 2009 A(H1N1) pandemic for Europe and what could have been worse

What was positive about the 2009 pandemic for Europe	What could have been worse
A pandemic strain emerging in the Americas.	Emerging in a less developed setting
Immediate virus sharing and so rapidly available diagnostics and vaccine development.	Delayed virus sharing
Based on an A(H1N1) currently not that pathogenic and without pathogenicity markers.	A more pathogenic virus
Residual cross-immunity in much of a large group (older people).	Near total population susceptibility
Sustained susceptibility to the most commonly used antivirals.	In-built or emerging drug resistance
Good data and information coming out of North America and the southern hemisphere (after the initial confusion over the Mexico data).	No data, incomplete or misleading data
Arriving in the more populous hemisphere in the spring and summer when transmission was muted.	Arriving in the northern autumn or winter
Mild presentation in most people infected.	A more pathogenic virus
A virus that is highly immunogenic, usually requiring only a single dose of vaccine	Poor immunogenicity and requiring larger amounts of antigen or multiple injections

The early detection of the pandemic strain, the immediate virus sharing (so diagnostic tests and then vaccines were available very rapidly), the chance to learn from others' experiences [125] and the presence of some pre-existing immunity among the elderly all contributed to help mitigate the impact of this pandemic in the EU. Finally, EU/EEA countries had been preparing for a pandemic for five years, albeit one rather different from that of 2009, hence unlike certain countries in the Southern Hemisphere, they were not caught unawares or totally unprepared. * The lesson here is that although they coped relatively well, the existing preparedness plans (both at the national and at the EU level) and systems need to be revised to build in the necessary flexibility to ensure they can be adapted rapidly to differing types and severity of crisis; should be to coping with a crisis. However it will be hard to proceed with planning all of these revisions until the global process is completed or nearing completion, otherwise the national plans may diverge and risk having to be revised a second time.

On the other hand the last pandemic before this one occurred more than forty years previously, in 1968. As a consequence there were a series of novel 'firsts' that made the 2009 one challenging among modern pandemics (see box below). Immediate communications and readily available television footage led to popular (mis) perceptions of severity in countries like Mexico and Ukraine that were misleading to the casual viewer who did not consult the technical WHO and ECDC risk assessments [17, 18]. The pandemic followed a period of preparation and investment that raised expectations that countries should be ready for anything and also that the expected pandemic would be more severe than what actually emerged [126].

* See more: http://ec.europa.eu/health/ph_threats/com/Influenza/influhome/influenza_level_en.htm and: http://www.ecdc.europa.eu/en/healthtopics/Pages/Pandemic_Influenza.aspx

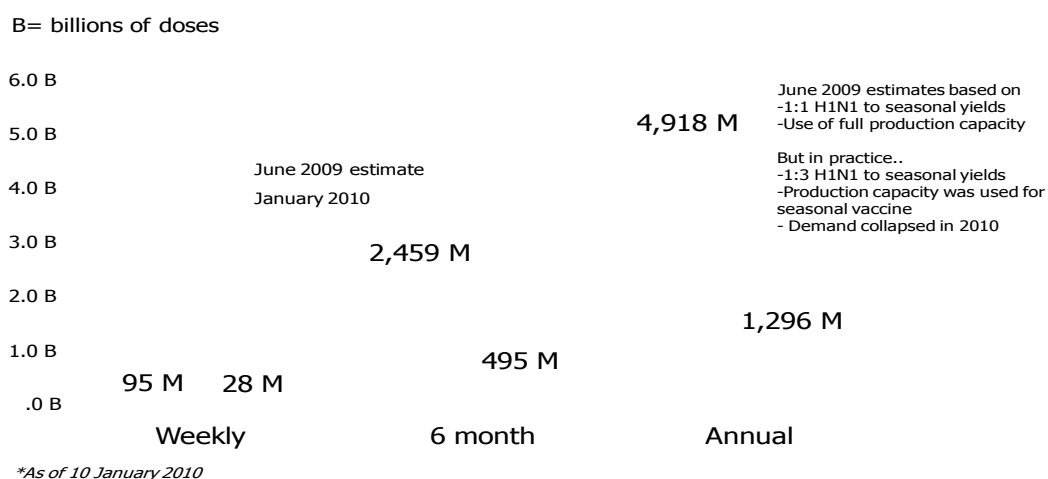
The following is a list of 'firsts' about the 2009 A(H1N1) pandemic:

- It was the first pandemic to occur after major global investments in pandemic preparedness had been initiated; therefore expectations to deal with it swiftly and efficiently were high.
- It was the first time in a pandemic where effective prevention and treatments (vaccine and antivirals) could be made available through healthcare professionals, implying that it was important to maintain high morale and confidence in these doctors and nurses.
- It was the first pandemic that took place within the context of a set of IHRs and global governance, which had not been tested until this crisis appeared.
- It was the first pandemic with early diagnostic tests, that led to rapid diagnosis but also a high demand from the media and policymakers for the latest numbers of those infected.
- It was the first pandemic with antivirals available in many countries that led to a hopeful expectation that the pandemic might be containable, leading to the implementation of a 'containment phase'.
- It was the first pandemic where intensive care was available in many countries to treat critically ill patients, fostering an expectation that everyone could be treated and cured.
- It was the first pandemic with instant communication, so that early impressions (such as the experience in Mexico and the Ukraine) could be shared ahead of proper scientific analysis.
- It was the first pandemic with a blogosphere and other rapid communication tools that were impossible to ignore.

For the first time there were effective preventive pharmaceutical countermeasures: antivirals and vaccines [127]. These had to be provided by primary care medical and nursing staff and it was essential that their confidence and morale were held high to facilitate acceptance, response and compliance by the general population. Unfortunately, there were a few instances where certain healthcare professionals cast doubts on the safety or effectiveness of these countermeasures, with serious repercussions on their general acceptance. Another consequence of the antiviral use was that, in combination with hopes for early containment in WHO Phase 4, they led some policy makers to attempt a policy of containment, despite WHO and ECDC advice to the contrary [69, 128].

Equally, the mass availability of tests in some countries led to the possibility of case-finding, contact tracing for prophylaxis or treatment, and then for numbers of cases to be counted. This, in turn, led to persistent demands for daily case counts by decision makers and the media, long after trends had become far more important than exact numbers. For the first time, rapid mass production of specific vaccines was attempted. Many EU/EEA countries, with or without advance-purchase agreements, asked companies to produce vaccines on a scale far greater than for interpandemic influenza. Decisions on risk and other target groups were coordinated by the WHO SAGE committee globally and, in Europe, the Health Security Committee agreed on at least a minimum list of target groups for all EU countries [115]. Licensing went smoothly and distribution plans were made. However, the tempo of production fell short of what was optimistically anticipated. Figure 15 summarises the situation as estimated by WHO [129, 130].

Figure 15: Global pandemic (H1N1) 2009 vaccine: planned vs. actual production (January 2010)



Note: reproduced with permission from WHO

There were also issues with distribution of the vaccine in a number of countries. Another concern was the publicity surrounding the varying belief in the need for vaccination expressed by healthcare professionals and by certain opinion leaders. As yet there are few data on coverage to allow comparisons between countries. In contrast to these problems, the post-marketing surveillance and pharmacovigilance worked well under the coordination of the EMA and an EU Vaccine Task Force [131] as well as with projects like VAESCO.

On the treatment side, hospitals' intensive care services had developed extensively since the last pandemic, but the general expectations of being able to treat all very sick people proved illusory in situations where there were many cases admitted at once. Many of the primary pneumonias proved highly resistant to treatment and support and, as with the SARS experience, a real difficulty emerged in sharing clinical experiences rapidly across language barriers in Europe [82].

On balance, it is probably fair to say that EU/EEA countries managed the response to the pandemic moderately well but if a more severe pandemic had hit, the situation may not have been so favourable. The lessons learned are the subject of multiple national, multinational and international reviews in European countries.

However, the definitive global review will be undertaken for WHO by an independent committee with a chairman who reviewed the 1976 swine flu outbreak in the USA [16, 132].

While it would be premature to prejudge the findings of the on-going reviews in detail, some initial comments are self-evident and can be stated now. Most preparedness plans and preparations were made in anticipation of something more severe than what emerged with the 2009 pandemic. There is evidently a need for greater flexibility to be built into future preparedness plans and to allow for a variety of scenarios.

The concept of severity needs to be further developed, acknowledging its complexity but not neglecting the other essential parameters for mitigation [12]. Engaging the EU Presidency is clearly important as leadership is vital to help achieve a harmonised approach to difficult risk management issues*.

Although virological and primary care-based surveillance worked better than expected during the pandemic, this does not mean they would prove to be resilient enough in a more severe pandemic. As with SARS, the biggest challenge for epidemiological surveillance proved to be at the hospital level more work in the EU/EEA is needed here to develop routine sentinel surveillance for SARI. Additionally, it is evident that joint microbiological, clinical and epidemiological protocols for investigating cases of outbreaks of severe respiratory infections and influenza need to be developed. Other observed weaknesses were seen in obtaining correlates of infection or protection by the use of seroepidemiology. It remains unclear just how to correlate the true degree of immunity to the pandemic virus as the role of cell-based immunity is ambiguous. For serology, it is unfortunate that analyses of the proportion of the population infected in the first winter were only becoming available nine months later. This can be improved if appropriate sites in Europe that could undertake quick serological work are identified in advance, including some where epidemiological data linkable to sera would be possible. The current tests (haemagglutination and microneutralisation) are labour intensive, demanding and often give unstable results. There is a need for a research initiative looking to develop less demanding and more reliable tests. Extending the general rule that a pandemic is an inopportune time to develop new surveillance systems, there should be annual serological collections or surveys possibly linking with those for other vaccine preventable diseases [67]. Routine serological standards should be produced, like those currently coming from the National Institute for Biological Standards and Control (NIBSC) in the UK. Finally, it has to be possible to increase laboratory capacity rapidly and reliably in a crisis, and perhaps a European mechanism to test specimens from anywhere in the world en masse. Preparedness plans should allow for spare capacity arrangements during a pandemic to avoid these same virologists having to continue carrying out the other routine diagnostic work as well as supervising these technically demanding serological investigations.

A general conclusion is that, in the future, there should be greater commitment to share early analyses from the first affected countries. Despite the obligations to do this under the IHRs and EU Decision 2119 [43, 133], this did not happen during the crisis. This was most likely due to people simply too busy to decide what could and should be shared with other countries, or perhaps the epidemiologists did not have sufficient confidence in their early data and analyses to share this with others. Unfortunately there were suggestions that some reports with early analyses were not shared because it was believed that this would possibly prejudice publication. A balance between these competing interests needs to be found. It is clear that in times of crisis there is a need to ensure a common approach at the EU level for rapid data sharing and sharing of analyses, which should then be included in the national preparedness plan. This may require a review of operational and notification tools.

Concerning the clinical care response, the main difficulties were most probably felt by the intensive care services and the paediatric care services. Surge capacity needs to be strengthened in these areas, especially if a more severe pandemic emerges. Also, the ability of clinicians to quickly share their clinical experiences and lessons

* For more information, click here:

http://ecdc.europa.eu/en/healthtopics/H1N1/Documents/110810_2009_pandemic_European_Timeline.pdf

between the affected countries and across the language barriers needs to be improved. This weakness was evident in the SARS crisis and it is disappointing to be faced with the same problem re-occurring seven years later.

The rapid and persistent efforts to ensure some degree of coordination of response by the EU/EEA countries made by the Commission, the ECDC and WHO certainly helped to maintain a greater level of control over the situation. These institutions were especially helpful in ensuring that MS technical advisors consistently countered the steady stream of myths and rumours that arose in or from the media.

Nevertheless, their main challenge was in dealing with the perception and communication of risks. In future, those involved in risk communication need to develop ways of better involving the scientific community and civil society. Their aim must be that risk is properly understood and trust maintained.

5.2 What next?

The timeframe for the transition from a pandemic to an interpandemic pattern is uncertain. It can happen promptly (1957 pandemic) or take two seasons (1918 and 1968 pandemics). The formal name of the transition phase (which is still in the pandemic period) is 'post-peak', which is then followed by a post-pandemic phase, sometimes with an intervening renewed wave of infection [23]. There is no sign of another spring/summer pandemic wave in EU/EEA. It seems likely that even though WHO has decided that the post-pandemic phase has been reached, the EU/EEA will continue to experience low-level transmission and small outbreaks of the pandemic 2009 A(H1N1) influenza during the next (2010/2011) winter season, at least in very young children and other susceptible individuals. Europe will now be dealing with a new interpandemic influenza [134].

The global review report on the pandemic will be presented at the World Health Assembly in May 2011. The EU/EEA will then work on revising its planning for the next pandemic; not solely based on its 2009 experiences however, as this was not a typical pandemic (not that such an entity exists) [135].

The work on improving surveillance of more severe disease will now be taken up in earnest. If routine surveillance of influenza (interpandemic variety) is strengthened and the initiatives that were started in response to this pandemic allowed to develop further, then these measures will not need to be modified in a crisis year or even a pandemic. This enhanced surveillance should be able to provide data to better determine and monitor burden and provide information on those at higher than average risk of adverse outcomes of infection with influenza, the risk groups most deserving of immunisation [136]. Europe had been preparing for a pandemic for five years, some countries for even longer. Despite this, in some countries, there is a sense that things did not go as well as planned. There is criticism of WHO and other international authorities suggesting that this was not the crisis expected of a true pandemic and a series of pandemic myths have emerged. In reality, much more went well than did not. It is hoped that the main lessons learned, from public health and clinical perspectives, and especially about the vital role good communication plays in such a crisis, will help refine plans and allocate enough resources to do better next time (all evidence available today suggests that there will be a next time), even if the severity of the next pandemic is worse than the 2009 pandemic A(H1N1).

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