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Special edition:
Influenza

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In this special edition Eurosurveillance covers various aspects of the 2009 influenza A(H1N1) pandemic. The compiled articles provide information and data on epidemiological patterns, surveillance trends and a first analysis of vaccine effectiveness of the trivalent seasonal influenza vaccine for 2010/11 influenza season and of the monovalent influenza A(H1N1) 2009 vaccines. It also features a paper on the possible impact of media coverage on consultation rates.

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EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

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Editorial team

Based at the European Centre for
Disease Prevention and Control (ECDC),
171 83 Stockholm, Sweden

Telephone number

+46 (0)8 58 60 11 38 or +46 (0)8 58 60 11 36

Fax number

+46 (0)8 58 60 12 94

E-mail

Eurosurveillance@ecdc.europa.eu

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2010-2011 influenza seasonal vaccine, preliminary mid-season effectiveness estimates: reason for concern, confounding or are we following the right track?

J Puig-Barberà (puig_joa@gva.es)[1]
1. Vaccines Research Unit, Centre for Public Health Research, Valencia, Spain

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During the last 10 years there have been major advances in influenza surveillance, vaccine production and methods to determine vaccine effectiveness (VE), influenza diagnosis by real-time polymerase chain reaction (PCR), and influenza virology. Most of these have been fostered by the threat of a possible pandemic and the planning efforts devoted to minimising its impact.

The Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network, funded by the European Centre for Disease Prevention and Control (ECDC), has made a substantial contribution to these efforts. Among other activities, it has endorsed,case–control test-negative studies focused on providing VE estimates for specific laboratory-confirmed influenza outcomes, especially medically attended influenza-like illness (ILI) [1-3]. As a result of this initiative, I-MOVE associates have published preliminary mid-season estimates of the VE of the 2010/11 influenza seasonal trivalent vaccine to prevent cases of medically attended ILI laboratory-confirmed for influenza [4,5]: two additional preliminary reports are published in this week's issue of *Eurosurveillance* [6,7].

The present influenza season, which is now coming to an end, has been characterised predominantly (70–80%) by influenza A/California/07/2009(H1N1)-like isolates. There has also been a smaller but notable proportion (15–24%) of B/Brisbane/60/2008 (Victoria lineage) isolates in the season thus far, but in week 9 of 2011, they accounted for 80% of virus isolates [8],Both virus types are included in the trivalent seasonal vaccines now used in Europe [8,9]. Thus, the currently circulating influenza A(H1N1)2009 virus and the currently used vaccine are similar but not identical to the virus circulating in the autumn 2009 pandemic wave [7,10] and the monovalent adjuvanted vaccines used then [4,5,7].

Perhaps not surprisingly, the published VE estimates for the current seasonal vaccine [4-7] were lower that those published for the pandemic vaccine used in 2009/10 [3,11-13]. They were, however, so low that when the usual confounding factors are taken into account, the estimates are compatible with a hypothesis of no effect. This raises the question of whether the lower adjusted VE of the 2010/2011 trivalent influenza vaccine is a real phenomenon or whether it is due to confounding, mismeasurement or other unknown factors. Some of the recent studies have mentioned the possible role of antigenic drift and differing study populations [4,6,7]. Although these possible explanations are intuitive and plausible – and no doubt partially explain the situation – there are some other issues that also merit discussion. Moreover one needs to keep in mind that the VE of the non-adjuvanted vaccines in the pre-pandemic area was lower than that of the adjuvanted monovalent pandemic vaccine.

From the data presented in these studies, we can build a scenario in which older age, the presence of risk factors and previous vaccination in the study population were highly correlated with being vaccinated with the 2010/2011 seasonal influenza vaccine. However, the data do not show that this was linked with a differential risk of acute respiratory infection due to influenza.

It should also be remembered that negative controls were negative for influenza, but may have had other infections. Influenza viruses are one of several groups of respiratory viruses that affect us at the same time of the year and at any age. Some of the test-negative controls probably went to their physicians with symptoms such as fever, cough, malaise and dyspnoea resulting from episodes of undetected respiratory syncytial virus (RSV), rhinovirus, coronavirus, metapneumovirus, or other unidentified viral infections that could not possibly be affected by influenza vaccination, but could be affected by the same underlying factors that increase the risk of becoming an influenza case.

If the analysis is adjusted for factors associated with influenza vaccination rather than for vaccination itself, the vaccine effect will be diluted and disappear, as can be seen when comparing the crude and adjusted effects reported. The test-negative approach can be

considered as a variant of a case–case comparison study [14], where recruitment has been prospective and within a short period, and where the most plausible factor associated with not being a true influenza case is having received influenza vaccination. For this reason any adjustment for factors correlated to vaccination must be dealt with caution [14,15]. The non-adjusted estimates might be a more plausible estimate of vaccine effectiveness than the adjusted results.

Even the crude VE estimates would still be confounded to the null because the study design was based purely on laboratory results. The negative controls were a mixed population of people most of whom were positive for viruses other than influenza, possibly including some false influenza-negatives and some people with non-infectious ailments. Therefore, a case–case approach comparing influenza-positive patients with those positive for other respiratory viruses (see [14,15]), with incidence sampling of both groups in periods of similar risk for influenza, would provide more realistic and convincing estimates of the influenza vaccination effect.

The authors also state that this year's study population was different from that of the previous year [4,6,7]. Vaccination recommendations differed, at least with respect to age, so age was a direct correlate of vaccination. Moreover, the population as a whole has had a wider exposure to influenza A(H1N1)2009 virus now than just a year ago [16]. Nevertheless, it is difficult to understand how this can explain the low VE results, unless this situation had an effect on the virus itself.

Another important element is therefore the influenza virus itself. Some of the recent reports on its evolution are reassuring and clearly state that the circulating viruses are well matched to the vaccine strains [7,10,17], while others propose that vaccination and previous exposure lead to immunological pressure that has driven virus evolution [7,10,17,18] in ways that could explain, at least in part, the observed differences between the highly effective monovalent pandemic vaccine and the lower effectiveness attributable to this year's seasonal trivalent vaccine. In fact, the reported observations point to a certain degree of mismatch between the circulating influenza A(H1N1)2009 strains and the corresponding vaccine component. The available results for the influenza B strain, however, point to a reasonable VE.

In conclusion, the four preliminary mid-season studies discussed provide timely and useful information. However, it is clear that we need a better understanding of the true impact of other respiratory viruses. To this end, we need to establish active, comprehensive and continuous surveillance systems that take advantage of the advances in diagnostic tools such as multiplex real-time PCR, which will allow us to conduct more focused case–case comparison VE studies. We need, without any doubt, better influenza vaccines, in terms of viral spectrum, and effectiveness, and we cannot forget the important seasonal impact that RSV, rhinovirus, coronavirus, parainfluenza or metapneumovirus infections have in all age groups. And last but not least, comprehensive and meticulous immunological and virological surveillance must be accompanied by timely communication and publication of observations, results and their interpretation.

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Are European immunisation programmes recession proof?

D O'Flanagan (darina.oflanagan@hse.ie)[1], D Lévy-Bruhl[2], S Salmaso[3]
1. Health Protection Surveillance Centre (HPSC) Health Services Executive (HSE), Dublin, Ireland
2. French Institute for Public Health Surveillance (Institut de Veille Sanitaire, InVS), Saint-Maurice, France
3. Istituto Superiore di Sanitá, Rome, Italy

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The activities during the European Immunisation Week demonstrate a common momentum by member states of the World Health Organization (WHO) European Region to increase the success of immunisation programmes through advocacy and targeted communication. These efforts ultimately aim to raise awareness and reach people who have not been immunised or did not receive all recommended vaccinations. Fifty-two countries agreed to participate in 2011, the largest number since the first European Immunisation Week in 2005 [1]. This proves increasing political commitment to vaccination throughout the region. It's thus a good time to celebrate advances in vaccination programmes as the first decade of the 21st century has been the most productive in the history of vaccine development. New life-saving and disease-preventing vaccines, such as conjugate vaccines against pneumococcal and meningococcal disease, human papilloma virus (HPV) and second-generation rotavirus vaccines have been developed, and others will soon be available.

These exciting advances, however, must not hide some major challenges of vaccination programmes in the European Region. The first one is illustrated by the failure of reaching the European measles elimination goal by 2010 [2]. In early 2011, thirty countries in the region have reported a marked increase in measles cases, with over 6,500 cases as of 20 April 2011 [1]. This demonstrates the difficulty in reaching in our societies the required high proportion of immune subjects, including the 95% coverage of those targeted for vaccination with two doses of a measles-containing vaccine, as a result of several problems. Firstly there is a growing paradigm where people feel more than in the past responsible for their own health. They wish to choose their own medical care in a context where vaccination is victim of its own success. As vaccine coverage has increased, the incidence of vaccine-preventable diseases has fallen and diseases as well as the related suffering have become less visible. At the same time as the perception of risk associated with the preventable disease has declined, concern about potential side effects of vaccines has increased.

Today, many are questioning national and regional vaccination strategies and methods for setting recommendations, asking for the reassessment of the benefit/risk balance at their own individual level i.e.'This vaccination is good from a public health perspective but do I really need it?' while failing to recognise that the solidarity and cooperation of all are needed to ensure the additional gain of herd immunity. This balance is often negatively biased by misinformation or rumours circulating through the new media (Internet, social networks), which creates doubts and fears. The example of the low vaccine coverage against the 2009 pandemic influenza A(H1N1) in 2009/10 in most members states is an illustration for this [3]. A paper by Betsch in this issue of *Eurosurveillance* discusses the increasing influence of the Internet on vaccine decisions and specifically investigates the influence of anti-vaccine information [4].

To counter the potential negative impact of misinformation, rumours and other misconceptions, well-targeted information and social mobilisation campaigns are required to transform passive acceptance of immunisation into a well-informed demand for vaccines that can protect against life-threatening diseases [5]. Such a transformation requires investment in form of human and financial resources and a strong commitment from health authorities. This is sometimes lacking. Again, using measles prevention as an example, the investment (time, energy, money, identification of innovative communication or vaccine delivery strategies and the staff to do it) required to gain the few per cent of coverage needed to reach the herd immunity threshold through reaching those underserved or reluctant, is considered in many countries as not worth the investment. The challenge is to convince decision makers that 90% coverage in children is unsatisfactory and that even 1% of the number of measles cases that occurred in the pre-vaccination era must now be considered a public health emergency! European failure to meet measles elimination means we must increase investment in supplementary and outreach vaccination activities to ensure we reach also underserved

and marginalised groups. In addition those older children and young people who are vulnerable due to sub-optimal immunisation coverage in the past should be offered catch-up opportunities to complete the recommended schedules. Failure to do so will leave Europeans susceptible to importations of measles as illustrated in the communication from Brown et al. in this issue describing the recent appearance of a novel measles G3 strain in multiple European countries [6]. Furthermore, Wicker et al. highlight in their paper that also healthcare workers need to be educated and convinced about the necessity to protect themselves and their patients through for example influenza vaccination [7]. Previous papers in this journal have demonstrated the same for the measles, mumps, rubella vaccine [8-10].

The second challenge is the growing gap in the number of vaccinations offered by the various European countries as new vaccines are marketed. These new vaccines are generally much more expensive than those that have been used for a long time. In the context of growing financial constraints, cost becomes a major impediment in integrating these new vaccines. The example of vaccination against HPV is illustrative of this situation, as shown by the results of the Venice surveys [11,12]. The financial barrier is documented in those surveys by the answers to the question: 'Why did you not introduce the HPV vaccination?' for which the main reason was: 'because of the cost of the vaccine or cost/effectiveness issue'.

The recent financial challenges threaten to unravel hard-won gains particularly in countries hardest hit by the economic turmoil. Many countries are now facing down-sizing of staff working in public health services. With an emphasis on protecting front-line services, vaccine programme functions such as collection of data on vaccine preventable diseases and monitoring vaccine coverage may be threatened. Effective surveillance systems are indispensable in guiding policy decisions for the introduction of new vaccines, monitoring their impact on disease incidence, and conducting post-marketing surveillance to ensure their safety.

It is also essential that we continue to ensure that all vaccines in our programmes continue to be reviewed and where no longer indicated discontinued after careful evaluation. Such a review has recently led the United Kingdom Joint Committee on Vaccination and Immunisation to consider cessation of the elderly pneumococcal polysaccharide vaccine programme [13]. In recent years countries such as France and Finland have discontinued routine universal BCG programmes [14,15].

On a more positive note, these recessionary times may be the impetus needed to review the process whereby European countries procure vaccine. In many countries vaccine procurement is devolved to local levels, losing the economies of scale that national procurement of vaccines can provide. We could learn from the experience of other WHO Regions such as provided by the Pan American Health Organization (PAHO). In 1979, PAHO established a revolving fund to help all countries in the region become more self-sufficient in the purchase of vaccines for routine immunisation [5]. The pooled fund is able to secure low vaccine prices through large volume contracts with manufacturers.

As the current economic downturn unfolds, it will be important for governments to sustain and, when possible, increase investments in immunisation. Comparison of vaccination programmes with other healthcare interventions indicates that vaccines are often one of society's best healthcare investments [16]. We, public health experts, need to ensure that we provide policy makers with the evidence to justify their investment decisions and ensure that our vaccination programmes are recession proof.

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Insights from Europe related to pandemic influenza A(H1N1)2009 have international relevance

H A Kelly (Heath.Kelly@mh.org.au)[1], B J Cowling[2]
1. Victorian Infectious Diseases Reference Laboratory, 10 Wreckyn St, North Melbourne, Victoria, Australia, 3051
2. School of Public Health, the University of Hong Kong, Hong Kong Special Administrative Region, China

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In this issue of Eurosurveillance Amato Gauci and colleagues collate a summary of surveillance data related to pandemic influenza A(H1N1)2009 from the 27 European Union Member States plus Norway and Iceland [1]. While much has already been published on experiences of individual countries, this report is an important summary of the impact of the first influenza pandemic of the 21st century in Europe as a whole. The authors acknowledge the inherent difficulties in summarising data collected from countries with varying surveillance systems and where the pandemic had differential impact. For instance, it was only in England – and only there in London and the West Midlands – that there was a significant spring pandemic wave in 2009 [2]. Like many aspects of the pandemic, this observation remains unexplained.

From a summary of the epidemiological and virological data, the authors recapitulate features of the pandemic that are now generally accepted (Box). However many of these features were not recognised early when an informed understanding was critical to an appropriate pandemic response. For instance, the authors quote a report from the World Health Organization published in 2009 that suggested early estimates of the effective reproduction number (R), defined as the average number of secondary infections attributable to one infectious case, were in the range 1.1-1.4 for the United Kingdom (UK) at the start of the pandemic, although up to 2.6 elsewhere [3]. Only the lower estimates for R are supported by recent studies [4]. Early estimates of R may have been overestimated for a number of reasons [5]. Firstly, ignoring imported cases or counting imported cases as locally acquired could increase the estimated R. Secondly, early estimates of R based on outbreaks could be overestimated due to selection bias. Thirdly, many early estimates of R reflected a high proportion of cases among school-age children, amongst whom R was higher than in the general population [3]. Finally, R could have been overestimated if transmission occurring prior to testing was not recognised [6].

The consensus estimates for R are now similar to those accepted for seasonal influenza [1], suggesting similar transmissibility for both viruses. While early outbreak investigations in schools or households, such as the UK First Few Hundred initiative [7], have the potential to provide timely data on the transmissibility characteristics of a new virus, further work is needed to clarify the extrapolation of transmissibility from outbreak studies to implications for population epidemiology.

Box

Generally accepted understanding of the 2009 influenza pandemic

- The highest cumulative incidence of disease was in the 0-4 year old age group, although the highest cumulative incidence of infection (including asymptomatic infection) was in school-aged children, the age group which was instrumental in the spread of the pandemic.
- Deaths associated with virologically confirmed influenza were lower than the number of excess deaths thought to occur from seasonal influenza, but the majority of deaths from pandemic influenza A(H1N1)2009 occurred at a younger age than is typically seen with seasonal influenza. However excess mortality and laboratory-confirmed deaths are not directly comparable.
- Although older adults were affected less commonly, this was the age group with the highest case fatality ratio.
- Intensive care units were stressed by the increase in the number of young adults with severe disease due to pandemic influenza A(H1N1)2009, a phenomenon first recognised in the southern hemisphere (19) but not experienced in all countries.
- Pregnant and post-partum women and indigenous people, both recognised risk groups for infection with seasonal influenza, were at apparently increased risk for a severe outcome from pandemic influenza A(H1N1)2009 infection.
- Although pandemic influenza A(H1N1)2009 appears to have completely replaced previous seasonal influenza A(H1N1) subtypes, it has not replaced influenza A(H3N2) subtypes which have continued to co-circulate as a small proportion of all typed influenza A viruses. This contrasts with the observations from previous pandemics, when the pandemic virus replaced all influenza A viruses.
- Unlike the pattern for seasonal influenza A(H1N1) viruses, no significant neuraminidase resistance of pandemic influenza A(H1N1)2009 has been detected to date, although variants with reduced oseltamivir sensitivity may be emerging in the Asia-Pacific region [20].
- The pandemic virus was less virulent than had been anticipated in many pandemic plans.

In trying to further disentangle the comparison of pandemic influenza A(H1N1)2009 and seasonal influenza in the community, the authors have re-examined data from sentinel surveillance schemes that were operating in Europe during the pandemic and shown that influenza-like illness (ILI) rates were higher during the pandemic than during the previous influenza season (Figure 1 in reference 1). However it is generally acknowledged that the pandemic was associated with increased testing for influenza as well as potential changes in healthcare-seeking behaviour [8]. The proportion of ILI patients who test positive for influenza can be a useful method for comparing influenza seasons, as it can potentially adjust for differential testing between jurisdictions and across seasons [9]. When the metric of percentage positive tests was applied to the European surveillance data, the predominantly pandemic season of 2009/10 looked similar in magnitude to the preceding 2008/9 influenza season (Figure 2 in reference 1).

Comparing ILI rates for pandemic and seasonal influenza is a specific example of a more general problem with influenza epidemiology – the extent to which common things are unknown. Further evidence of this problem is provided in the European review when it is suggested that asymptomatic infection was more common for pandemic influenza A(H1N1)2009 than for seasonal influenza, an observation based on admittedly weak evidence [1]. While around one third of experimental infections with a range of influenza types and sub-types are asymptomatic [10], this proportion depends on the definition of asymptomatic infection. Prospective intensive follow-up of people in household studies has found that only around 10% of virologically-confirmed A(H1N1)2009 infections were completely asymptomatic, while around one half were associated with febrile illness [11-13]. The precise asymptomatic fraction of naturally acquired infections due to seasonal and pandemic influenza remains uncertain, as does the potential for variability in this fraction by age.

Trying to understand the pandemic in Europe and around the world has highlighted other uncertainties about influenza epidemiology.

- Except for infants and children aged 0-4 years, for whom routine laboratory testing is common in many places, the number of hospitalisations due to laboratory-confirmed influenza is poorly estimated for other age groups. This number will vary by year, and by influenza type and subtype. The proportion of those requiring admission to intensive care will also vary by these parameters.
- Similarly, the number of deaths that can be directly attributed to laboratory-confirmed influenza is not known for the same parameters. Although underestimated, the increased testing associated with the pandemic provided estimates of laboratory confirmed deaths, but generally only for A(H1N1)2009 infections.
- Controversy persists over estimates of excess deaths attributable to influenza. These estimates place a substantial burden of seasonal influenza on the elderly and are not directly comparable to estimates of virologically confirmed deaths. Although estimates of years of life lost have been made, these have not yet been adjusted for the presence of pre-existing conditions.
- The proportion of people with confirmed influenza who seek medical attention is poorly understood in most countries. This proportion is very likely to reflect differences in cultural attitudes to illness, the provision of medical services and the public health interventions implemented in different countries. Serologic studies in combination with outpatient and inpatient surveillance can improve these estimates [14,15].
- There are very limited published data on the proportion of people with naturally acquired laboratory-confirmed influenza whose infections are asymptomatic. The likelihood of transmission from people with asymptomatic infections to susceptible contacts is not known.
- Vaccine is known to be effective in healthy children and adults but vaccine effectiveness is poorly understood in the elderly and in individuals at higher risk of severe disease if infected. These are the groups targeted for vaccination [1,16].
- Influenza usually circulates in the winter in temperate settings, but was able to spread in the spring in some parts of Europe and North America, raising questions about the diverse causes of influenza seasonality.

Three of the highlighted recommendations made by Amato Gauci and colleagues reflect the importance of filling these gaps in our knowledge of influenza epidemiology [1]:

Firstly, they recommend making ‘severe end’ influenza surveillance routine. Routine community-based influenza surveillance was very useful during the pandemic and routine hospital-based surveillance (’severe end’ surveillance) would have been equally useful. A study from Australia suggested that the hospital course for adults was similar for those infected with pandemic influenza A(H1N1)2009 and those infected with seasonal influenza - but that the burden on the hospital system resulted from the increased number of adults admitted to hospital during the pandemic [17]. Uncertainties surround this issue because of the lack of quality surveillance data from hospitals over a number of influenza seasons [18].

Secondly, they recommend sharing data early in any future outbreak. Data sharing facilitated international attempts to gauge the severity of the pandemic in 2009. This undertaking was supported by the unique rapid peer-reviewed publication policy of Eurosurveillance. The accuracy of shared articles was less certain when rapid publication dispensed with peer-review.

Thirdly, they suggest that sero-epidemiological studies should be included in revised pandemic plans to provide information in real time. This may be the most optimistic of the recommendations [15]. Serological studies remain the best approach to estimate the cumulative incidence of infection following a wave of infection but technical issues remain unsolved. These include the correlation between antibody titres and immunity, the characteristics of antibody profiles over time, the potential effect of antiviral treatment on convalescent antibody [11], and the interpretation of serological data after the introduction of a vaccine. The use of serological data for real-time evaluation of severity also requires reliable surveillance of severe infections [14].

Many aspects of improved understanding require descriptive and analytical epidemiological studies in diverse countries over consecutive influenza seasons in order to capture the range of potential outcomes due to laboratory-confirmed influenza, the outcome of choice in attempting to understand influenza control measures [16]. This level of understanding appears to be long overdue and should not be deferred until the next pandemic.

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Initial surveillance of 2009 influenza A(H1N1) pandemic in the European Union and European Economic Area, April – September 2009

I Devaux (Isabelle.Devaux@ecdc.europa.eu)[1], P Kreidl[1], P Penttinen[1], Mika Salminen[1], P Zucs[1], A Ammon[1], on behalf of the ECDC influenza surveillance group[2], and the national coordinators for influenza surveillance[3]
1. European Centre for Disease Prevention and Control (ECDC) Stockholm, Sweden
2. The members of this group are listed at the end of this article
3. The members of the group are listed at the end of the article

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European Union (EU) and European Economic Area (EEA) countries reported surveillance data on 2009 pandemic influenza A(H1N1) cases to the European Centre for Disease Prevention and Control (ECDC) through the Early Warning and Response System (EWRS) during the early phase of the 2009 pandemic. We describe the main epidemiological findings and their implications in respect to the second wave of the 2009 influenza pandemic. Two reporting systems were in place (aggregate and case-based) from June to September 2009 to monitor the evolution of the pandemic. The notification rate was assessed through aggregate reports. Individual data were analysed retrospectively to describe the population affected. The reporting peak of the first wave of the 2009 pandemic influenza was reached in the first week of August. Transmission was travel-related in the early stage and community transmission within EU/EEA countries was reported from June 2009. Seventy eight per cent of affected individuals were less than 30 years old. The proportions of cases with complications and underlying conditions were 3% and 7%, respectively. The most frequent underlying medical conditions were chronic lung (37%) and cardio-vascular diseases (15%). Complication and hospitalisation were both associated with underlying conditions regardless of age. The information from the first wave of the pandemic produced a basis to determine risk groups and vaccination strategies before the start of the winter wave. Public health recommendations should be guided by early capture of profiles of affected populations through monitoring of infectious diseases.

Introduction

When the 2009 influenza A (H1N1) pandemic started in April 2009 and first cases appeared in Europe, aggregated (number of cases) and case-based (patient-based records) reporting systems were rapidly implemented by the European Centre for Disease Prevention and Control (ECDC), the European Union (EU) and the European Economic Area (EEA) countries to fulfil the reporting requirements of the World Health Organization (WHO) and the EU [1]. The Early Warning and Response System (EWRS) was used to confidentially report aggregated and case-based data [2]. The EWRS was primarily designed as a communication platform and not as surveillance application. However, one of the main advantages of the system at the beginning of the pandemic was that it relies more on a human driven approach to reporting and this allowed timely (daily) reporting of aggregated data by the EWRS focal points in the EU/EEA countries to ECDC. The European data was then rapidly published in the ECDC's daily situation reports [3] to guide and support the response of the countries and the European Commission. Laboratory-confirmed cases of pandemic influenza were reported according to the EU case definition [4] which includes laboratory confirmation by PCR, antigen detection and a four-fold rise in influenza specific antibodies. A preliminary communication in this journal in June 2009, and the 2009 pandemic influenza A(H1N1) individual case reports from 2 June to 10 August 2009 [5,6], showed that community transmission had developed in several of the EU/EEA countries since the beginning of the epidemic. A large proportion (77%) of cases was reported in children and young adults less than 30 years of age. The frequency of reported symptoms was 89% for respiratory and 14% for gastro-intestinal symptoms and for 10% of pandemic influenza cases at least one underlying medical condition was reported. A number of reports from individual countries show similar data [7-15].

The objective of this article is to describe the main characteristics and risk factors of pandemic influenza cases reported by EU/EEA countries during the first pandemic wave from April to September 2009.

Methods

The investigators extracted two datasets from the EWRS to provide numbers and characteristics of

the populations infected by the pandemic influenza virus. Aggregated numbers of 2009 pandemic influenza A(H1N1) virus infections were reported by 30 EU/EEA countries by notification date from 27 April to 22 September 2009. Characteristics of cases were described on a weekly basis using case-based data reported from 5 May to 22 September 2009 (Figure 1).

Adoption of a mitigation strategy was defined as the point when a country was no longer recommending laboratory tests for all suspected cases and therefore not all pandemic influenza cases were reported to national public health authorities.

Aggregated data

Weekly notification rates were calculated by dividing the weekly aggregated number of cases reported by EU/EEA countries by their respective population extracted from the Eurostat website in August 2009 [16]. The weekly denominator only included the population of countries for as long as they reported cases to ECDC.

Individual, case-based data

The set of variables reported in the case-based system were compiled using the WHO guidance for surveillance of human infection with the 2009 pandemic influenza A(H1N1) virus [17]. The variables for the characterisation of the cases were: age, sex, travel-association, vital status (alive or dead), dates (notification, onset of symptoms, treatment started and death), clinical presentation, underlying conditions, complications, antiviral treatment and prophylaxis, seasonal influenza vaccination status, and hospitalisation. Trends over time were analysed by calendar weeks (week starting on Monday).

For cases reported from 5 May to 22 September 2009, the proportion of hospitalised cases was calculated using a weekly median (by country with an interquartile range (IQR) and the 95th percentile), the distribution of travel and non travel-associated cases was described by week of onset over 22 weeks and geographic area visited, age-specific notification rates were calculated over the 20 weeks reporting period.
Completeness of reporting was calculated for sex, travel-association, antiviral treatment and prophylaxis, seasonal influenza vaccination and complication. If no data was missing, completeness equalled 100%. It was not possible to calculate completeness of reporting for underlying condition as there was no option for 'none' or 'unknown' underlying condition (see list below).

Age distributions were compared between groups of persons for the variables, sex, travel-association, antiviral treatment or prophylaxis, vaccination status, underlying conditions and complications, by using two-sample Wilcoxon rank-sum (Mann-Whitney) tests.

Underlying conditions were reported according to the following pre-defined categories: cancer, diabetes mellitus, human immunodeficiency virus (HIV) infection and other immune deficiencies, heart disease, seizure disorder, lung disease, pregnancy and malnutrition. Underlying conditions could also be reported in a free-text field. When conditions reported in the free-text fields matched one of the pre-defined categories mentioned above, they were re-classified into this category.

Figure 1

Data for analyses of 2009 pandemic influenza A(H1N1) cases reported through the Early Warning and Response System to the European Centre for Disease Prevention and Control by European Union and European Economic Area countries, 27 April - 22 September 2009

	Aggregated data	Case-based data
Overall analyses	n= 51,768 27 April - 22 September 2009	n = 11,037[a] 5 May - 22 September 2009
Trend over time	By date of notification n= 51,575 27 April - 20 September 2009	By date of onset n= 8.197 17 April - 20 September 2009
Frequency of symptoms and underlying condition[b]		n=5,205 5 May - 22 September 2009
Risk factor analysis (hospitalisation and complication)[c]		n= 3,381 5 May - 22 September 2009

[a] No data submitted by Greece and Liechtenstein.

[b] Cases for 26 countries, cases excluded from United Kingdom (inclusion of the first 301 cases only), Belgium and Slovenia (all cases excluded).

[c] Cases for 18 countries, cases excluded from Austria, Bulgaria, France, Latvia, Poland, Portugal, Romania.

Associations between outcomes of pandemic influenza, hospitalisation or complications, and the variables sex age, fever, respiratory/gastro-intestinal symptoms, antiviral treatment or prophylaxis, seasonal influenza vaccination status, underlying conditions, were analysed by unadjusted and adjusted (for other variables) logistic regression models using STATA software. Interactions between variables were tested by using the likelihood ratio test to assess the significance of each variable in the model.

Datasets for specific analyses

Figure 1 shows how subsets of data are analysed. Analyses related to the epidemiological characteristics of cases reported with pandemic influenza were performed on the full dataset (n= 11,037) for most of the variables. Frequency of symptoms and underlying conditions were analysed on a subset of data (n=5,205) including all cases for countries other than the United Kingdom (UK) (inclusion of the first 301 cases only), Belgium and Slovenia (all cases excluded). Seven countries (Austria, Bulgaria, France, Latvia, Poland, Portugal, Romania) where hospitalisation was performed mainly for isolation purposes, leading to an over-representation of mild cases among hospitalised cases, were not included in risk factor analyses (n=1,748).

Table 1

Number of cases, notification rate, and hospitalisation rate of 2009 pandemic influenza A(H1N1) cases in European Union (EU) and European Economic Area (EEA) countries, 27 April – 22 September 2009

	Aggregated reporting 27 April to 22 September 2009[a]			Individual, case-based reporting 5 May to 22 September 2009[b]			
	Number of cases	Average weekly notification rate (per 1,000,000)	Week change to mitigation	Number of cases (individual data)	Week of last individual case	Medianweekly hospitalization proportion (%)	Inter-quartile interval of median weekly hospitalisation proportion (95th percentile, %)
Austria	361	2.06	32	357	-	75(3)	18 – 92 (100)
Belgium	126	0.98	29	124	28	5	0 – 58 (100)
Bulgaria	70	0.44	-	68	37	47(3)	5 – 75 (100)
Cyprus	297	31.4	-	205	27	33	20 – 45 (92)
Czech Republic	281	1.29	-	258	36	19	10 – 38 (63)
Denmark	636	5.53	28	97	28	10	5 – 20 (75)
Estonia	68	2.41	-	68	37	0	0 – 27 (100)
Finland	259	2.33	30	175	31	9	0 – 13 (38)
France	1,125	1.10	28	553	29	80[c]	19 – 94 (100)
Germany	19,207	11.01	-	704	27	29	14 – 40 (80)
Greece	2,149	9.13	-	-	-	-	-
Hungary	206	0.98	33	110	31	13	4 – 32 (75)
Iceland	193	29.33	-	87	34	-	-
Ireland	885	10.05	29	174	30	3	0 – 15 (75)
Italy	2,384	1.90	-	134	26	30	20 – 37 (50)
Latvia	30	0.63	-	29	37	47[c]	0 – 71 (94)
Liechtenstein	5	6.73	-	-	-	-	-
Lithuania	51	0.76	-	51	35	15	0 – 36 (86)
Luxembourg	190	18.70	-	267	-	0	0 (19)
Malta	298	34.59	29	105	29	4	0 – 7 (11)
Netherlands	1,473	5.61	33	246	30	0	0 (5)
Norway	1,336	13.43	30	60	31	0	0 – 3 (22)
Poland	164	0.20	35	66	30	100[c]	67 – 100 (100)
Portugal	2,983	13.38	34	344	34	47[c]	40 – 66 (89)
Romania	333	0.73	-	331	37	83[c]	67 – 100 (100)
Slovakia	131	1.15	33	130	37	15	9 – 73 (100)
Slovenia	244	5.74	36	7	26	-	-
Spain	1,538	2.61	28	113	20	-	-
Sweden	1,274	6.61	29	172	28	0	0 – 11 (21)
United Kingdom	1,3471	10.48	30	6,002	26	1	0 – 2 (5)
EU/EEA	51,768	5.33		11,037		21	13 – 29 (40)

[a] Cases were reported by date of notification from 27 April to 22 September 2009.

[b] Cases were reported by date of notification from 5 May to 22 September and by date of onset from 19 April to 20 September 2009.

[c] Countries with high hospitalisation rate.

Results

Aggregated data - weekly notification rates

In total, 51,768 confirmed cases of pandemic influenza were reported as aggregated case reports by all EU/EEA countries. The weekly notification rate was calculated for the 51,575 cases reported from 27 April to 20 September 2009 (Figure 1). It increased from week 18 to week 27 (end of June) where it peaked with eight cases per million population. A second peak in the weekly notification rate was observed in week 32, in early August, with 13.6 cases per million population, and was followed by a decrease from week 33, when countries progressively adopted mitigation strategies (Table 1, Figure 2).

The population used as a denominator for the weekly notification rate decreased after week 29, when countries stopped reporting pandemic influenza cases to ECDC.

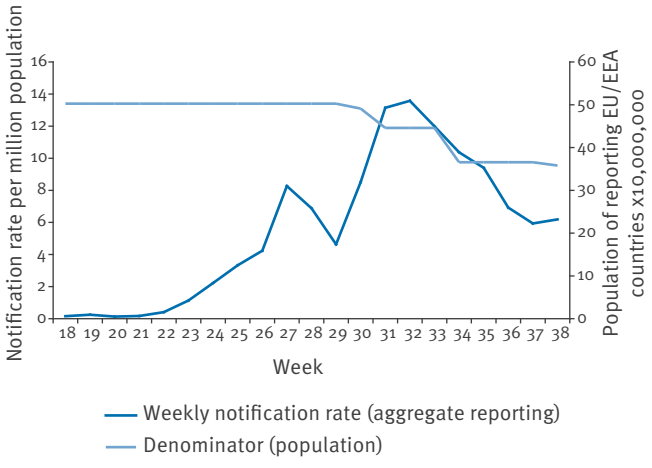
The average weekly notification rate over the period described above was greater than 10 per million population in Cyprus, Germany, Iceland, Luxembourg, Malta, Norway, Portugal and the UK.

Case-based data

A cumulative number of 11,037 cases of pandemic influenza were reported as individual reports by 28 EU/EEA countries (no data submitted by Greece and Liechtenstein) from 5 May to 22 September 2009 (Table 1).The number of cases reported by the UK accounts for more than half (54%) of the individual case reports. Germany and France reported more than 500 cases; Spain stopped reporting individual cases before the end of June 2009. Data by week of onset were available for 8,197 (74%) cases. The weekly distribution of individual cases reported by date of onset of symptoms peaked in week 25 (mid-end June) with 1,684 cases reported in week 25 and 1,549 in week 26. The decreasing numbers observed after week 26 and until September 2009 can be explained by the fact that the UK, followed by other countries stopped reporting individual cases to ECDC (Figure 3).

Figure 2

2009 pandemic influenza A(H1N1) notification rate (per million population, n=51,575) and population of reporting European Union and European Economic Area countries by week of report, 27 April (week 18) – 20 September (week 38) 2009



EEA: European Economic Area; EU: European Union

Travel-associated cases

Of 10,643 cases with travel-related information i.e. having been outside the country of notification during the incubation period, 7,101 (67%) were reported as domestic cases i.e. having acquired the infection in the country where they were reported. Data on travel history and week of onset of symptoms were available for 7,974 cases (75% of cases with travel-related information) and among those, 3,333 had travelled abroad. The proportion of travel-associated pandemic influenza cases was 100% in week 16 and decreased progressively to 19% in week 25, when the total number of reported cases was highest. In week 25, a large proportion of cases were reported as community-acquired by the UK. The proportion of travel-associated cases increased again after week 25 and remained above 50 % until week 37. Large proportions had travelled to North America (1,314 cases, 39%) or within EU/EEA countries (1,528 cases, 46%). At the start of the pandemic, during weeks 16 to 23, almost all travel-associated cases (≥92%) were linked to travel to North America, and this was gradually replaced by travel within EU/EEA countries after week 24 and, from week 31 to week 38, almost all travel-associated cases were reported within EU/EEA countries (≥83%). The percentage of cases who had travelled to other continents was 6% or less: 159 of 3,333 cases (5%) returned from Asia, 130 (4%) returned from South America and 99 (3%) returned from another country, mainly Australia.

Hospitalised cases

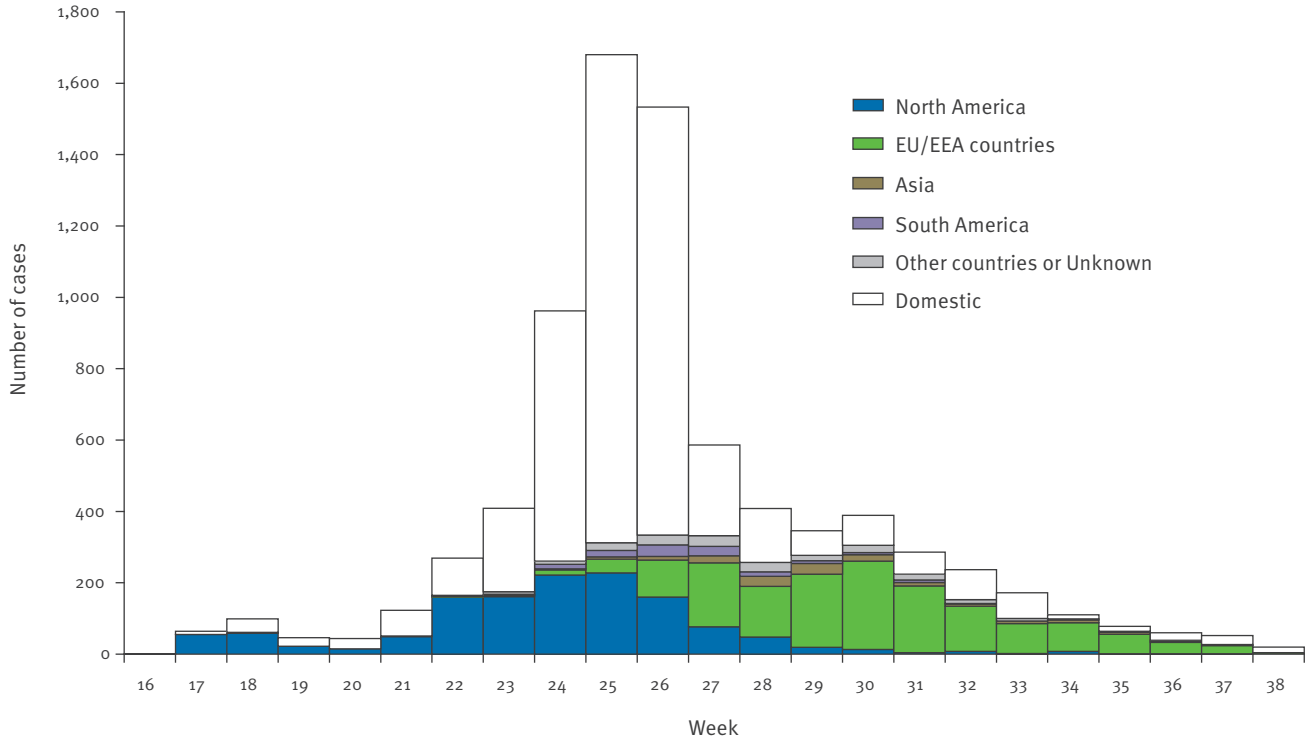
The median of the weekly percentage of hospitalised cases by country was 21% with an IQR of 13 to 29% and a 95th percentile of 40% in 25 EU/EEA countries. Information on hospitalisation was not reported by Iceland, Spain and Slovenia (Table 1). Seven countries were identified with a median proportion of hospitalised cases greater than 40 % (95th percentile): Austria, Bulgaria, France, Latvia, Poland, Portugal and Romania. These countries had similarly high hospitalisation rates during their containment phase of the pandemic which decreased when hospitalisation was no longer recommended for isolation purposes in these countries.

Age, sex and antiviral treatment

In 28 EU/EEA countries, children and young adults less than 30 years of age represented 78% (n=10,846) of cases reported and the highest age-specific notification rate was observed in the age group 10 to 14 years with 7.7 per 100,000 population (Figure 4). Two peaks were observed in those under 30 years of age: the first peak, in 10 to 14 year-olds, corresponded to a series of school outbreaks reported for example in

Figure 3

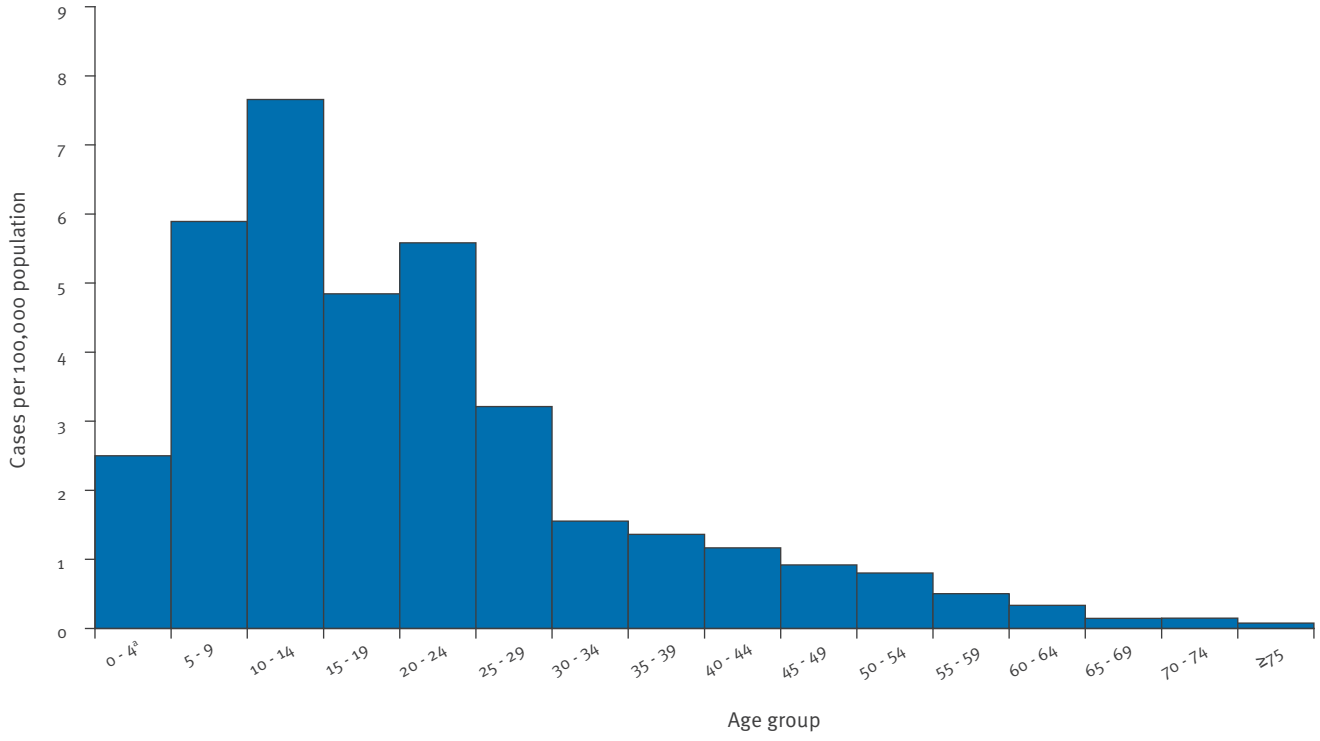
Total (n=7,974), domestic (n=4,641) and travel-associated (3,333) cases of 2009 pandemic influenza A(H1N1) virus infection in European Union and European Economic Area countries by week of onset and continent of travel, 19 April (week 16) – 20 September (week 38) 2009



EEA: European Economic Area ; EU: European Union.

Figure 4

Age-specific notification rate of 2009 pandemic influenza A(H1N1) cases reported by 28 European Union and European Economic Area countries, individual case reports, 5 May – 22 September 2009, (n=10,846)



[a] 212 cases are reported below 1-year-old with an age-specific rate of 4 per 100,000 population.

the UK and Germany [7,8]. The second peak was attributed to a higher number of travel-associated cases in 20 to 24 year-olds. A decreasing trend over time in the notification rate was observed in individuals aged over 29 years (Figure 4). Five age groups were further analysed: 0 to 9 years (20% of all cases), 10 to19 years (32%), 20 to 29 years (26%), 30 to 59 years (20%), and over 60 years (2%).

Table 2 describes the pandemic influenza cases, completeness of reporting, median age and distribution by age group for the variables defined above. Completeness of reporting was over 80% for all variables except antiviral prophylaxis (28%) and complication (26 %).

The male-to-female ratio was 1.1 (n=9,872 cases with available information). The median age of pandemic influenza cases was significantly higher among those who had travelled abroad (24 years) than among domestic cases (14 years), (z=-31.4, p<0.001). Forty-five per cent (n=9,392) of cases did not receive any antiviral treatment, 26% (2,415) received oseltamivir, 0.3% (25) zanamivir and 29% (2,759) another treatment which was specified in 104 (4%) persons only, 66 of those had received antibiotics. As expected, the proportion of patients who received oseltamivir was significantly higher among hospitalised cases (74%) compared with non-hospitalised cases (18%). Prophylaxis was administered to 4% (110 of 3139 cases) and previous vaccination for seasonal influenza was reported for 3% (264 of 8,913 cases). Seventy-two of 262 cases (28%) with available information on vaccination and underlying condition had at least one underlying condition. Complication(s) were reported in 3% (94 of 2,878 cases with available information). Sixty persons (2%) were reported with pneumonia, 25 (0.8%) with other respiratory infections, and six with non-specified complications.

Symptoms and underlying conditions

Frequencies of symptoms were calculated based on 4,452 cases, after exclusion of 753 (14%) cases reported without any symptom. Fever was reported in 87%, respiratory symptoms were reported in 85%, gastro-intestinal symptoms in 18%, and for 27% of cases other symptoms, mainly fatigue or asthenia, chill, loss of appetite were noted. The proportion of gastro-enteritis was 26 % among children aged less than 10 years.

Three hundred and forty-three of 5,205 (7%) pandemic influenza cases were reported with at least one underlying condition. Underlying conditions were specified in 331 (96%) of them. They were described as free text for 137 (41%) cases. The most common underlying conditions were unspecified chronic lung diseases, including asthma (124 cases, 37%). Other underlying conditions reported and associated or not with other conditions, were cardiovascular-diseases, diabetes, gastro-intestinal diseases, allergy, liver or kidney related conditions, neurological disorders, cancer, HIV. Pregnancy was reported in 14 women (4%) (Figure 5).

Epidemiological characteristics and outcomes

For analyses of associations between hospitalisation and potential risk factors the age group 10 to 19 years was chosen as reference group as it had the highest age-specific notification rate. Univariate analysis shows that factors associated with hospitalisation are underlying condition (Odds ratio (OR) 1.95, 95% confidence interval (CI) 1.00-2.73), seasonal influenza vaccination (OR 1.59, 95% CI 1.04-2.41), and age group 20 to 29 years (OR 1.32, 95% CI 1.00-1.74). In the multivariate model only underlying condition remained associated with hospitalisation (OR 1.61, 95% CI 1.07-2.43). Analysis of associations between complications and potential risk factors for complications were performed on data reported by 25 countries (n=2,878, no data

Table 2

Characteristics of 2009 pandemic influenza A(H1N1) cases reported in 28 European Union and European Economic Area countries (n=11,037, except for underlying conditions, n=5,205), 5 May – 22 September 2009

Variables	Category	Number of cases (%)	Completeness %	Age					
				Median age	% 0-9	% 10-19	% 20-29	% 30-59	% ≥60
Sex	M	5,224 (53)	89	19	19	32	28	20	2
	F	4,648		20	18	31	27	23	2
Travel-associated	Y	3,542 (33)	96	24	8	22	39	28	2
	N	7,101		14	26	37	20	16	1
Treatment	Antiviral	2,440 (26)	85	22	12	28	33	25	2
	Other	2,759 (29)		15	25	34	22	17	1
	N	4,193 (45)		16	24	33	23	18	1
Prophylaxis		110 (4)	28	21	17	26	26	28	3
Vaccination against seasonal influenza		263 (3)	81	28	9	17	25	36	12
Complication		94 (3)	26	26	10	19	28	37	6
Underlying condition[a]		343 (7)	-	28	8	23	21	38	10

F: female; M: male; N: no; Y: yes

[a] It was not possible to calculate the proportion of completeness for underlying condition as the category 'none' did not exist for this variable.

reported on complication by Belgium, Slovenia and Spain). Univariate analysis shows that factors associated with complication were: age groups 30 to 59 years (OR 2.1, 95% CI 1.22-3.88) and over 60 years (OR 4.13, 95% CI 1.58-10.8) and underlying condition (OR 3.65, 95% CI 2.24-5.95). In the multivariate model only underlying condition remained associated with complication (OR 3.18, 95% 1.91-5.27).

Discussion

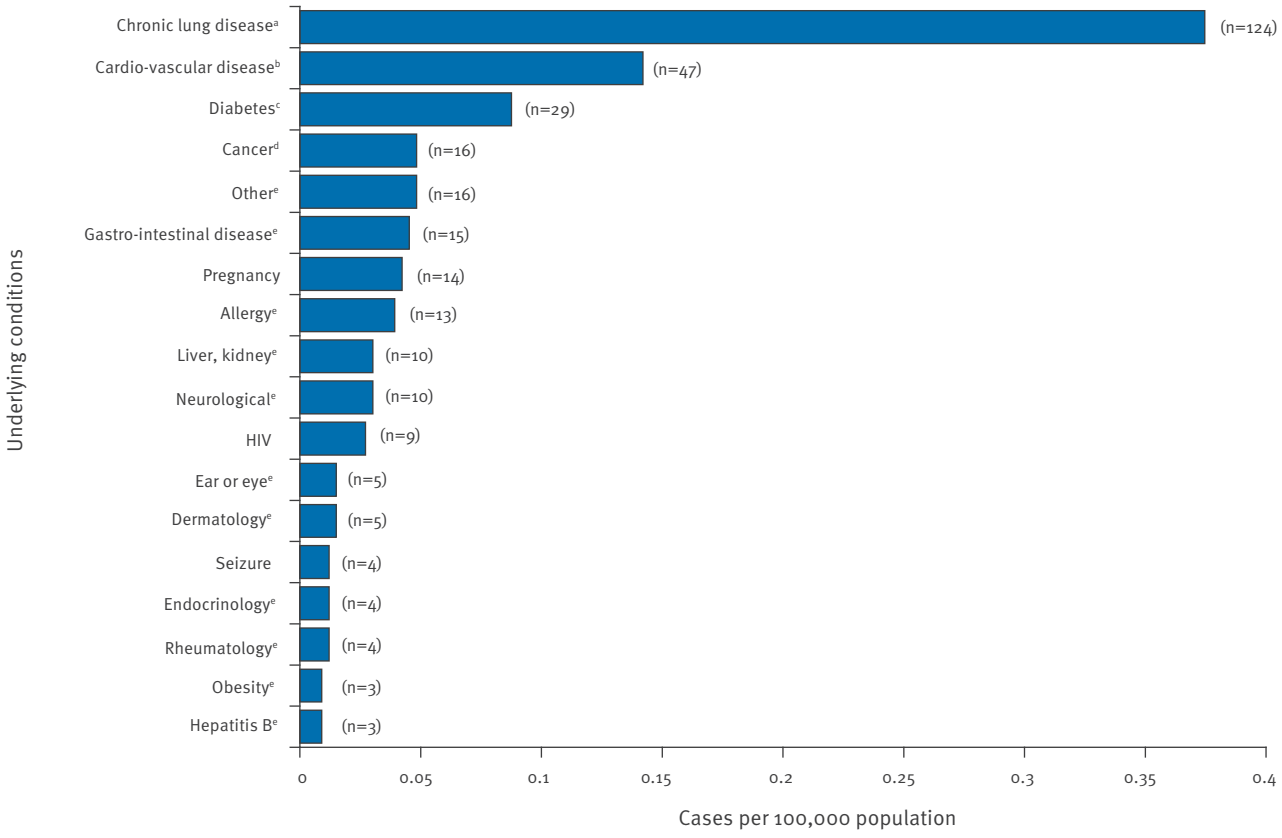
The pandemic influenza cases reported in this article characterise the first wave of the 2009 pandemic in EU/EEA countries. They include a large proportion of travel-related cases that are not necessarily representative of the population affected by the pandemic during the following winter wave. Also representativeness of data varied between countries. The weekly notification rate calculated for aggregated data is a proxy for the notification rate of pandemic influenza over the summer months of 2009. Two peaks were observed: one in week 26 and one in week 31. The first is probably due to a reporting artefact in week 26, when a large number of cases from previous weeks were reported by the UK. The second peak marks the maximum number of cases reported during the first pandemic wave in EU/EEA countries. The sentinel surveillance of influenza-like illness (ILI) and acute respiratory infections (ARI) also showed two peaks at a time similar to that of the reporting data: one in week 25 and one in week 31 [18].

High notification rates in specific countries like Cyprus and Malta can probably be explained by an increase of their population during the summer holiday season that could not be taken into account in the denominator.

The reported percentage of hospitalised patients in (21%) seems extremely high. At the beginning of the pandemic, hospitalisation was used for isolation purposes in some countries and this may have inflated the percentage rather than a high number of severe cases. In the Netherlands, a country that did not recommend hospitalisation for isolation purposes, a hospitalisation rate of only 2.2% (35 of 1,622 patients with confirmed pandemic influenza) was reported until 14 August 2009, when a change in notification criteria to only hospitalised patients was implemented [19].

Figure 5

Underlying conditions of 2009 pandemic influenza A(H1N1) cases reported in 26 European Union and European Economic Area countries, 5 May – 22 September 2009 (n=331)



HIV: Human immunodeficience virus.

[a] Include 33 cases reported with asthma as a text field.

[b] Include cases reported with other conditions: hypertension, lung disease, kidney disorder, obesity.

[c] Include cases reported with other conditions: hypertension, asthma, obesity.

[d] Include cases reported with other conditions: seizure and/or diabetes and/or other condition.

[e] Reported as text field.

Table 3

Univariate and multivariate analysis for factors influencing hospitalisation and complications of 2009 pandemic influenza A(H1N1) cases in 18 European Union and European Economic Area countries, 5 May – 22 September 2009

		Hospitalisation					Complication				
	Category	Total number of cases	% hospitalised	OR	OR lower limit	OR upper limit	Total number of cases	% complication	OR	OR lower limit	OR upper limit
Univariate analysis											
Gender	Male	1,609	13%	1	–	–	1,563	3%	1	–	–
	Female	1,380	14%	1.12	0.91	1.38	1,297	4%	1.16	0.77	1.75
Age	0–9	353	14%	1.21	0.81	1.8	318	3%	1.26	0.56	2.84
	10–19	963	11%	1	–	–	766	2%	1	–	–
	20–29	1,027	15%	1.32	1	1.74	961	3%	1.2	0.65	2.21
	30–59	915	14%	1.23	0.93	1.65	732	5%	2.1	1.22	3.88
	≥=60	72	11%	0.83	0.39	1.76	69	9%	4.13	1.58	10.8
Treatment	Yes	1,447	14%	1.25	0.96	1.63	1,770	4%	1.21	0.75	1.96
	No	783	11%	1	–	–	754	3%	1	–	–
Prophylaxis	Yes	83	18%	1.43	0.8	2.54	59	2%	0.47	0.06	3.43
	No	1,658	13%	1	–	–	2,255	4%	1	–	–
Vaccination	Yes	156	19%	1.59	1.04	2.41	171	6%			
	No	1,909	13%	1	–	–	1,840	3%	1	–	–
Underlying	Yes	222	22%	1.95	1	2.73	250	9%	3.65	2.24	5.95
conditions	No	2,778	13%	1	–	–	2,628	3%	1	–	–
Multivariate analysis											
Age	0–9	–	–	0.92	0.58	1.47	–	–	1.06	0.49	2.3
	10–19	–	–	0.77	0.55	1.06	–	–	0.86	0.46	1.58
	20–29	–	–	1	–	–	–	–	1	–	–
	30–59	–	–	0.85	0.61	1.18	–	–	1.67	0.99	2.81
	≥60	–	–	0.51	0.21	1.26	–	–	2.32	0.89	6.05
Vaccination	Yes	–	–	1.48	0.95	2.33	–	–	–	–	–
	No	–	–		–	–	–	–	–	–	–
Underlying	Yes	–	–	1.61	1.07	2.43	–	–	3.18	1.91	5.27
conditions	No	–	–	1	–	–	–	–	1	–	–

OR: Odds ratio.

Table 4

Percentage of underlying and co-morbid conditions reported in studies performed among patients hospitalised with 2009 pandemic influenza A(H1N1)

Study	Number of patients	Chronic lung disease, including asthma	Cardio-vascular disease	Diabetes	Obesity	Pregnancy
US [11]	272	36%	13%	15%	-	7%
US, California [12]	1,088	37%	15%	11%	48%	10%
Canada[a] [13]	168	32%[b]	15%	21%	33%	8%
Australia & New Zealand[a] [14]	722	33%	11%[c]	16%	29%	9%
Mexico[a] [15]	58	7%	10%[d]	17%	36%	n.a.
EU/EEA	331	37 %	15%	9%		4%

EEA: European Economic Area; EU: European Union; US: United States.

[a] Patients hospitalised in critical care units.

[b] Asthma and/or chronic obstructive pulmonary disease.

[c] Only chronic heart failure.

[d] Arrhythmia and valvular heart diseases.

Case-based data was available for merely 21% of the reported aggregated cases. However, this was expected because the purpose of the case-based system was to capture the first few hundred cases of pandemic influenza reported in all Member States, while case-based reporting was still feasible. This purpose was achieved in most countries that have reported more than 100 cases in the aggregated reports.
The completeness of data for prophylaxis (28%) and complication (26%) was low. This can be interpreted in two different ways: either the missing information corresponds to 'no prophylaxis' or 'no complication', or to unknown information. As we chose to remove missing values from the denominator, proportions of persons who have received prophylaxis or with complication(s) may be over-estimated in our analysis.
Clinical presentations of patients reported in our system are similar to those listed in a review (WHO consultation) of clinical aspects of 2009 pandemic influenza [20]. In September 2009, the number of cases reported without any symptom was considered as quite high (14%) as information about the proportion of asymptomatic cases was still scares at that time. Asymptomatic cases when reported in the context of tracing contacts during the containment phase could have been underestimated if contact tracing was not systematically performed.

However, it is not known if these cases were really asymptomatic or if symptoms were not reported. In the latter case, 14% would be an over-estimation of the proportion of asymptomatic cases. Serological surveys are the only way to estimate the proportion of asymptomatic 2009 pandemic influenza cases. In the meanwhile, results from such studies suggest that a considerable number of those infected with pandemic influenza A(H1N1) virus may have been asymptomatic [21,22].

The overall proportion of underlying conditions (7%) reported in our dataset is similar to the information reported by WHO for Ontario, Canada in June 2009 [23]. We compared proportions of underlying conditions with results from other studies among hospitalised patients with pandemic influenza in the United States [24,25], Canada [26], New Zealand [27] and Mexico [28] (Table 4). Although not necessarily all cases reported with underlying conditions in our dataset were hospitalised, the proportion of chronic lung diseases (including asthma) and cardio-vascular diseases among hospitalised patients were similar to those reported elsewhere [24-27]. However, the proportions of cases reported with metabolic conditions (diabetes and obesity) and pregnancy are lower in EU/EEA countries than those reported in hospitalised patients in the countries mentioned above. In our dataset, patients with underlying conditions were more likely to be hospitalised and underlying conditions were associated with complications regardless of age.

The fact that 45% of our cases did not receive any treatment may either indicate that they did not have a severe condition or it may reflect the treatment policies in the countries who may have only recommended treatment for severely ill.

Most cases were found in younger or middle-aged age groups. Above the age of 60, there was a steep decline in the number of pandemic influenza A(H1N1) cases. This could be related to previous exposure of individuals over 60 years to influenza A(H1N1) viral strains circulating after the 1918 pandemic until the 1950s [29]. Recent sero-surveys conducted in the UK [30] and in Finland [31] support this hypothesis.

Only three deaths were reported in the individual case data, this contrasts with the 159 deaths reported in EU/EEA countries in the ECDC situation report of 22 September 2009 [3]. Information about deaths is essential to assess severity of the disease appropriately. Additional monitoring systems are needed to collect this type of information in a timely manner.

Conclusion

The primary focus of this article was to present the case-based data collected during the first phase of the pandemic in EU/EEA countries and their implications for rapid public health action. The case-based reporting system was stopped in September 2010, due to the associated heavy work load and the high numbers of affected people. Case-based data were not collected in the population-based system during the second phase of the pandemic and thus our data cannot be used for comparison between the two waves. Overall, our results are in line with other observations that the early phase of the pandemic mainly affected children and young adults in European countries [7-15]. Individuals infected with 2009 pandemic influenza A(H1N1) and with underlying condition(s) were more likely to be hospitalised or to develop (severe) complications regardless of their age, particularly those with underlying respiratory diseases. The epidemiological information collected during the first wave of the pandemic provided some initial indication to determine risk groups and vaccination strategies. In the early phase of the pandemic, results from serological studies would have been helpful to determine if and to what extent individuals over 60 years have pre-existing immunity against pandemic 2009 pandemic influenza A(H1N1) from H1N1 strains circulating after the 1918 pandemic up until the 1950s. Our reporting system provided baseline data and helped to guide initial public health recommendations, however, as the profile of the affected population may have changed over time it is important to continue monitoring. The initial surveillance system was followed by a case-based reporting system of severe acute respiratory infections among influenza cases. Both systems provided timely information of public health relevance about profiles of populations affected by 2009 pandemic influenza.

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The ECDC working group on influenza surveillance
Bruno Ciancio, Flaviu Plata, Vladimir Prikazsky, Rene Snacken, Thomas Mollet, Denis Coulombier, Angus Nicoll, Andrew Amato-Gauci.

National coordinators for influenza surveillance
Gabriela El Belazi, Hubert Hrabcik, Peter Lachner, Reinhild Strauss, Robert Muchl, Theresia Popow – Kraupp, Françoise Wuillaume, Leen Meulenbergs, Sophie Quoilin, Mira Kojouharova, Rositsa Kotseva, Teodora Georgieva, Avraam Elia, Chryso Gregoriadou, Chrystalla Hadjianastassiou, Despo Pieridou Bagatzouni, Olga Kalakouta, Jan Kyncl, Jitka Castkova, Martina Havlickova, Andreas Gilsdorf, Brunhilde Schweiger, Gabriele Poggensee, Gerard Krause, Silke Buda, Tim Eckmanns, Anne Mazick, Annette Hartvig Christiansen, Kåre Mølbak, Lars Nielsen, Steffen Glismann, Inna Sarv, Irina Dontsenko, Jelena Hololejenko, Natalia Kerbo, Olga Sadikova, Tiiu Aro, Amparo Larrauri, Pedro Arias, Pilar Perez-Brena, Inmaculada Casas and Francisco Pozo, Markku Kuusi, Petri Ruutu, Thedi Ziegler, Sophie Vaux, Isabelle Bonmarin, Daniel Lévy-Bruhl, Bruno Lina, Martine Valette, Sylvie Van Der Werf, Vincent Enouf, Ian Fisher, John Watson, Joy Kean, Maria Zambon, Richard Pebody, Mike Catchpole, Colin Campbell, Jane Jones Joanna Ellis, Jim McMenamin, Louise Shaw, Peter Coyle, William F Carman, Stefanos Bonovas, Takis Panagiotopoulos, Sotirios Tsiodras Ágnes Csohán, Istvan Jankovics, Katalin Kaszas, Márta Melles, Monika Rozsa, Zsuzsanna Molnár, Darina O'flanagan, Derval Igoe, Joan O'Donnell, Margaret Fitzgerald, Sarah Jackson, Lisa Domegan, Gillian Cullen and Aidan O Hora Suzie Coughlan, Arthur Löve, Gudrun Sigmundsdottir, Isabella Donatelli, Maria Grazia Pompa, Stefania D'amato, Stefania Iannazzo, Sabine Erne, Algirdas Griskevicius, Nerija Kupreviciene, Rasa Liausediene, Danielle Hansen – Koenig, Joel Mossong, Mathias Opp, Jacques Kremer, Pierre Weicherding, Antra Bormane, Irina Lucenko, Natalija Zamjatina, Raina Nikiforova, Charmaine Gauci, Christopher Barbara, Gianfranco Spiteri, Tanya Melillo, Christopher Barbara, Daniel Cauchi,, Adam Meijer, Frederika Dijkstra, Ge Donker, Guus Rimmelzwaan, Paul Bijkerk, Tessa van 't Klooster, Lieke Wielders, Wim van der Hoek, Katerine Borgen, Susanne Dudman, Siri Helene Hauge, Olav Hungnes, Anette Kilander, Preben Aavitsland, Andrzej Zielinski, Lidia Brydak, Magdalena Romanowska, Malgorzata Sadkowska – Todys, Maria Sulik, Carlos Manuel Orta Gomes, Jose Marinho Falcao, Raquel Guiomar, Teresa Maria Alves Fernandes, Adriana Pistol, Emilia Lupulescu, Florin Popovici, Viorel Alexandrescu, Annika Linde, Asa Wiman, Helena Dahl, Sandra Rubinova, Mia Brytting, Eva Grilc, Irena Klavs, Katarina Prosenc, Maja Socan, Hana Blaskovicova, Margareta Slacikova.

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Surveillance of influenza in Iceland during the 2009 pandemic

G Sigmundsdottir (gudrun@landlaeknir.is)[1], T Gudnason[1], Ö Ólafsson[2], G E Baldvinsdóttir[3], A Atladottir[1], A Löve[3], L Danon[4], H Briem[1]

1. Centre for Health Security and Communicable Disease Control, Directorate of Health in Iceland, Seltjarnarnes, Iceland
2. Public Health Sciences, University of Iceland, Reykjavík, Iceland
3. Department of Virology, Landspitali University Hospital, University of Iceland, Reykjavík, Iceland
4. Department of Biological Sciences, University of Warwick, Warwick, United Kingdom

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In a pandemic setting, surveillance is essential to monitor the spread of the disease and assess its impact. Appropriate mitigation and healthcare preparedness strategies depend on fast and accurate epidemic surveillance data. During the 2009 influenza A(H1N1) pandemic, rapid improvements in influenza surveillance were made in Iceland. Here, we describe the improvements made in influenza surveillance during the pandemic , which could also be of great value in outbreaks caused by other pathogens. Following the raised level of pandemic influenza alert in April 2009, influenza surveillance was intensified. A comprehensive automatic surveillance system for influenza-like illness was developed, surveillance of influenza-related deaths was established and laboratory surveillance for influenza was strengthened. School absenteeism reports were also collected and compared with results from the automatic surveillance system. The first case of 2009 pandemic influenza A(H1N1) was diagnosed in Iceland in May 2009, but sustained community transmission was not confirmed until mid-August. The pandemic virus circulated during the summer and early autumn before an abrupt increase in the number of cases was observed in October. There were large outbreaks in elementary schools for children aged 6–15 years throughout the country that peaked in late October. School absenteeism reports from all elementary schools in Iceland gave a similar epidemiological curve as that from data from the healthcare system. Estimates of the proportion of the population infected with the pandemic virus ranged from 10% to 22%. This study shows how the sudden need for improved surveillance in the pandemic led to rapid improvements in data collection in Iceland. This reporting system will be improved upon and expanded to include other notifiable diseases, to ensure accurate and timely collection of epidemiological data.

Introduction

The first reports of 2009 pandemic influenza A(H1N1) in humans in the United States and Mexico appeared in April 2009 [1]. Initial descriptions of the outbreak in Mexico were alarming, with severe cases of pneumonia and high mortality in previously healthy young adults being reported [1]. On 27 April 2009, the World Health Organization (WHO) raised the level of pandemic influenza alert from phase three to four and two days later from phase four to five [2,3]. Countries were encouraged to activate their pandemic preparedness plans and remain on high alert for unusual outbreaks of influenza-like illness and severe pneumonia. In a pandemic, both clinical and epidemiological data are essential in attempts to assess the severity of the illness. The allocation of healthcare resources and choice of appropriate intervention strategies also rely on accurate and timely surveillance data. Such data are essential in identifying groups at risk of severe illness and who should be prioritised in vaccination strategies. Surveillance is also needed to evaluate the impact of different interventions. Heightened surveillance was therefore a high priority during the pandemic in order to detect the first cases and monitor the spread of the disease.

Conventional surveillance methods for influenza are mostly based on laboratory surveillance and sentinel surveillance of influenza-like illness (ILI), but interest in mortality surveillance has increased during the last decade [4,5]. Unconventional surveillance methods, such as school absenteeism, syndromic surveillance and mobile phone surveillance, have also been used but these methods require further validation [6-8]. All elementary schools for children aged 6–15 years in Iceland enter information on school absenteeism into a common database, but these data have not been analysed for epidemiological purposes so far [9].

There were differences in healthcare services, surveillance and interventions between European countries during the 2009 pandemic. Reports from individual countries on the pandemic are therefore crucial to compare experiences, share knowledge and maximise the lessons learned after the pandemic. In this article we report the changes made in the surveillance of influenza in Iceland and describe the data collected during the pandemic.

Surveillance systems in Iceland

Surveillance of influenza-like illness

In April 2009 surveillance of ILI in Iceland was based on monthly paper-based reporting of aggregated data from primary healthcare centres to the Centre for Health Security and Communicable Disease Control (CHS-CDC). After WHO initially raised the pandemic alert level, Icelandic legislation was changed allowing personal, identifiable information to be collected for each case. Simultaneously, an online automatic system for immediate reporting of ILI and cases with laboratory-confirmed influenza to the CHS-CDC was developed, using the same software used for electronic patient records in primary health care and hospitals in Iceland [10].

The current International Classification of Diseases (ICD-10) for standard diagnostic classification and International Classification of Primary Care (ICPC-2) for standard classification of a patient's reason for encounter were used to identify ILI and confirmed influenza cases for automatic online reporting in the system [11,12]. The following ICD-10 codes were used: J10, J10.0 J10.1, J10.8, J11, J11.0, J11.1, J11.8 and U05.9; the ICPC-2 code used was R80. Whenever physicians suspected ILI or diagnosed confirmed influenza they were asked to use the appropriate ICD-10 code in their reporting. After the physician confirmed his record for the patient visit in the electronic patient journal cases with ICD-10 codes for ILI and confirmed influenza were automatically selected and automatically reported within 24 hours via a closed electronic network to the CHC-CDC comprising all healthcare centres and hospitals in Iceland. The data collected for each case included: name, personal identification number, date of birth, place of residence, date of visit to the healthcare centre or hospital, patient's age, sex, which healthcare service the case attended, medical licence number and name of attending physician, the ICD-10 code and the ICPC code. Patients registered with ICD-10 codes for the most common acute respiratory infections (ARI) were also reported automatically and online in the same way as the influenza and ILI cases. Unlike sentinel systems, the automatic reporting system allowed data to be collected from each and every primary healthcare centre and hospital emergency room, thus capturing the vast majority of all diagnosed cases.

The European case definitions for ILI, confirmed cases of seasonal influenza and confirmed cases of

Figure 1

Weekly number of reported cases of influenza-like illness by sex, Iceland, 1 July to 31 December 2009 (n=9,887)

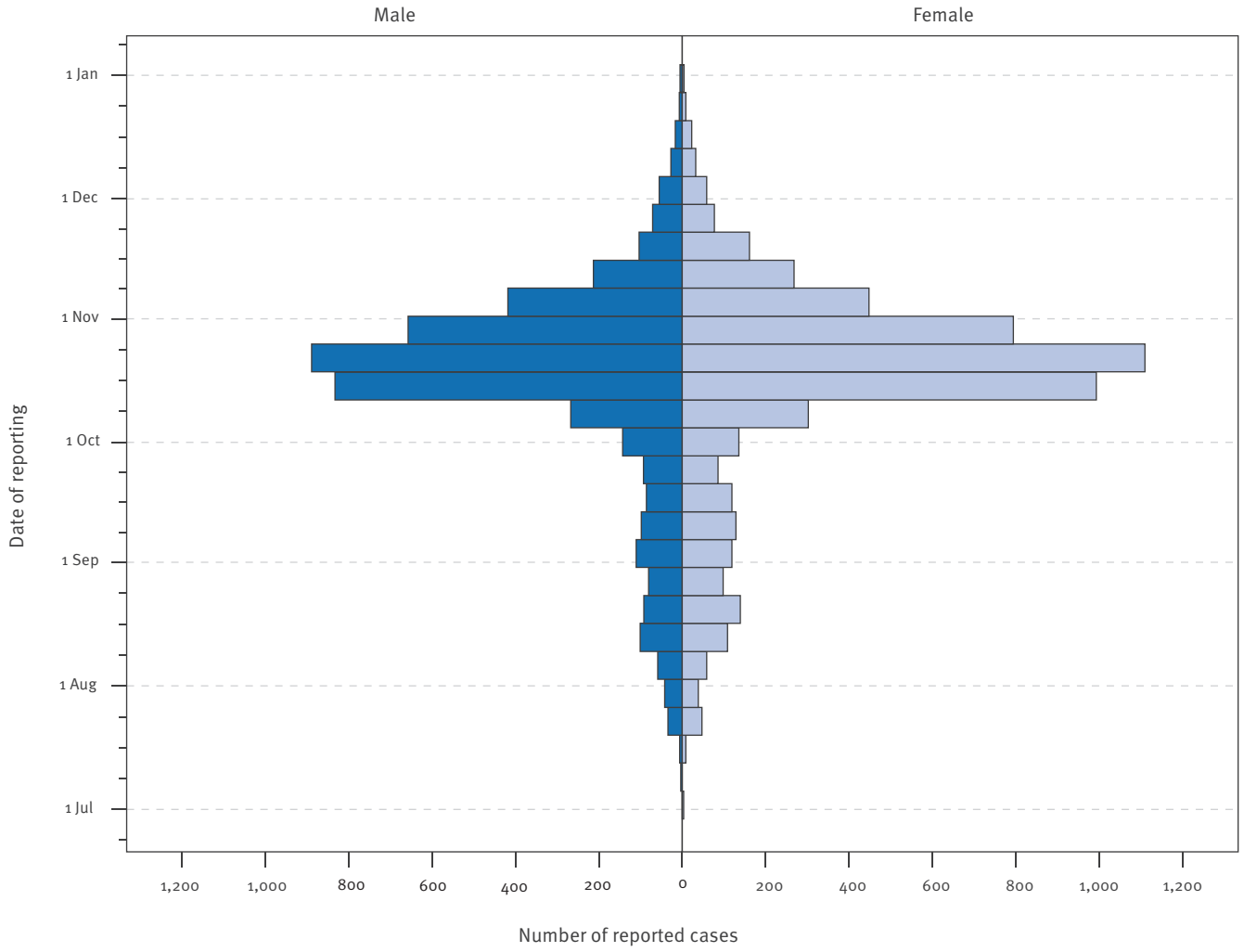


Figure 2

Age-specific incidence of reported influenza-like illness cases by sex, Iceland, 1 July to 31 December 2009

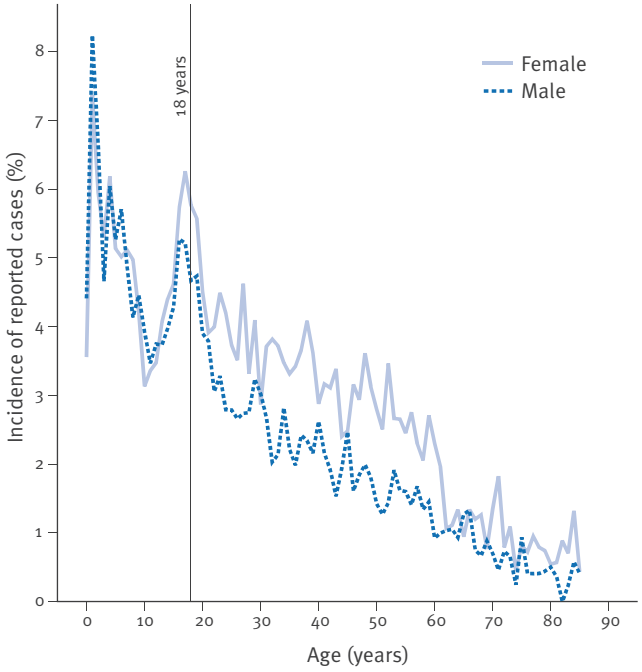
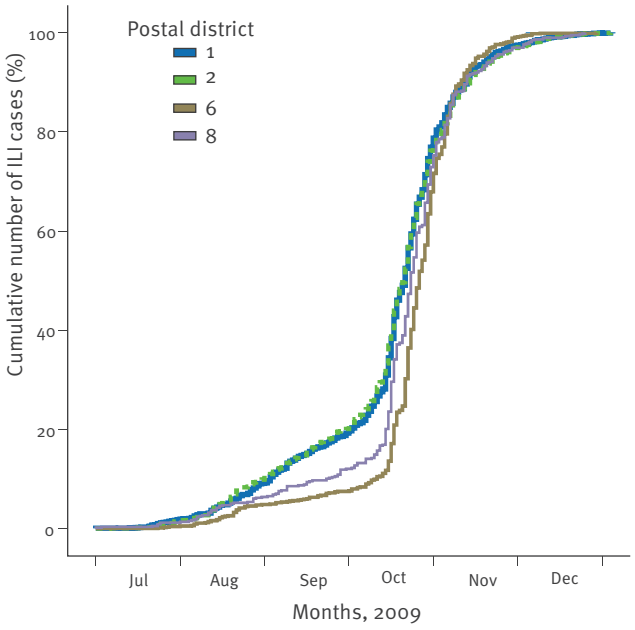


Figure 4

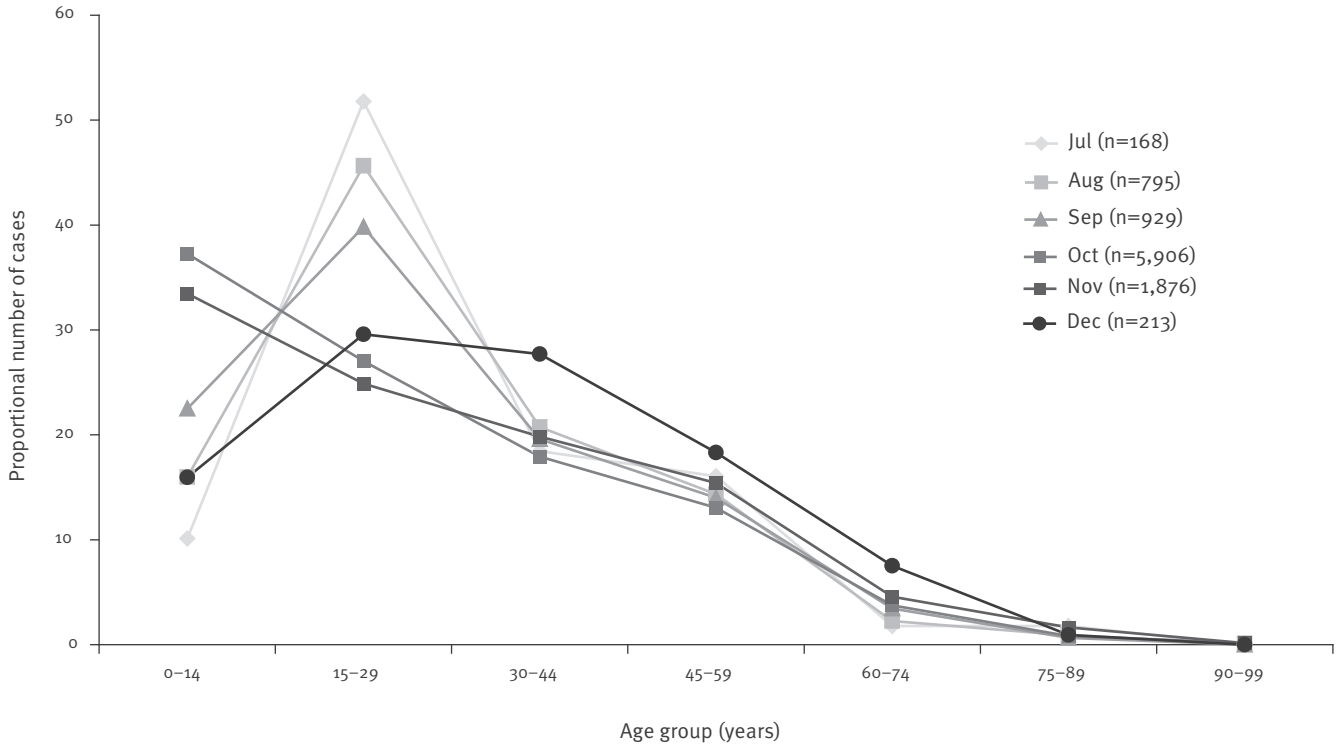
Cumulative number of reported ILI cases as a proportion of the total number of ILI cases by postal district, Iceland, 1 July to 31 December 2009



ILI: influenza-like illness.

Figure 3

Proportional number of reported influenza-like illness cases by age group, Iceland, July to December 2009



2009 pandemic influenza A(H1N1) were used and the selected ICD-10 and ICPC-2 codes were recorded by the physicians [13-14]. In mid-June, when the system was in place, it was also possible to gather data retrospectively from 1 April 2009.

Laboratory surveillance

The Department of Virology at the Landspitali University Hospital in Reykjavik is the sole diagnostic laboratory for influenza in the country. The laboratory received respiratory samples from the nasopharynx and/or throat that were collected from patients with ILI by physicians in primary healthcare centres and at hospitals.

Influenza was diagnosed by real-time polymerase chain reaction (PCR) according to a recommended protocol from the United States Center for Disease Control and Prevention (CDC) [15]. Clinical information and the country of infection were collected on confirmed cases both at the laboratory and at the CHS-CDC. The weekly number of tested respiratory samples and personal information on confirmed cases was reported to the CHS-CDC.

Surveillance of school absenteeism

All elementary schools in Iceland routinely enter information on school absenteeism for schoolchildren aged 6–15 years into a central database maintained by the information technology company Mentor ehf in Reykjavik [9]. School absence was recorded as the number of days absent; comparable data were available for 2007, 2008 and 2009.

Mortality surveillance

Mortality data are collected by the National Registry and sent to the CHS-CDC routinely on a weekly basis. The data included the name, personal identification number, date of birth, place of residence and date of death for each individual. A temporary system for surveillance of patients with ILI and confirmed pandemic influenza admitted to hospital was developed within all hospitals and these cases and deaths in this group were reported immediately to the CHS-CDC. Unexpected deaths in the community in patients with ILI or confirmed pandemic influenza were also to be reported by the physicians to the CHS-CDC.

Table

Reported cases of influenza-like illness by region, Iceland, July to December 2009 (n=9,887)

Region	Postal district	Number of reported ILI cases	Median time[a]
Capital area	1	3,643	19 Oct
	2	3,019	19 Oct
West Iceland	3	404	22 Oct
West fjords	4	109	21 Oct
North West	5	340	27 Oct
North East	6	1,016	24 Oct
East Iceland	7	466	22 Oct
South Iceland	8	598	21 Oct
Westman Islands	9	80	27 Oct
Unknown	Missing	212	–
Total	**1–9**	**9,887**	**20 Oct**

ILI: influenza-like illness.

[a] The date (in 2009) when half of the ILI cases were reported in the postal district.

Data analysis

Estimated number of infections in the community

The percentage of positive laboratory samples was used as an estimate of the proportion of ILI cases in the community with pandemic influenza. To estimate the total number of infected individuals in the community, we therefore multiplied the weekly number of reported ILI cases by the weekly percentage of laboratory samples confirmed positive for pandemic influenza and summed over the course of the pandemic.

The denominators used in this study were mid-2009 demographic data from the Icelandic Population Registry, according to age, sex and place of residence, as appropriate.

Surveillance data

Influenza-like illness

Throughout May and June 2009, few cases of ILI and confirmed pandemic influenza were reported. An increase in the number of laboratory-confirmed cases of pandemic influenza was observed from mid-July, when there was a simultaneous absence of confirmed seasonal influenza. Cases of ILI reported from 1 July 2009 onwards were therefore considered to represent the illness caused by pandemic influenza.

From 1 July to 31 December 2009 a total of 9,887 cases of ILI were reported, of whom 5,372 (54%) were female and 4,515 (46%) were male. The number of cases increased slowly from mid-July to the end of August and fell slightly in mid-September (Figure 1). A sharp increase was observed in October: the number of cases peaked later that month, followed by a rapid decrease. Only sporadic ILI cases were reported in late December.

The incidence of ILI was highest in children and young adults and decreased with age, as shown in Figure 2. ILI incidence was similar in both sexes in people aged under 18 years. However, in people over 60 years, the incidence was higher in women ($p=0.003$), but the largest difference by sex was observed in people aged 18–59 years, with incidence again higher in females ($p<0.001$) (Figure 2).

Figure 3 shows how the age of the reported ILI cases changed with time. In July to September 2009, most cases were reported in the 15–30 years age group, but a sudden change was observed in October, when the majority of cases were aged from 0 to 15 years (Figure 3).

Reported ILI cases were categorised by the postcode of their place of residence. The cumulative number of reported cases over time is given for the four most populated postal districts in the south-west, north and south of the country (Figure 4). There was some indication of spatial dispersal in late September 2009; the number of reported cases increased earlier in the south-west postal districts 1 and 2, followed by an abrupt increase in mid-October in all districts at the same time. The overall number of cases peaked shortly after mid-October (Figure 1, Table).

Data from the surveillance of ARI from the same automatic online system showed similar trends over time as the ILI cases, with a peak in early to mid-October 2009 (week 41) (unpublished data).

Laboratory-confirmed cases of pandemic influenza

From May to mid-August 2009, physicians were encouraged by the chief epidemiologist to take samples from patients with ILI. The first case of pandemic influenza in the country was laboratory confirmed on 19 May

Figure 5

Number of respiratory samples and proportion positive for 2009 pandemic influenza A(H1N1), Iceland, 29 June to 27 December 2009

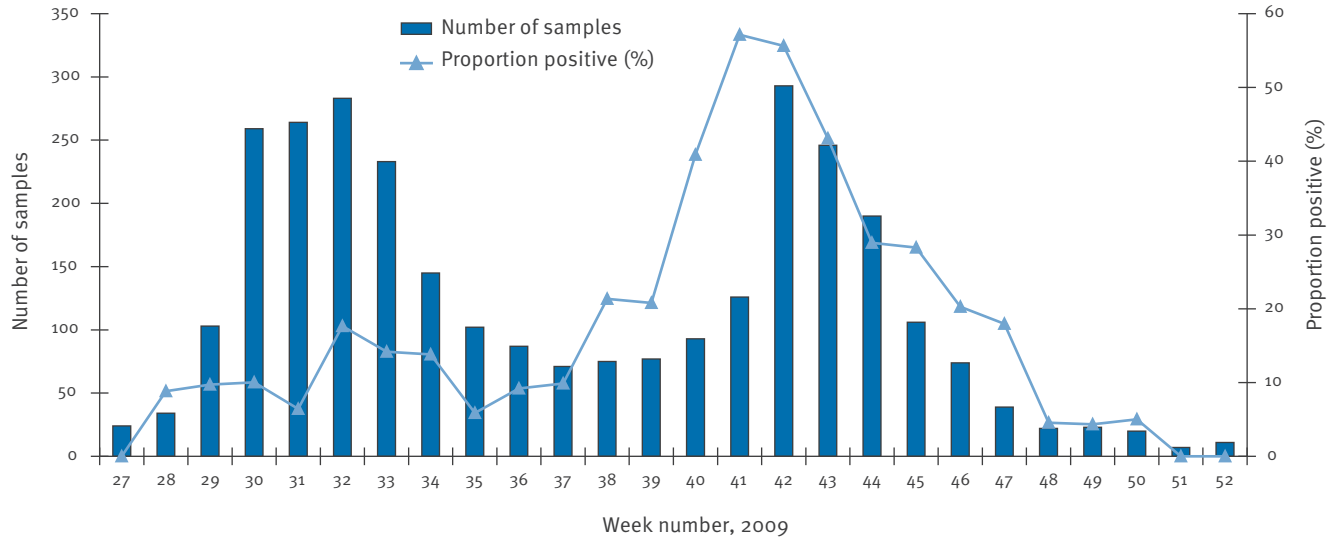
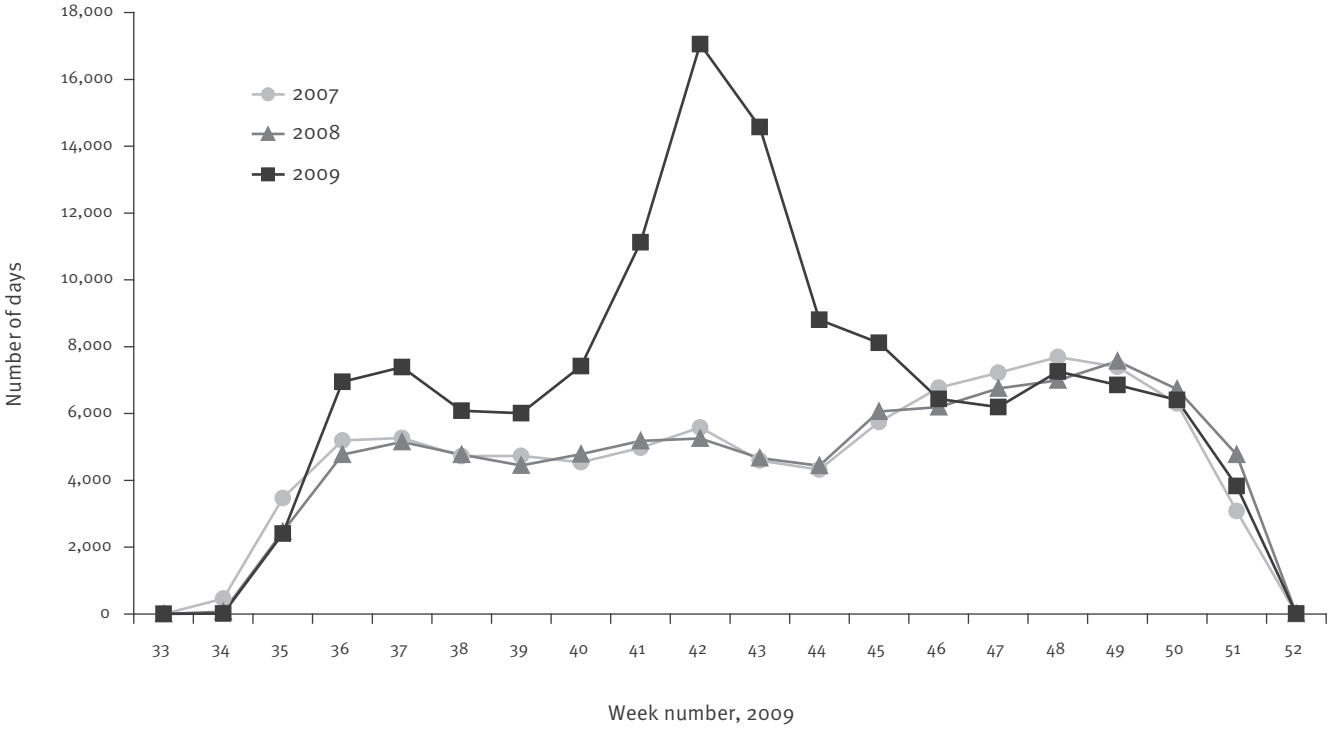


Figure 6

School absenteeism in elementary schools counted in number of days missed, Iceland, weeks 33–52 in 2007–2009



2009. Three confirmed cases were identified in June, but in late July and August (week 30 to 33) an increase in the number of cases was observed. The first cases in May and June acquired the infection abroad or their infection was domestically acquired with known connection to another confirmed case. The proportion of domestic cases with no known connection to other confirmed cases increased rapidly in July and August. In mid-August (week 33), sustained transmission of infection was confirmed in Iceland and decreased sampling was recommended by the Chief Epidemiologist. From that point on, diagnosis of influenza was based on the physician's clinical examination, and samples were to be obtained only from patients with severe illness or increased risk of serious illness.

Following this recommendation, there was a decrease in late August 2009 (week 34 and 35) in the number of respiratory samples collected, with a concomitant decrease in the number of laboratory-confirmed cases (Figure 5). From the end of June to the end of December (weeks 27–53), 3,011 samples were collected, of which 702 (23%) tested positive for the pandemic virus. The number of samples and the percentage of samples positive increased in late September (week 40) and peaked in mid-October (week 42), when 293 samples were collected, 56% of which tested positive. These patterns were consistent with the changes observed in the number of reported ILI cases.

Pandemic influenza was laboratory confirmed in people living in all regions of the country. The age distribution of cases with laboratory-confirmed infections was the same as that observed for reported ILI cases (unpublished data).

School absenteeism

In September 2009 (week 40), shortly after the school year started, an increase in school absenteeism was observed, compared with the levels at that time in the previous two years (Figure 6). A sharp increase was observed in October 2009, compared with the same period in the previous two years, with a high peak in mid-October (week 42) (Figure 6). In late October and November (week 43 to 46), there was a rapid fall in school absenteeism and from mid-November to the end of December it was similar to that seen in the two previous years.

Mortality levels

No increase in overall mortality was observed from September to December 2009, according to data from the National Registry. Two persons with laboratory-confirmed pandemic influenza died during this time: an 18-year-old woman and an 81-year-old man who both had underlying conditions.

Estimated number of pandemic influenza infections in the community

A total of 3,336 cases were expected to be positive if all ILI cases were tested. This is a lower bound estimate since, in the latter part of the epidemic; tests were performed primarily on severe cases that could be caused by complications, rather than influenza. According to previous studies, approximately 10% of symptomatic influenza cases occur in the community for each ILI case detected by the surveillance system [16,17]. The expected number of symptomatic cases would therefore be 33,368 or 10.4% of the total population (n=319.246). A large number of asymptomatic infections are also expected to have occurred. A more detailed model has been used to estimate the number of 2009 pandemic influenza infections in the United Kingdom more closely [18], but such modelling is beyond the scope of our study.

Discussion

This article summarises the surveillance and epidemiology of the pandemic influenza in Iceland in 2009, showing how rapid improvements in influenza surveillance were feasible by connecting the existing structure in the healthcare system for patient records to electronic surveillance system for reporting ILI cases. This system does not require any additional input from physicians, enabling comprehensive data from the entire country to be collected with near real-time information on the geographical spread, age and sex of ILI cases.

The initial increase in the number of ILI cases was first observed in the western regions of the country, with eastern regions following approximately one week later; the peak of ILI activity showed a similar delay (Figure 2 and Table). A west-to-east spread has been described in four of eight influenza seasons from 1999 to 2007 in Europe [19]. The most likely explanation for the direction of spread of the epidemic in Iceland is that the densely populated area of the capital Reykjavik in the south-west corner of Iceland provides ample opportunities for the spread of the pandemic virus; most foreign travel, whether for business or leisure, begins or ends in Reykjavik.

The difference in the number of reported ILI cases by sex in our data could be due to females being more prone to the disease than men, but this hypothesis is not supported by previous studies, with the exception of increased risk of severe illness in pregnant women [20]. An alternative explanation could be that females contact physicians more often than males. The initiative to contact the physician for children and older people who are ill often comes from parents or other close relatives without regard the patient's sex, which could explain equal ILI reporting rate by sex for children and minor sex differences in the rates of reporting of older people. Adults from 18 to 60 years, however, decide themselves when to contact the physician and the differences between males and females observed in that age group in our data probably reflect more frequent visits to the physicians by females in general. Analysis of all encounters by age and sex in primary healthcare centres in Iceland during 2005, which shows a pattern

similar to that observed in our data, gives support to this explanation [21].

People aged 15–30 years were probably at increased risk of acquiring the pandemic virus during July to September 2009 due to risky behaviour with frequent travel abroad and spending weekends at crowded outdoor festivals in Iceland. The age distribution in Iceland is in accordance with a recently published serological study from England that showed pre-existing antibodies in older age groups that protected against infection [22].

There are uncertainties in our estimate of the true number of pandemic influenza cases in the community. The number of samples sent for virological analysis varied over time and it is possible that some samples were false negative. The exact proportion of patients with ILI in community who contacted healthcare was unknown and may have varied between regions and by sex and age group. Multiplying each reported ILI case by 10 should give a rough estimate of the number of cases in the community. Although the care-seeking behaviour for influenza in Iceland has not been studied, an estimate of 1 in 10 seeking care is supported by a recent serological study [22]. It may be possible to estimate the proportion of infected individuals seeking healthcare more accurately using a detailed disease transmission model, but such analysis is beyond the scope of this paper and we leave this for future study.

A small study, based on a questionnaire, carried out in the Akureyri municipality in northern Iceland in mid-November 2009 on the true incidence of ILI in the community showed a 22% cumulative attack rate (unpublished data), supporting the outcome of the simple model described in this study with regard to age, sex and timing of the epidemic curve by onset of illness. We therefore estimated that the percentage of symptomatic people infected in the community ranged from 10% to 22%. Estimates from other countries for the 2009 pandemic also concluded that the percentage of people infected with the pandemic virus was less than 30% of the population [18,22].

There are limitations to our ILI surveillance system. It was developed just in time for the pandemic, had not been adequately tested and baseline data for ILI had not been established. It is possible that physicians were affected by the introduction of a new reporting system and the ongoing pandemic in their clinical assessment. However, the ARI surveillance data do not support this hypothesis. They showed that physicians used ICD-10 codes for ARI when influenza was not suspected. The number of ARI cases peaked in week 41, which probably reflects the increase in illness caused by respiratory viruses other than influenza and/or the pandemic virus in cases with mild symptoms. In our study, ARI was used for quality assurance but further development is intended to enable timely and accurate ARI surveillance.

Our analysis of the data from elementary schools accounts for school absenteeism in number of days absent. The analysis of school absenteeism needs to be developed further with age-specific data on the number of children absent in each school. It is a novel method to estimate the number of children with ILI in the community for every ILI case registered in the healthcare system. It also enables assessment of the socio-economic impact of parents caring for sick children at home and ultimately enables real-time monitoring of local or widespread outbreaks in schools.

The pandemic virus circulated in the community in Iceland during summer and autumn. Elementary schools started in late August, with moderate spread of ILI in schoolchildren during September. But it remains unclear why a large outbreak occurred in October in children attending these schools, rather than in early September, immediately after the schools started.

Our study shows how the sudden need for improved surveillance during the pandemic led to rapid improvements in data collection. However, it is, of course, preferable to have a system in place when pandemics hit. Retrospective data were not collected during the pandemic for two main reasons: firstly, the amount of data would have overloaded both the database and the electronic reporting system and secondly, there was no time to check the validity of the older data and compare with the real-time data during the pandemic. Retrospective data will be collected and a baseline for ILI will be established in future work.

Using the same software for patient records and for surveillance provides a unique opportunity for real-time surveillance and risk assessment. No human input is needed to report the cases, which secures the sustainability of the system and improves the data delivery, compared with the old paper-based reporting system, with regard to the completeness and the timeliness of the data. The data are delivered when the physician has confirmed his record for the patient visit in the electronic patient journal, which can be a problem if physicians postpone their confirmation for weeks, months or even longer. The physicians were, however, constantly reminded during the pandemic to confirm the patient record, but this may need improvements.

The surveillance system established during the pandemic has replaced the older paper-based reporting system for ILI and will be expanded and improved to replace the current system of surveillance of all other notifiable diseases, thus eliminating all paper-based reporting, Changes to the system can be done rapidly, enabling real time surveillance of new and emerging diseases and syndromes that may appear in hospitals and primary healthcare centres in Iceland.

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National surveillance of pandemic influenza A(H1N1) infection-related admissions to intensive care units during the 2009–10 winter peak in Denmark: two complementary approaches

S Gubbels (gub@ssi.dk)[1,2], A Perner [3], P Valentiner-Branth [1], K Mølbak[1]
1. Department of Epidemiology, Statens Serum Institut, Copenhagen, Denmark
2. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, Stockholm, Sweden
3. Intensive care unit, Rigshospitalet, Copenhagen, Denmark

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Surveillance of 2009 pandemic influenza A(H1N1) in Denmark was enhanced during the 2009–10 winter season with a system monitoring the burden of the pandemic on intensive care units (ICUs), in order to inform policymakers and detect shortages in ICUs in a timely manner. Between week 46 of 2009 and week 11 of 2010, all 36 relevant Danish ICUs reported in two ways: aggregate data were reported online and case-based data on paper. Cases to be reported were defined as patients admitted to an ICU with laboratory-confirmed 2009 pandemic influenza A(H1N1) infection or clinically suspected illness after close contact with a laboratory-confirmed case. Aggregate numbers of cases were reported weekly: during weeks 48-51 (the peak), reporting was daily. The case-based reports contained demographic and clinical information. The aggregate surveillance registered 93 new cases, the case-based surveillance 61, of whom 53 were laboratory confirmed. The proportion of beds used for influenza patients did not exceed 4.5% of the national capacity. Hospitals with cases used a median of 11% of bed capacity (range: 3–40%). Of the patients for whom information was available, 15 of 48 patients developed renal insufficiency, 19 of 50 developed septic shock and 17 of 53 died. The number of patients with pandemic influenza could be managed within the national bed capacity, although the impact on some ICUs was substantial. The combination of both reporting methods (collecting aggregate and case-based data) proved to be useful for monitoring the burden of the pandemic on ICUs.

Introduction

The first case of 2009 pandemic influenza A(H1N1) in Denmark was diagnosed on 1 May 2009. The incidence, assessed as the percentage of influenza-like illness (ILI) seen by general practitioners in the national sentinel system, rose in July 2009 and remained stable at around 0.75% for many months, until it started rising again in the week of 8 November 2009 (week 45) and peaked at 5.03% in the week of 22 November 2009 (week 47) [1]. Surveillance of ILI seen by the Danish medical on-call service showed a similar pattern [2]. Considering that the age distribution of patients with pandemic influenza as well as the distribution of risk factors differed from those seen in seasonal influenza [3-5], the impact on the healthcare system was also likely to be different from that during a seasonal influenza epidemic. Moreover, as the pandemic vaccine was available in week 45, a vaccination campaign after that would possibly not have been able to prevent many of the severe cases. It was therefore important to monitor severe disease due to the pandemic influenza.

Surveillance systems were enhanced to include hospitalisations and admissions to intensive care units (ICUs), as recommended in the Danish influenza pandemic plan [6]. The surveillance system to monitor the burden on ICUs was created in weeks 45 and 46 of 2009 in cooperation with the ICU of the Copenhagen University Hospital, Rigshospitalet, Denmark. The Danish Society for Anaesthesia and Intensive Care endorsed the system and the National Board of Health recommended that all ICUs in Denmark participated in the reporting. The system was set up to assess the ICU bed capacity used for pandemic influenza patients, and to provide demographic and clinical data as well as risk factors for death in order to estimate the impact of the pandemic on ICUs and contribute to an assessment of the severity of the pandemic and the severity of disease.

Methods

Clinical notification of patients with pandemic influenza was not mandatory in Denmark. Danish ICUs were, however, requested to report two types of data

to the Statens Serum Institut: (i) aggregate numbers of pandemic influenza patients by age group and (ii) clinical information for each individual patient. A case that should be reported was defined as a patient admitted to an ICU with laboratory-confirmed pandemic influenza A(H1N1) infection or a patient whose infection was clinically suspected and had had close contact with a patient with laboratory-confirmed pandemic influenza.

All hospitals with acute care facilities (n=53) in the five hospital regions of Denmark, excluding the Faroe Islands, were invited to take part in the surveillance system. The system started in week 46 of 2009 and was planned to continue until week 20 of 2010, or until no new cases had been reported by the ICUs for three consecutive weeks, and other surveillance systems, such as the sentinel system, also showed low and stable incidence levels.

Aggregate data

Starting on 15 November 2009 (week 46), ICUs reported aggregate data once a week on a Monday morning before 12:00. During weeks 48 to 51 inclusive of 2009, they were asked to report on a daily basis. Then the deadline was 09:00 on Mondays to Thursdays; data for Fridays and the weekends were reported on Mondays.

A web-based reporting form was created on the homepage of the Statens Serum Institut. A dedicated contact person in the ICUs reported the number of new cases, as well as the number of cases present in the ICU at 08:00 on the day of reporting. The number of cases was reported by the following age groups: <1 year, 1–4 years, 5–14 years, 15–24 years, 25–64 years, 65–74 years and ≥75 years.

We entered the data from the web-based form to a master dataset in a Microsoft Access database. Each report in the aggregate system was evaluated and validated. Reports were corrected for double reporting when a case was transferred to another hospital, but this could only be done if the hospitals actively informed us. Similarly, reports were amended or removed when we were informed of errors or when they contained obvious inconsistencies that needed further follow-up. Bed capacity, expressed as a percentage, was calculated as the number of cases present in an ICU divided by the total number of beds available at that moment.

A summary of the data received was disseminated to the ICUs and the National Board of Health once a week and each day during weeks 48–51 of 2009 (the winter peak). The National Board of Health presented these reports in the parliamentary standing committee on health.

Case-based data

The form used to gather information on each patient included demographic and clinical data, such as underlying medical conditions, co-presenting illnesses, dates of onset of symptoms and admission to ICU and details on treatment. A physician completed this paper form. ICUs were asked to send the completed forms as soon as possible after a patient was admitted and to send any additional information at a later stage if anything was unknown on admission.

A unique patient identifier (the person's number from the Danish Civil Registry System [7]) was reported on the case-based form. The Civil Registration number enabled us to complement the case-based surveillance with data from several registers. From the Danish Civil Registry System we could verify cases who had died as a result of pandemic influenza. A case who died of pandemic influenza after ICU admission was defined as a patient reported in the case-based surveillance who died within 30 days after initial laboratory confirmation of the infection. The Statens Serum Institut laboratory database was used to verify the laboratory confirmation of the patients reported in the case-based surveillance. During the pandemic, laboratories in Denmark were obliged to send samples from patients with ILI to the reference laboratory in Statens Serum Institut, either for initial testing or for confirmation. Vaccination status was verified using the Danish vaccination registry, which was set up in 2009 and was assumed to cover the majority of pandemic vaccine recipients. The vaccination registry also included the reason for vaccination.

Data were analysed using Fisher's exact test for categorical variables with a binary outcome and the Mann–Whitney test for continuous variables. The level of significance was set at $p<0.05$.

Results

We implemented the pandemic surveillance system, both for aggregate and individual data in week 46 of 2009. The system was discontinued after week 11 of 2010 as no new cases had been reported for three consecutive weeks and both sentinel surveillance and on-call monitoring showed low activity for several weeks [2].

Of the 53 hospitals in Denmark with acute care facilities, five had no ICU and 16 were part of a larger group of hospitals that reported for them. As a result 32 hospitals across Denmark were identified for reporting. They reported for 36 ICUs: 32 general ICUs, two paediatric ICUs and two ICUs for neurosurgery.

Aggregate data

All 36 ICUs took part in the surveillance system, although the level of participation varied: until week 8 of 2010 the number of reporting ICUs varied between 22 and 29 after which the numbers dropped to 15 and 16, in weeks 10 and 11 of 2010, respectively. Late reports usually did not contain any cases. Personal contact with hospitals that had a low response rate confirmed that they had not reported because they had no cases.

After data cleaning, 355 weekly and 758 daily reports were validated and used for analysis. During the

surveillance period 93 new cases were reported. Figure 1 shows the number of new cases by week of admission and the timeliness of reporting. Late reports were usually received within a week after the deadline. Only two cases admitted during the Christmas week were reported two weeks later. Data from the national sentinel surveillance system were added, showing the proportion of patients with ILI among the total number of patients who consulted a general practitioner. The peak of new pandemic influenza cases in ICUs was seen in week 48 of 2009, one week later than the peak seen in the sentinel data and two weeks after the on-call monitoring peak [2]. The last new case in an ICU was reported in week 8 of 2010.

The proportion of beds used for pandemic influenza cases did not exceed 4.5% of the total national ICU bed capacity. Hospitals with cases used a median of 11% of ICU beds for pandemic influenza patients (range: 3–40%).

Case-based data

A total of 74 case-based forms were received from 19 hospitals. These forms contained details of 61 individual patients: for 13 patients we received a second, updated form, either from the same hospital or from another hospital to which the patient had been transferred. Of the 61 reported cases, 53 were laboratory confirmed by polymerase chain reaction (PCR). Four cases tested negative in several PCR tests; for another four, the laboratory results could not be traced. Only the 53 laboratory-confirmed cases were used for analysis.

The number of laboratory-confirmed cases from the case-based surveillance is shown in Figure 2 by week of admission, as well as data from the sentinel system. Unlike the epidemic curve of the aggregate data, the peak of the case-based data coincided with the peak of the sentinel data and was one week after the on-call monitoring peak [2].

Demographic data

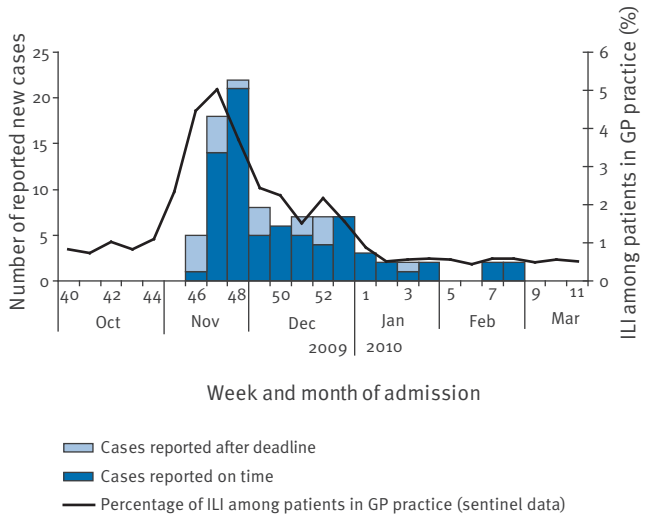
Of the 53 laboratory-confirmed cases, 31 were male and 22 were female. The median age was 47 years (range: 3–80 years). Figure 3 shows the age- and sex-specific incidence. The median age among men was 50 years (range: 3–75 years) and among women 45 years (range: 5–80 years; Mann–Whitney test p=0.96).

Medical history

Details on medical history were complete for most cases, but for a few patients some details were missing. The presence or absence of an underlying medical

Figure 1

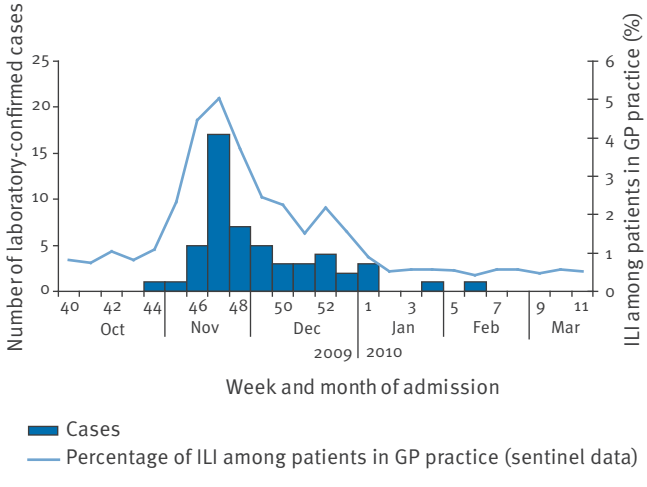
Weekly aggregate data: reported new 2009 pandemic influenza A(H1N1) cases by week of admission (n=93) by timeliness of reporting and data from the national sentinel system, Denmark, week 40 of 2009 to week 11 of 2010



GP: general practioner; ILI: influenza-like illness.

Figure 2

Case-based data: laboratory-confirmed 2009 pandemic influenza A(H1N1) cases by week of admission (n=53) and data from the national sentinel system, Denmark, week 40 of 2009 to week 11 of 2010



GP: general practioner; ILI: influenza-like illness.

Figure 3

Case-based data: incidence of laboratory-confirmed 2009 pandemic influenza A(H1N1) cases by sex and age group, Denmark, week 46 of 2009 to week 11 of 2010

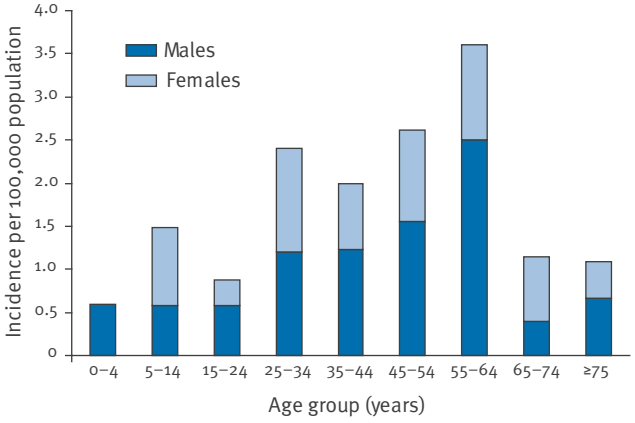


Table 1

Case-based data: frequency of underlying conditions reported in cases with laboratory-confirmed 2009 pandemic influenza A(H1N1), Denmark, week 46 of 2009 to week 11 of 2010 (n=52)

Underlying condition	Age 0–14 years		Age ≥15 years		Total		
	Number of relevant cases	n	Number of relevant cases	n	Number of relevant cases	n	%
None	1	6	10	46	11	52	21.2
Renal insufficiency (creatinine levels 1.5 times above normal)	0	5	3	44	3	49	6.1
Cancer	2	5	7	43	9	48	18.8
Immunocompromised condition	3	5	6	42	9	47	19.1
Neurological illness	2	5	7	42	9	47	19.1
Diabetes	1	6	9	46	10	52	19.2
Chronic lung disease, including asthma	1	5	10	44	11	49	22.4
Obesity (BMI>30)	NA	NA	10	41	10	41	24.4
Cardiovascular disease	1	5	11	44	12	49	24.5
Other underlying illness	0	5	14	42	14	47	29.8
Pregnancy	NA	NA	1	20	1	22	4.5
<42 days post-partum	NA	NA	1	20	1	22	4.5

BMI: body mass index; NA: not applicable.

Table 2

Case-based data: symptoms, treatment, interventions and outcome in cases with laboratory-confirmed 2009 pandemic influenza A(H1N1), Denmark, week 46 of 2009 to week 11 of 2010 (n=53)

Description		Total		
		Number of relevant cases	n	%
Symptoms				
Pneumonia		41	51	80.4
	Viral	15	41	36.6
	Bacterial	5	41	12.2
	Viral + bacterial	21	41	51.2
Renal insufficiency (creatinine levels 1.5 times above normal)		15	48	31.3
Septic shock		19	50	38.0
Treatment and interventions				
Antiviral treatment		47	51	92.2
	Oseltamivir alone	27	47	57.4
	Zanamivir alone	1	47	2.1
	Oseltamivir + zanamivir	19	47	40.7
No antiviral treatment		4	51	7.8
Mechanical ventilation		42	52	80.8
	Invasive	26	42	61.9
	Non-invasive	4	42	9.5
	Invasive + non-invasive	12	42	28.6
Haemodialysis		10	50	20.0
Extracorporal membrane oxygenation		6	53	11.3
Outcome				
30-day mortality		17	53	32.1

condition was reported for 52 of the 53 laboratory-confirmed cases: 11 had no pre-existing underlying medical condition, while 41 had at least one. Table 1 shows the underlying conditions for cases under 15 years of age and those aged 15 years and older. The presence of specified underlying illnesses varied between 9 of 47 and 12 of 49 except for renal insufficiency, which was observed in fewer (3 of 49) cases. In addition, 14 of 47 of the cases had other underlying illnesses that were not further specified. One case was reported to have been pregnant when admitted to the ICU and one had recently given birth.

According to the vaccine registry 10 of the 53 cases had been vaccinated against pandemic influenza A(H1N1): they had been vaccinated because of an underlying chronic illness. One of the 10 had been vaccinated twice, with an interval of a month between the vaccinations. The median time between vaccination and admission to an ICU was seven days (range: 3–35 days); seven cases were admitted to an ICU within 14 days of vaccination. Of the 41 patients reported to have at least one underlying medical condition in the case-based system, 32 were not vaccinated. The pregnant case who had been admitted to an ICU was not vaccinated.

Clinical presentation, treatment, interventions and outcome

Table 2 shows the available data on clinical symptoms related to severe illness as well as treatment, interventions and outcome. The median interval between onset of symptoms and hospitalisation for 47 of the cases was three days (range: –78 to +33). Four of the 47 had already been hospitalised for 1, 5, 10 and 78 days when they developed pandemic influenza. When those four are excluded, the median time between symptom onset and hospital admission was four days. For these patients (n=43), the median interval between hospital admission and ICU admission was one day (range: ‹1–21 days,). The median time between onset of symptoms and the date of ICU admission was five days (range: ‹1–15 days, with one outlier of 54 days, n=43). The number of days in the ICU was calculated for 40 of these patients and ranged from less than one to 65, with a median of 10 days.

A majority of patients (41 of 51) developed pneumonia and 19 of 50 had septic shock. Of 48 patients, 15 developed renal insufficiency, 12 of whom had no history of this condition. Ten patients developed both renal insufficiency and septic shock.

Of 51 patients, 47 were reported to have been treated with antiviral medication, mostly oseltamivir (n=27) or a combination of oseltamivir and zanamivir (n=19). The median interval between onset of symptoms and the start of any antiviral treatment was five days (range: –6 to +53 days, n=42). One person was already on antiviral treatment before symptom onset. The median interval between ICU admission and start of antiviral treatment was less than one day (range: –9 to +8 days, n=47). A total of 13 patients were on antiviral treatment before ICU admission. A total of 42 of 52 patients received mechanical ventilation: most of them received ventilation immediately when they were admitted to the ICU. The median time between admission and ventilation was less than one day (range: ‹1–4 days, n=42). The median period of ventilation was 7.5 days (range: ‹1–45 days, n=22). Of 50 patients, 10 underwent haemodialysis and six of the 53 were treated with extracorporeal membrane oxygenation (ECMO).

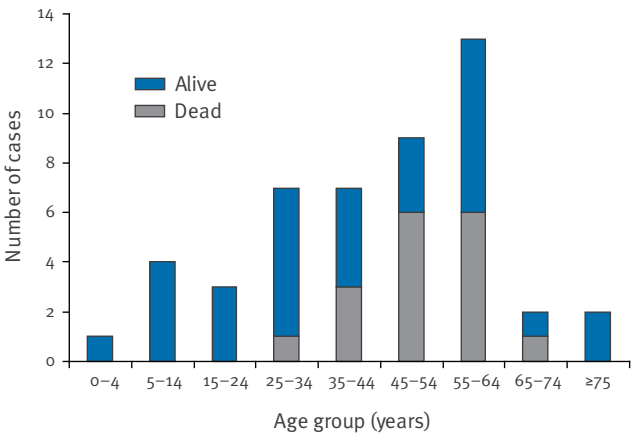
The death rate was 32% (17 of the 53 cases). Three patients died more than 30 days after confirmation of their infection with pandemic influenza (34, 41 and 169 days after confirmation). As of 22 October 2010, the other 33 patients were alive. Of the 17 patients who died within 30 days 11 were male and six were female (Fisher's exact test p=0.57). Of the 17 cases whose deaths were related to the pandemic influenza, 13 had a pre-existing underlying medical condition. This was not associated with death (Fisher's exact test p=1.0). ECMO treatment was also not associated with a higher risk of death (three of six patients died after ECMO). Figure 4 shows the number of cases who died by age group. Of the 17 whose deaths were related to pandemic influenza, 12 were aged between 45 and 65 years.

Discussion

The aggregate data obtained through the surveillance system employed between week 46 of 2009 and week 11 of 2010 served as a tool to monitor the capacity in ICUs and to assist in planning for referral of severe cases as the epidemic progressed. Our results showed that the trend in incidence of pandemic influenza A(H1N1) infection was visible from the aggregate data even when only cases reported within the deadlines were considered. The aggregate data showed that the number of new cases reached its maximum a week later than the peak observed from the case-based surveillance

Figure 4

Case-based data: laboratory-confirmed 2009 pandemic influenza A(H1N1) cases by outcome 30 days after initial laboratory confirmation and by age group, Denmark, week 46 of 2009 to week 11 of 2010 (n=17)



and sentinel surveillance. This can be expected as the median period between onset of symptoms and ICU admission was five days.

The aggregate data enabled us to assess the number of patients with pandemic influenza in ICUs, but there are some uncertainties. We consider that the extent of the underestimation, due to inconsistent participation of some hospitals, is limited as we found that hospitals that had not reported usually had no cases. However, there might have been a slight overreporting of patients who had been transferred to another hospital. The choice of case definition, which included patients with an epidemiological link to a laboratory-confirmed patient, might have led to some false-positive cases. Due to the aggregate nature of the data, we cannot quantify this. All things considered, the extent of the uncertainties seems limited and we estimate that the number of reported cases (n=93) closely approaches the actual number of patients with pandemic influenza in Danish ICUs. Therefore, the 53 confirmed cases used in the analysis of the case-based system can be assumed to represent approximately 57% (53 of 93) of the patients with pandemic influenza in Danish ICUs.

Severity of the pandemic

This surveillance system can assess certain aspects of the severity of the winter peak of the pandemic in Denmark: the number of severe cases in the general population, the death rate among severe cases and the specific groups that developed severe illness.

On the basis of the 93 cases reported in the aggregate data, the estimated incidence in Denmark (with a population of 5.5 million) was 1.7 per 100,000 population. This suggests that the overall impact of severe illness was not high at the population level and is in line with the incidence of ICU admissions observed in Australia and New Zealand during the 2009 winter peak [8]. In our study, the death rate was 32% (17 of 53 cases admitted to an ICU). These deaths occurred mainly in the age groups 44–54 years and 55–64 years. A cut-off point of 30 days after initial laboratory confirmation was chosen, to increase specificity, but it is possible that some of the deaths more than 30 days after confirmation were associated with pandemic influenza.

During seasonal influenza epidemics, children under two years of age and adults over 64 years are mostly affected, whereas the 2009 pandemic typically affected young adults [3-5]. The World Health Organization stated that people older than 65 years were the least likely to be infected with pandemic influenza, but if infected they would be at high risk of developing serious complications [9]. In Denmark, children aged 5–14 years contributed heavily to the number of patients admitted to hospitals [10], which was less prominent in the ICU admissions. The median age of 47 years of the cases in our study is within the range described in other studies of ICU patients with pandemic influenza [11-16]. While healthy adults generally do not suffer from severe illness when infected with seasonal influenza, the pandemic showed a different picture worldwide [3-5]. Our case-based data also showed a relatively high number of severe cases among previously healthy individuals.

The pandemic vaccination campaign started in week 45 of 2009 in Denmark. The strategy – to vaccinate all individuals with risk factors independent of age – was in line with the wide range in age distribution seen among patients with pandemic influenza in ICUs. It is important to note that the majority of the reported ICU cases with an underlying disease was not vaccinated. For those ICU patients who were vaccinated the vaccine probably came too late. However, vaccine effectiveness studies are needed to draw conclusions on these issues.

Severity of disease

The median period of five days between onset of symptoms of pandemic influenza and ICU admission was consistent with observations in other studies in Argentina (median of six days) and in Australia, New Zealand and Canada (median of four days) [11-13]. This interval will be influenced by access to healthcare and the perception of severity of symptoms by patients and physicians.

Severe respiratory failure occurred in 42 of 52 cases and for most of them, mechanical ventilation was started the same day they were admitted to the ICU. Also in other ways, the clinical presentation of pandemic influenza patients in Danish ICUs was severe, with 10 of 48 cases developing both renal insufficiency and septic shock, and several cases developing either renal insufficiency or septic shock. Davies *et al.* predicted that Europe had to prepare for an estimated 2.6 persons per million inhabitants needing ECMO treatment as a result of pandemic influenza [12]. Since ECMO treatment was only performed in one hospital in Denmark during the pandemic, we could verify that the six cases reported in our case-based surveillance to have received ECMO were in fact all pandemic influenza cases in Denmark who received ECMO during the surveillance period. This number is of the order of magnitude Davies *et al.* predicted.

Impact of the pandemic on Danish intensive care units

The aggregate data showed that the burden on the ICUs was limited, at a national level. However, for hospitals that had pandemic influenza cases the ICU bed capacity used for these patients was substantial. Similar findings on ICU bed capacity were reported from Australia and New Zealand during the 2009 winter peak [8]. Our case-based data showed that the vast majority of cases needed ventilation and a high number of cases presented with complications, requiring treatment such as haemodialysis and ECMO. This required a high level of care and led to extra pressure on ICU facilities and staff. Due to the absence of baseline data

it is, however, not possible to compare this to the situation in ICUs during seasonal influenza epidemics.

The combination of aggregate and case-based data proved to be a useful tool to assess the situation in ICUs during the 2009 pandemic. Since both epidemic curves followed the same trend as the data from sentinel surveillance and on-call monitoring, the sentinel and on-call systems can be used to decide when to put the ICU surveillance in place during the next winter season. The ICU surveillance system could also be used during a seasonal epidemic in order to learn more about the baseline situation for seasonal influenza.

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Mortality of 2009 pandemic influenza A(H1N1) in Germany

H Wilking (WilkingH@rki.de)[1,2,3], S Buda[1], E von der Lippe[4], D Altmann[1], G Krause[1], T Eckmanns[1], W Haas[1]
1. Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
2. Postgraduate Training for Applied Epidemiology (PAE, German Field Epidemiology Training Programme), Robert Koch Institute, Department for Infectious Disease Epidemiology, Berlin, Germany
3. European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
4. Department of Epidemiology and Health Reporting, Robert Koch Institute, Berlin, Germany

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The mortality in Germany caused by the 2009 pandemic influenza A(H1N1) seems to have been one of the lowest in Europe. We provide a detailed analysis of all 252 fatal cases of confirmed infection with the pandemic virus notified between 29 April 2009 and 31 March 2010. The overall mortality was 3.1 (95% confidence interval (CI): 2.7 to 3.5) per one million inhabitants. We observed an increase in the case fatality rate of notified cases over time; notified cases aged 60 years or older had the highest case fatality rate (2.16%; 95% CI: 1.61 to 2.83; odds ratio: 5.4; p<0.001; reference group: 35–59 years). The median delay of four days (interquartile range (IQR): 2–7) between symptom onset and antiviral treatment was significantly longer in fatal cases than for non-fatal cases (median: two days (IQR: 1–3; p<0.001). Analysis of the underlying medical conditions of fatal cases, based on the observed frequency of the conditions in the general population, confirms the risk for fatal outcome, which is most notably due to immunosuppression, diabetes and respiratory diseases. Our results suggest that early treatment might have had an impact on overall mortality. Identification of risk groups for targeted intervention to prevent fatalities needs to take into account the distribution of underlying conditions in the population.

Introduction

Based on initial reports from Mexico, the case fatality rate (CFR) of 2009 pandemic influenza A(H1N1) was estimated to be 0.09% (range: 0.07–0.4) and there was considerable uncertainty over what could be expected in other countries [1]. Since March 2009, various countries in Europe and worldwide have experienced one or more pandemic waves, with remarkable differences in the number of reported deaths between countries [2-9]. On 27 April 2009 the first symptomatic cases positive for the pandemic virus were notified in Germany [10]. The first death associated with laboratory-confirmed pandemic influenza was reported on 25 September 2009 from North Rhine-Westphalia, just before the number of autochthonous cases started to rise exponentially in week 42 [11,12]. Despite more than 200,000 cases of laboratory-confirmed pandemic influenza, the overall mortality in Germany based on the notified cases is one of the lowest in Europe. However, an intriguing number of deaths occurred after the incidence of influenza at the population level had already subsided at the end of 2009.

This article presents a detailed analysis of all 252 notified fatal cases in Germany, from the first detection of pandemic cases in April 2009 up to 31 March 2010. We focused on the course of disease, antiviral treatment and the risk factors involved in order to better understand how the situation in Germany differed from that in other countries and to identify groups at risk of severe disease and fatal outcome, in preparation for potential subsequent waves.

Methods

In Germany, in accordance with the protection against infection act, every laboratory-confirmed case of influenza has to be notified by the laboratory to the local health authority and additional clinical information is actively retrieved from the physician [13]. Additionally, on 2 May 2009, a special legal ordinance for pandemic influenza came into force. German physicians had to notify suspected cases of pandemic influenza to the local health authorities. For this the case ascertainment followed the recommendations given by the professional medical societies [12,14]. Suspected cases were tested for presence of the pandemic virus and only laboratory-confirmed cases or clinical cases with an epidemiological link to a laboratory-confirmed case were transmitted for whole Germany from the local health authorities via the federal states to the Robert Koch Institute in Berlin, Germany. These cases are included in this study.

A fatal case is defined as a person whose death was in temporal relation to an infection with pandemic

influenza confirmed by direct identification tests using standard laboratory methods (polymerase chain reaction (PCR) or viral culture) irrespective of other diagnoses. Laboratory confirmation could be ante- or post-mortem. Proof of a causal relationship between death and laboratory-confirmed influenza was not established. All cases (fatal and non-fatal) are transmitted using the official electronic notifying system in Germany (SurvNet) [15]. The system includes information on age, date of onset of illness, hospitalisation and fatal outcome. It allows the update of information including additions and corrections.

Starting on 17 July 2009, the following additional case-based information was included for all notified and transmitted cases, using a standardised free-text format: antiviral treatment (none; oseltamivir; zanamivir), date of start of treatment, reason for hospitalisation (Influenza; other disease, unknown), pneumonia (yes; no) and underlying chronic medical disease conditions (none; diabetes mellitus; impairment of the cardiovascular system including hypertension; impairment of the respiratory system; obesity defined as a body mass index (BMI)›30; pregnancy; immunosuppression; other specified). Data sets of fatal cases in the central database at the Robert Koch Institute were additionally checked for possible inconsistencies and only validated data sets were included in the analysis. A more detailed description of the special issues concerning German data acquisition during the pandemic has been published recently [12].

Cross-sectional data on the 12-monthly prevalence for chronic disease conditions in Germany was collected via a telephone-based self-reported survey – Gesundheit in Deutschland Aktuell [German Health Update]. For detailed information on the method, see reference 16. The target population was the German-speaking resident population aged 18 years and above. The current survey was conducted from July 2008 to June 2009, covering the start of the pandemic.

The overall mortality for Germany is based on the total population in 2009 reported by the Federal Statistical Office (82,200,000) and we calculated cumulative mortality stratified by age group. For the comparison of mortality between different countries, data provided by the European Centre for Disease Prevention and Control (ECDC) were used [5]. As denominator, estimates for the total populations of European countries were obtained from Eurostat, the United States Census Bureau and Statistics Canada (all 2009 estimates).

All calculations were based on cases with available information as denominator. To calculate the case fatality, we used the number of laboratory-confirmed or epidemiologically confirmed pandemic influenza cases notified in Germany for each week as the denominator. Odds ratios (ORs) were given for the influence of age group on the incidence of fatal outcome in all notified influenza cases. Relative risks (RRs) were calculated as risk of death in persons with underlying chronic conditions divided by the risk of death in persons without these reported risk factors; sex and 10 age strata were used for adjustment, except for pregnancy. We included the exact binomial 95% confidence intervals (CIs) for proportions and the test on the equality of medians if appropriate. For time spans, the median and interquartile range (IQR) as measure of statistical dispersion were given. Stata was used for calculations.

Results

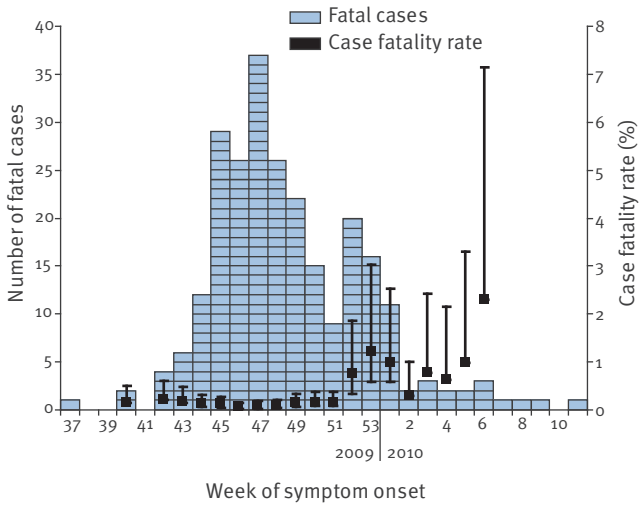
Disease frequency

In Germany 252 fatal cases associated with laboratory-confirmed 2009 pandemic influenza A(H1N1) were reported, starting with the first case on 25 September 2009. The first increase in the number of fatal cases occurred in week 44 of 2009 and within one month the notification of fatal cases rose to a maximum of 37 (in week 47) (Figure 1). A second peak was observed, with 20 fatal cases per week from week 52 of 2009 to week 1 of 2010. Taking all notified and transmitted cases as the denominator (n=226,075), the overall CFR of notified cases (nCFR) was calculated to be 0.11% (95% CI: 0.10 to 0.13). The cumulative mortality by 31 March 2010 was 3.1 (95% CI: 2.7 to 3.5) per million inhabitants. The majority (58%; 95% CI: 52 to 64) of fatal cases was male. In cases aged below 15 years a high proportion (66%: 95% CI: 46 to 82) of fatal cases was female.

During the pandemic wave, the weekly nCFR changed with a period with low values before the calendar week 52 and high thereafter (Figure 1). Taking week 52 as a cut-off date we divided the fatal cases into early (n=189) and late cases (n=63). In a univariate analysis there was a significant association of the late

Figure 1

Notified fatal cases of 2009 pandemic influenza A(H1N1) and case fatality rate, by week of symptom onset in 2009 and 2010, Germany (n=252)



Black bars represent 95% confidence intervals.

cases with advanced age (≥60 years; p=0.016) and being male (p=0.038). Underlying medical risk factors (p=0.17), interval between the onset of symptoms and death (p=0.56) and the time from onset of symptoms to the start of antiviral treatment (p=0.34) were not associated with late cases. The multivariate model with the above independent variables failed to achieve statistical significance, but this is probably due to small numbers of cases.

Age distribution

The median age of the fatal cases was 47 years (IQR: 29–57), which is significantly higher than for the non-fatal cases (median: 16 years; IQR: 10–28; p<0.001). Generally, all age groups were affected: the age group with the highest mortality was children aged less than 1 year with a cumulative mortality of 4.4 (95% CI: 1.6 to 9.5) per one million children of this age group (Table 1), followed by the age group 35–59 years with 4.2 (95% CI: 3.5 to 5.0) per one million people of this age. However, the 95% CIs and the Kruskal–Wallis rank test (p=0.41) indicate that differences in mortality between the age groups was not pronounced and did not achieve statistical significance.

In contrast, the nCFR was highest in elderly people (≥60 years), at 2.16%, with an OR of 5.4 (95% CI: 3.9 to 7.6) in comparison with the age group 35–59 years. Schoolchildren (5–14 years) showed the lowest nCFR of 0.03% (95% CI: 0.02 to 0.04) with an OR of 0.07 (95% CI: 0.04 to 0.12).

Course of disease

The median interval between the onset of symptoms and death was 13 days (IQR: 6–22). Symptom onset in adult cases was reported to have occurred more than 14 days before the date of death for 91 of 233 (39%) cases and more than 28 days for 44 of 233 (19%) cases. However, this was observed only for adult cases. In children (<15 years), this interval was significantly shorter, with a median of six days (IQR: 3–13), than in the other age groups (p=0.01).

The majority of notified fatal cases (211 of 233, 90.6%) had been admitted to a hospital. In 125 of 164 (76.2%) cases, the influenza infection was indicated as the cause for hospitalisation. The median length of hospitalisation overall was 12 days (IQR: 4–23); in children (<15 years), the median (five days; IQR: 3–12) was significantly shorter than that in the other age groups (p=0.04). Pneumonia was diagnosed in 200 of 220 (90.9%) cases.

Antiviral treatment

Antiviral therapy was started in more than half of the fatal cases (148 of 230; 64.3%), with oseltamivir in 141 cases and zanamivir in seven cases. In those patients with available data, the median time from onset of symptoms to the start of antiviral treatment was four days (IQR: 2–7) (Figure 2). This interval was significantly longer than that for non-fatal cases (two days; IQR: 1–3; p<0.001). In 11 of 15 (73.3%) fatal cases below 15 years of age and in 93 of 125 (74.4%) of the adult fatal cases, treatment was not carried out within 48 hours of the onset of symptoms as recommended [14]. The median time from the start of antiviral treatment to death was five days (IQR: 2–12).

Risk factors

At least one risk factor for severe influenza illness was present in 200 of the 252 fatal cases (79.4%). More than one underlying medical condition was reported for 61(24.2%) of the patients. For 34 (13.5%) of the fatal cases, no underlying condition regarded as a risk factor was reported. Of these 34 cases, four were aged below 15 years and 13 were female. Half of these cases (16 of 32 with available information) had received anti-

Table 1

Age distribution of fatal cases of 2009 pandemic influenza A(H1N1), Germany, 29 April 2009 to 31 March 2010 (n=252)

Age group (years)	Number of cases	Percentage male	Cumulative mortality in one million population (95% CI)[a]	Notified case-fatality rate as percentage[b]	Odds ratio (95% CI)[c]	P value
0–1	6	66	4.4 (1.6–9.5)	0.18	0.47 (0.21–1.06)	0.07
2–4	4	50	1.9 (0.5–4.9)	0.05	0.13 (0.05–0.35)	<0.001
5–14	19	21	2.5 (1.5–3.9)	0.03	0.07 (0.04–0.12)	<0.001
15–34	42	57	2.2 (1.6–3.0)	0.07	0.18 (0.13–0.26)	<0.001
35–59	130	62	4.2 (3.5–5.0)	0.40	Reference group	Reference group
≥60	51	63	2.4 (1.8–3.2)	2.16	5.4 (3.86–7.56)	<0.001
Total	**252**	**58**	**3.1 (2.7–3.5)**	**0.15 0.11[d]**	–	–

CI: confidence interval.

[a] Based on the German population of 2008. The output of the Kruskal–Wallis rank test was p= 0.41, which indicates that there were no significant differences in cumulative mortality between the age groups.

[b] Denominator: all notified and transmitted pandemic influenza cases with detailed information on age, unless otherwise indicated.

[c] Odds ratio for the influence of the age group on the incidence of fatal outcome in all pandemic cases. The age group 35–59 years was set as the reference group.

[d] Denominator: all notified and transmitted pandemic influenza cases.

viral treatment, which was significantly less often than in cases with reported risk factors (p=0.039).

Measures of disease frequency and association with underlying medical conditions among adult (≥18 years) fatal cases are given in Table 2. The relative risk of death of infected individuals with underlying chronic disease conditions in comparison with that for infected individuals without any reported risk factors was 10.0 (95% CI: 6.7 to 15.0). Immunosuppression was most frequently notified, with a proportion of 26.0% (95% CI: 20.0% to 32.7%) fatal cases. This is in keeping with the fact that immunosuppression was notified in 34 of 138 (24.6%) of the fatal cases with only one underlying disease as a risk factor. This is by far the highest proportion in this group of patients, indicating a strong association to severe cases of pandemic influenza. However, no population-based survey data are available to calculate the relative risk.

Diseases of the cardiovascular system were reported, with a proportion of 23.5% (95% CI: 16.7 to 29.3), which is in the same range as the sum of self-reported population-based 12-month prevalences of hypertension: 21.4% (95% CI: 20.9 to 22.0), angina pectoris: 1.7% (95% CI: 1.5 to 1.9) and heart failure: 2.4% (95% CI: 2.2 to 2.6). Obesity was notified with a proportion of 19.9% (95% CI: 14.5 to 26.2) and showed a slight association with fatal outcome RR: 1.2 (95% CI: 0.8 to 1.8). Underlying chronic respiratory disease was notified, with a proportion of 19.9% (95% CI: 14.5 to 26.2). This proportion was twice as high as the combined prevalence of asthma: 5.2% (95% CI: 4.9 to 5.5) and chronic (obstructive) bronchitis: 4.5% (95% CI: 4.3 to 4.8) in the German population. Furthermore, diabetes was frequently reported for the fatal cases (17.2%) and doubled the risk of a fatal outcome (RR: 2.3; 95% CI: 1.5 to 3.6).

Figure 2

Notified fatal cases of 2009 pandemic influenza A(H1N1) by time between symptom onset and start of antiviral treatment, by age group, Germany, 29 April 2009 to 31 March 2010 (n=140)

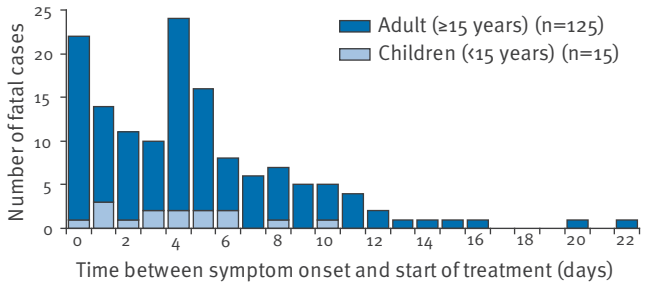


Table 2

Underlying medical conditions of the first fatal cases of 2009 pandemic influenza A(H1N1) in adults ≥18 years, Germany, 29 April 2009 to 31 March 2010 (n=196)

Underlying conditions[a]	Number of notifications in fatal cases (%)	Proportion in fatal cases as percentage (95% CI)	12-month prevalence as percentage (95% CI)[b]	Relative risk (95% CI)[c]
Yes	169 (100)	86.2 (80.6–90.7)	37.4 (36.8–38.1)	10.0 (6.7–15.0)
Immunosuppression[d]	51 (30)	26.0 (20–32.7)	NA[e]	NA
Cardiovascular disease	46 (27.2)	23.5 (16.7–29.3)	NA	NA
Hypertension	NA	NA	21.4 (20.9–22.0)	NA
Angina pectoris	NA	NA	1.7 (1.5–1.9)	NA
Heart failure	NA	NA	2.4 (2.2–2.6)	NA
Obesity[f]	39 (23.1)	19.9 (14.5–26.2)	13.4 (12.9–13.9)	1.2 (0.8–1.8)
Respiratory disease	39 (23.1)	19.9 (14.5–26.2)	NA	NA
Asthma	NA	NA	5.2 (4.9–5.5)	NA
Chronic bronchitis	NA	NA	4.5 (4.3–4.8)	NA
Diabetes	29 (17.2)	14.8 (10.1–20.6)	5.7 (5.4–6.0)	2.3 (1.5–3.6)
Pregnancy	2 (1.2)	1.0 (0.1–3.6)	NA	2.2 (0.5–9.4)[g]
Other	50 (29.6)	25.5	NA	NA
None	27	13.8 (9.3–19.4)	NA	NA
Total	**196**	**100.0**	**NA**	**NA**

CI: confidence interval.

[a] Mutiple answers possible.

[b] German Health Update - Telephone Health Survey 2008/2009 (Germany) [16].

[c] Age- and sex-adjusted relative risk: risk in the exposed divided by the risk in the unexposed.

[d] Including three reported cases with leukaemia.

[e] NA= Not available

[f] Body mass index (BMI)›30 or being treated for obesity or international statistical classification of disease (ICD-10) Code E66 obesity (self-reported).

[g] Estimate for the relative risk of pregnancy: number of births in 2009: 682,514; population based on the female general population in women of child-bearing age (15–45 years): 16,129,518; corrected for the duration of pregnancy: 267 days and the days of the risk period: 338 days. Relative risk = 2 / 682,514 / 365 x 267 / 365 x 338 / 27 / 16,129,518.

Two of the fatal cases were pregnant. One presented no other additional risk factor; the other was reported to be obese. Considering all pregnant women of childbearing age in the general population at risk of infection, a rough estimate of the relative risk is possible. Taking 27 April 2009 as the start of the risk period, the relative risk was 2.2 (95% CI: 0.5 to 9.4).

Discussion

Disease frequency

The detailed analysis of notification data and risk factors in the general population of Germany presented in this paper gives insight into what might play a role in the differences between countries. Based on reported cases, the overall mortality in Germany of 3.1 (95% CI: 2.7 to 3.5) per one million inhabitants is lower than that in North America – United States: 7.0 (95% CI: 6.7 to 7.3) and Canada: 13.7 (95% CI: 12.4 to 15.1) and shows more similarities to that in other European countries. However, while in some neighbouring countries such as the Netherlands 3.7 (95% CI: 2.8 to 4.7), Belgium 1.8 (95% CI: 1.1 to 2.8) and Austria: 4.8 (95% CI: 3.4 to 6.5), the reported mortality was in the same range, Spain 6.3 (95% CI: 5.6 to 7.1), the United Kingdom 7.6 (95% CI: 6.9 to 8.3) and France 5.1 (95% CI: 4.6 to 5.7) reported a substantial higher overall mortality than that observed in Germany. Special care should be taken when comparing and interpreting CFRs as the number of cases in the denominator is often difficult to estimate [3]. A right shift of the epidemic curve for fatal cases when compared with the non-fatal cases contributing to an increase in CFR might suggests that the risk of severe outcome changed during the pandemic (Figure 1). We consider it more likely, however, that the affected age groups as well as the probability of laboratory confirmation and reporting might have varied during the course of the pandemic wave.

Age distribution of fatal cases

The population-based cumulative mortality in elderly people (≥60 years) was lower than that in adults aged 35 to 59 years. However, this contrasts with the highest nCFR in the age group above 60 years and older. Serology data for pre-existing immunity from the United States, United Kingdom and Finland suggest that this might be the result of lower susceptibility of the oldest age group to an infection with the newly emerged influenza viral genotype, thus causing fewer cases [17-19]. Alternatively, age-dependent contact frequency can become the driving force for an age-related distribution of cases, as studies on contact patterns show that the main contacts occur mostly within the same age strata [20].

Disease course

An intriguing observation has been the difference in the interval between onset of symptoms and death between children younger than 15 years and adults. This might suggest a frequent fulminant course of disease in children, despite the same frequency of hospitalisation and pneumonia in both groups.

Antiviral treatment

In two thirds of the fatal cases, antiviral treatment was started after the 48-hour window following the onset of symptoms (Figure 2) and in half of the patients only after four days. This shows that some patients may not treated optimally, according to the recommendations for antiviral treatment [14]. On the other hand, the earlier treatment start reported for non-fatal cases suggests that specific antiviral treatment can reduce untoward outcome. Similar observations have been made in other countries [3,21].

Risk factors

It can be assumed that acute infection interacting with underlying chronic diseases plays a pivotal role in the outcome, as has been described by a number of studies on disease severity of pandemic influenza. Old and newly suggested risk factors, such as obesity, might also impair physiological mechanisms of compensation [22]. This is why it is important to report fatal cases of influenza virus infection even when the contribution of the infection to the detrimental course of disease cannot be quantified precisely.

Most (86.2%) of the reported fatal cases in Germany had an increased likelihood of a severe disease course because of chronic illnesses, including a quarter of patients with more than one underlying disease condition. The proportions of specific underlying conditions vary between different countries or regions, with obesity most frequently observed in California (United States), neurological disorders in England and human immunodeficiency virus (HIV) infections in South Africa [2,3,7]. In our analysis we could show that the relative risk calculated on the basis of population data allows a more precise definition and ranking of risk groups, which might also allow for better comparison between countries. The fifth most frequent underlying disease, showing the highest estimate of risk in our study, was diabetes. As this condition is widely distributed in the European population it has probably been underestimated as a risk factor, so far and further research seems to be warranted. Other studies identified pregnancy as an important risk factor [23,24]. However, due to the small number of deaths in pregnant cases, our results are neither able to confirm nor exclude this for Germany.

Study limitations

Given the high disease awareness during the pandemic in the general population, among medical staff and the reporting authorities, it can be assumed that notified fatal cases with laboratory-confirmed pandemic influenza present a good source of data for the elucidation of underlying medical conditions and other factors related with severe cases of this infection. Nevertheless, artefacts such as underreporting and misclassification of outcome or risk factors are possible and might conceal the real disease burden. Even though case-based information on risk factors was also available for non-fatal cases, analysis showed that reporting was much more complete for patients who

died. Therefore, we calculated the relative risk based on a self-reported population survey. In addition, as notification of deaths is mandatory for laboratory-confirmed cases only, such deaths might represent only the tip of the iceberg, since in the course of the pandemic wave it is estimated that fewer than every tenth case seen by a physician will be laboratory confirmed [25]. Information on other factors for the development of severe illness, such as infectious dose, general immune status (pre-existing immunity), nutrition, access to healthcare or unrecognised comorbidity is lacking and might also influence the risk of death from pandemic influenza.

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Response to the 2009 influenza A(H1N1) pandemic in Italy

C Rizzo (caterina.rizzo@iss.it)[1], M C Rota[1], A Bella[1], S Giannitelli[1], S De Santis[1], G Nacca[1], M G Pompa[2], L Vellucci[2], S Salmaso[1], S Declich[1]

1. National Centre for Epidemiology, Surveillance and Health Promotion, Istituto Superiore di Sanità (ISS, National Institute of Health), Rome, Italy
2. Department of Prevention and Communication, Ministry of Health, Rome, Italy

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In Italy, the arrival of the 2009 pandemic influenza A(H1N1) virus triggered an integrated response that was mainly based on the 2006 National Pandemic Preparedness and Response Plan. In this article we analyse the main activities implemented for epidemiological surveillance, containment and mitigation of the pandemic influenza and the lesson learned from this experience. Overall, from week 31 (27 July – 2 August) of 2009 to week 17 (26 April – 2 May) of 2010, we estimate that there were approximately 5,600,000 cases of influenza-like illness (ILI) who received medical attention (with almost 2,000 laboratory-confirmed cases of pandemic influenza from May to October 2009). A total of 1,106 confirmed cases were admitted to hospital for serious conditions, of whom 532 were admitted to intensive care units. There were 260 reported deaths due to pandemic influenza. Approximately 870,000 first doses of the pandemic vaccine were administered, representing a vaccine coverage of 4% of the target population. One of the possible reasons for the low uptake of the pandemic vaccine in the target population could be the communication strategy adopted, for both the general population and healthcare workers, which turned out to be a major challenge. Active involvement of all health professionals (at local, regional and national level) in influenza pandemic preparedness and response should be encouraged in the future.

Background

Since the emergence of the avian influenza threat in 1999, the Italian Ministry of Health in collaboration with the Istituto Superiore di Sanità, the national institute of health, started to work on an influenza pandemic preparedness plan. The first National Pandemic Plan for Preparedness and Response was developed in 2003 and subsequently updated in 2006 [1] according to the 2005 recommendations of the World Health Organization (WHO) [2]. The 2006 Plan was aimed at strengthening preparedness and response for an influenza pandemic at both national and local level by improving epidemiological and virological surveillance (identification, confirmation and timely reporting of cases), implementing containment measures at the early stage of a pandemic (e.g. border restrictions, isolation of the first possible, probable and confirmed cases, contact tracing), reducing the impact of the pandemic through the implementation of mitigation measures (pharmaceutical and non-pharmaceutical), ensuring communication strategies to inform healthcare workers, the media and public about decisions, and monitoring the efficiency of the interventions undertaken.

Since 2001, the National Health System has been decentralised and the 21 Italian regions are responsible for organising and delivering health services according to the Ministry of Health recommendations, including the necessary actions to contain and mitigate a pandemic. Each region was requested to produce its own Regional Pandemic Preparedness and Response Plan. This report summarises the response to the 2009 pandemic influenza A(H1N1) in Italy and the lessons learned from this experience.

Initial response strategies

After the first pandemic influenza alert was announced by WHO in late April 2009 [3], a National Crisis Management Committee, headed by the Minister of Health was established, in charge of coordinating the strategies related to preparedness, response and communication during the pandemic.

Enhanced surveillance and data collection

Seasonal Influenza surveillance is based on a nationwide sentinel surveillance network (INFLUNET) combining clinical and virological information. The system is based on sentinel practitioners (general practitioners and paediatricians) covering about 1.5–2% of the general population, with the aim of monitoring the incidence of medically attended influenza-like illness (ILI), identifying the extent of the seasonal epidemics and collecting information on circulating viral strains from week 42 to week 17 of the following year each influenza season. A case of medically attended ILI is defined as a patient attending a sentinel practitioner

with acute onset of fever >38 °C, respiratory symptoms and one of following symptoms: headache, general discomfort or asthenia. Data collected through INFLUNET are also uploaded weekly into the European Influenza Surveillance Network (EISN) database coordinated by the European Centre for Disease Prevention and Control (ECDC) [4].

Immediately after its formation, the National Crisis Management Committee recommended enhancing INFLUNET surveillance, so that it start earlier than usual in order to detect any sudden increase in the number of ILI cases in the community. The committee also decided that an active surveillance system should be set up to detect individuals presenting with ILI with a recent history of travel to the affected areas (Mexico and United States), as well as their close contacts. As previously described [5], individuals coming from affected areas received specific medical advice through the health authorities at airports and seaports to go immediately to a hospital if they developed symptoms of ILI. Any possible, probable or confirmed case of pandemic influenza – defined according to the European Union case definitions [6] – was immediately reported to the Ministry of Health. Moreover, laboratory confirmation of all suspected cases was required. Demographic data and information about symptoms and travel history were collected.

The first 200 confirmed cases of pandemic influenza were thoroughly investigated by local health authorities, using specific online epidemiological investigation forms, within 12 hours after case confirmation. Follow-up information was requested by the local health authorities for each case after 15 days. Data on contacts were also collected including exposure data (e.g. relationship to case, type and date of contact, household information) and subsequent development of illness and/or asymptomatic infection.

Containment measures implemented

Containment measures were implemented in April 2009 and included social distancing measures (early isolation of cases and precautionary closure of schools with more than five ILI cases with at least two confirmed) and antiviral prophylaxis for close contacts of cases. A stockpile of 40 million doses of antiviral drugs (sufficient for a complete treatment for approximately 4% of the whole population) stored by Ministry of Health was distributed to the regions, together with recommendations for their correct use [7]. Any person reporting to have been in close contact with a confirmed case was asked to remain at home for seven to 10 days, thus avoiding contact with others. This recommendation was maintained until the end of July 2009.

Modelling disease spread

As soon as the pandemic threat emerged, it was crucial for national policymakers to have early predictions on the possible spread of the pandemic virus. Since the early phase of the epidemic in Italy, real-time analysis was undertaken to provide weekly advice, together with epidemiological data, to the National Crisis Management Committee. Since the National Health Authorities request relevant information to tailor containment and mitigation measures to be implemented in the population and to understand the possible scenarios of the pandemic influenza burden in case of disease spread at the national level, a reference scenario on the spatio-temporal spread of the pandemic virus was provided, using mathematical modelling, and the effectiveness of mitigation measures, both pharmaceutical and non-pharmaceutical (such as school closure and social distancing measures), was assessed. Briefly, a stochastic, spatially explicit, individual-based simulation model was used. Individuals are explicitly represented and can transmit the infection to household members, to school or work colleagues and in the general population (where the force of infection is assumed to depend explicitly on geographical distance). The national transmission model was coupled with a global homogeneous mixing Susceptible Exposed Infected Removed (SEIR) model accounting for the worldwide pandemic, which was used for determining the number of cases imported over time. The transmission model used was parameterised, based on the existing evidence, derived from the analysis of data from the national surveillance system until 17 June 2009 and on estimates of key epidemiological parameters available at that time [8].

Fine-tuning surveillance

On 11 June 2009, the WHO Director-General raised the pandemic level to level 6 [3]. In July 2009, WHO made changes in the reporting requirements for pandemic influenza, because of the worldwide spread of the disease [9]. The Italian Ministry of Health modified the previous requirements: regions were required to report weekly an aggregate number of probable, possible and confirmed cases, confirmed hospitalised cases and deaths due to pandemic influenza [8].
In addition, the following pre-existing surveillance systems were expanded.

- A web-based emergency room hospital admissions and hospitalisations sentinel surveillance system had been in place since 2008. In August 2009, the system was enhanced, by increasing the number of emergency rooms surveyed. A network was established among Italian emergency services that had an automatic recording system for admissions. Of the 21 Italian regions, 12 identified at least one emergency service that would send data for surveillance; to date, these constitute the reporting units of the system. Data from the previous year, were used when available to estimate the number of weekly admissions. Epidemic thresholds were calculated using a Poisson regression model.
- A surveillance system of drug purchase – collecting data from a representative sample of 2,500 public and private pharmacies in Italy on the purchase of antibiotics (belonging to the Anatomical

Therapeutic Chemical (ATC) Classification System (ATC J01), painkillers (ATC N02B) and antiviral drugs (ATC J05AH) – was incorporated into pandemic surveillance activities. All data refer to prescribed drugs except painkillers, which are also available in Italy over the counter. The system had been in place since January 2005.

In addition, the following surveillance systems were set up during the pandemic.

- A web-based data collection form for surveillance of severe confirmed hospitalised cases and deaths due to pandemic influenza was set up in mid-September 2009. Forms were filled in by regional and local authorities and data were analysed daily at the national level (by the Istituto Superiore di Sanità and the Ministry of Health).
- To monitor vaccination coverage, in October 2009 a specific web-based data collection form was developed to be filled in by local health authorities (with details of the number of vaccine doses administered weekly to the target population, by age, risk conditions and region). Moreover, denominators for each target groups were also requested for each region in order to calculate vaccination coverage. The data were subsequently aggregated at the national level. Vaccination coverage reported always refers to the target population.

Communication of data

In order to inform the public about the pandemic in Italy and abroad, and to minimise conflicting information from different sources, communication to the public through the media was centralised at the national level and daily reports were published on the Ministry of Health website. When all surveillance activities were well established, a weekly report – including data and trends of ILI cases, vaccination coverage, emergency room admissions for acute respiratory syndromes, purchase of painkillers, antibiotics and antiviral drugs, and mortality – was released, in both Italian and English [10].

Mitigation measures implemented

Since 22 July 2009, the Ministry of Health recommended the use of antiviral drugs only for severe cases of pandemic influenza and for symptomatic patients with underlying medical conditions. In September 2009, the Ministry of Health started a health education campaign targeted at the general population recommending the adoption of basic non-pharmaceutical measures, such as staying at home if ill and covering noses or mouths with tissues, handkerchiefs or elbows when sneezing or coughing. Moreover, a specific hotline was set up to give advice and information regarding pandemic influenza prevention to both the general population and healthcare professionals.

Also in September 2009, according to the National Pandemic Preparedness and Response Plan before the pandemic vaccine became available, the Ministry of Health on 30 September 2009 identified the priority categories to be vaccinated, in a stepwise manner:

1. healthcare personnel and essential services personnel (e.g. police, firefighters, military corps) including blood donors;
2. pregnant women in their second and third trimesters and women who delivered in the previous 6 months or persons who take care of the baby;

Table

Vaccination coverage for first dose of pandemic influenza vaccine by target group, Italy, October 2009 to May 2010

Target groups	Number of first doses administered	Number of persons in target group	Vaccine coverage (%)
Healthcare personnel	165,562	1,069,264	15.5
Essential services personnel (e.g. police, firefighters, military corps)	72,181	1,228,155	5.9
Blood donors	6,329	742,349	0.8
Pregnant women in their second and third trimesters	23,016	189,915	12.1
Women who delivered in the previous 6 months or person who take cares of the baby	8,170	237,594	3.4
Individuals with at least one chronic underlying condition aged 6 months–65 years	549,167	4,309,466	12.7
Individuals with at least one chronic underlying condition aged >65 years	13,562	710,862	1.9
Children aged >6 months attending day-care centres	4,618	89,394	5.2
Children aged <18 years resident in long-term care facilities	1,120	10,155	11.0
Children aged <24 months born pre-term	1,595	20,657	7.7
Healthy children and adolescents aged 6 months–17 years	20,307	7,671,581	0.3
Healthy individuals aged 18–27 years	5,650	4,642,188	0.1
Total	**871,277**	**20,921,580**	**4.2**

3. individuals with at least one chronic underlying condition aged 6 months–65 years putting them at high risk of severe or fatal complications due to pandemic influenza and children aged ‹24 months born pre-term;
4. children aged ›6 months attending day-care centres
5. healthy children and adolescents (aged between 6 months and 17 years);
6. healthy individuals aged 18–27 years;
7. individuals with at least one chronic underlying condition aged ›65 years.

The Table shows the vaccination coverage for the first dose of the pandemic vaccine during October 2009 to May 2010.

Agreements with pharmaceutical companies regarding the availability of pandemic vaccine according to the WHO indications [11] on the pandemic strain were signed by the Ministry of Health in 2005. On these bases and with the support of mathematical modelling showing that vaccinating 40% (24 million) of the Italian population (60 million) was adequate to mitigate the pandemic, the Ministry of Health decided to buy 24 million doses of adjuvated (MF59) vaccines from only one supplier. The selected company delivered half of the purchase to the Ministry of Health central storage from where vaccines have subsequently been distributed to the 21 Italian regions (since 12 October 2009) through the network of the Italian Red Cross.

Evaluation of the pandemic in Italy

Active surveillance of imported pandemic cases

In Italy, the first imported confirmed case of pandemic influenza was detected on 24 April 2009 (week 17) [12]; by the end of July 2009 approximately 250 imported confirmed cases had been reported, with more than 2,000 suspected cases being investigated. In August 2009 the total number of medically attended ILI cases reached 5,000, of whom approximately 2,000 (40%) were laboratory confirmed. Since then the number of autochthonous clusters increased, suggesting sustained transmission in Italy, supported by the schools re-opening in mid-September. By mid-October 2009 (week 43) approximately 14,000 ILI cases had been reported.

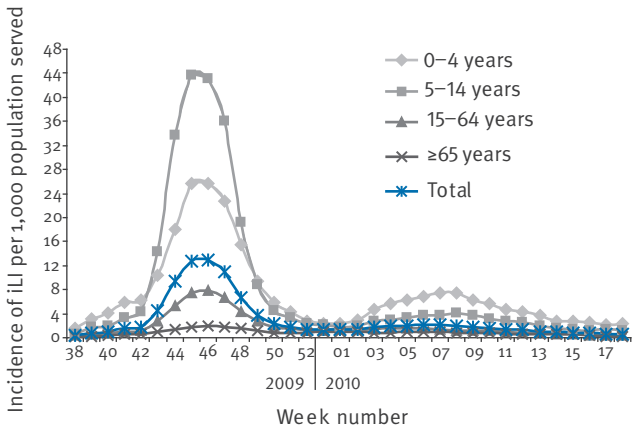
INFLUNET sentinel surveillance system

Even though the INFLUNET surveillance system had been in place from week 17 of 2009, no significant signals of increased influenza activity were detected until week 43, when an incidence of 4.5 cases per 1,000 served population of each reporting physician was observed. Two weeks later (week 45), the epidemic curve reached its peak, with a total incidence of 12.9 per 1,000 served population (Figure 1).

From week 31 of 2009 to week 17 of 2010, there were an estimated of approximately 5,600,000 medically attended ILI cases. The ILI incidence observed during the 2009–10 influenza season was 97 cases per 1,000 served population. This incidence estimate is similar to that described during the 2004–05 season, when the incidence rate reached the highest value ever described in Italy (116 cases per 1,000 served population). However, during the 2009–10 season, the number of ILI cases in the age group 0–14 years (270 cases per 1,000 served population) was the highest ever reported since the beginning of the INFLUNET surveillance system (which began in the 1999–2000 influenza season). In contrast, incidence in the age group ›64 years was very low (26 cases per 1,000 served population).

Figure 1

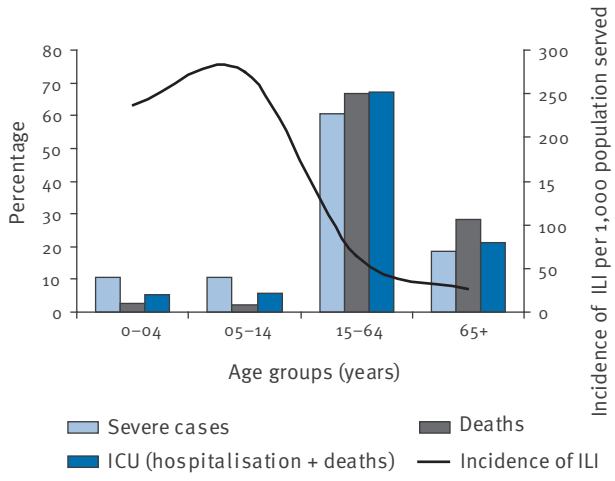
Incidence of influenza-like illness by age group, Italy, week 38 of 2009 to week 17 of 2010



ILI: influenza-like illness.
Source: INFLUNET data.

Figure 2

Proportion of severe cases, admission to intensive care unit and deaths and incidence of influenza-like illness[a], by age group, Italy



ICU: intencive care unit; ILI: influenza-like illness.
[a] Source: INFLUNET.

Surveillance of the first 200 confirmed pandemic influenza cases

The epidemiological investigations of the first 200 confirmed pandemic influenza cases were collected using an online database established at the end of April 2009 after the first Italian laboratory confirmed imported pandemic influenza cases in the country. By the last week of October 2009, a total of 1,286 cases had been included in the database, with reported symptom onset dates from 24 April to 31 October 2009. Details of approximately 3,900 contacts were also included in the database. Most (1,093 of 1,286; 85%) of the reported cases were notified by local health authorities within 12 hours after laboratory confirmation. Follow-up data were available for 1,040 of 1,286 (81%) of the cases. In the later stage of the surveillance of the first 200 confirmed cases (end of September 2009 to November 2009), the proportion of cases that were followed-up decreased because the number of cases increased dramatically.

Surveillance of laboratory-confirmed severe cases

Approximately 1,100 cases were admitted to hospital for serious conditions, of whom 532 were admitted to intensive care units, 49 needed extracorporeal membrane oxygenation, 166 were diagnosed with acute respiratory distress syndrome and 166 required oro-tracheal intubation. A total of 260 deaths due to complications arising from pandemic influenza were reported. In total, 476 of 1,100 (43%) of hospitalised cases with available information were reported to have an underlying risk factor for severe disease, including pregnancy and obesity. Proportional distribution by age group of severe cases, number of cases who were admitted to an intensive care unit and number of deaths is shown in Figure 2. Data are compared with INFLUNET and clearly show that the incidence of ILI cases was higher in the children aged less than 14 years, while disease severity and fatal outcomes were concentrated in those aged over 15 years, with a mean of 43 years.

Figure 3

Regions participating in the sentinel emergency room surveillance system, Italy, August 2009 to May 2010

Emergency room admissions

The emergency room admission system collates data from 73 major, representative hospitals in 13 regions (Figure 3). Data reported during the week 43 of 2009 showed that (3,269/43,335) 7.5% of all people who visited hospital emergency rooms were diagnosed with acute respiratory infection. Of these 653 (20%), were admitted to hospital after being in an emergency room, with the baseline for admissions reached for the first time for all age groups. During week 45 of 2009, the peak was reached, with 12.2% of acute respiratory infection cases among emergency room visits (4,995 of 41,037); of these 863 (17.3%) were hospitalised (Figure 4).

Drug purchase

A first peak in the purchase of antiviral drugs was registered in weeks 28 (6–12 June) to week 31 (July 27 to 2 August) of 2009, corresponding to the first pandemic wave registered in some northern European countries. In week 45, when the first peak of the ILI cases reported by INFLUNET in Italy was reached, a 90% increase in the purchase of antiviral drugs, and a 41% increase of antibiotics and a 95% increase of painkillers purchases were recorded, compared with the same week in 2008. Antiviral drug purchases reached 47 items per 100,000 inhabitants, more than double the amount bought the previous week, in line with the increase in the incidence of ILI.

Mathematical modelling

Simulations obtained by mathematical modelling were in agreement with the INFLUNET data in the early phase of the epidemic (April 2009 to September 2010), when containment measures were implemented. Briefly, by assuming isolation of confirmed cases, antiviral treatment and prophylaxis to 90% of symptomatic cases until 8 July 2009, and 33.3% natural immunity in the population aged more than 59 years, the peak of the ILI cases in Italy was expected on week 44 (95% confidence interval: 44 to 45). Estimates were consistent with the INFLUNET data showing that the peak in Italy was reached in week 45-46 [8].

Vaccine administration

The pandemic vaccine was administered mostly by vaccination services; however, some regions also involved general practitioners and paediatricians in

the pandemic vaccination campaign. Overall, 871,277 first doses and 52,723 second doses were administered (giving a total of 924,000 vaccine doses) and a national coverage among the target population of 4% (Table). Coverage was 15% of healthcare workers, 12% of pregnant women, 13% of persons aged under 65 years at high risk, and 11% of institutionalised individuals aged under 18 years old.

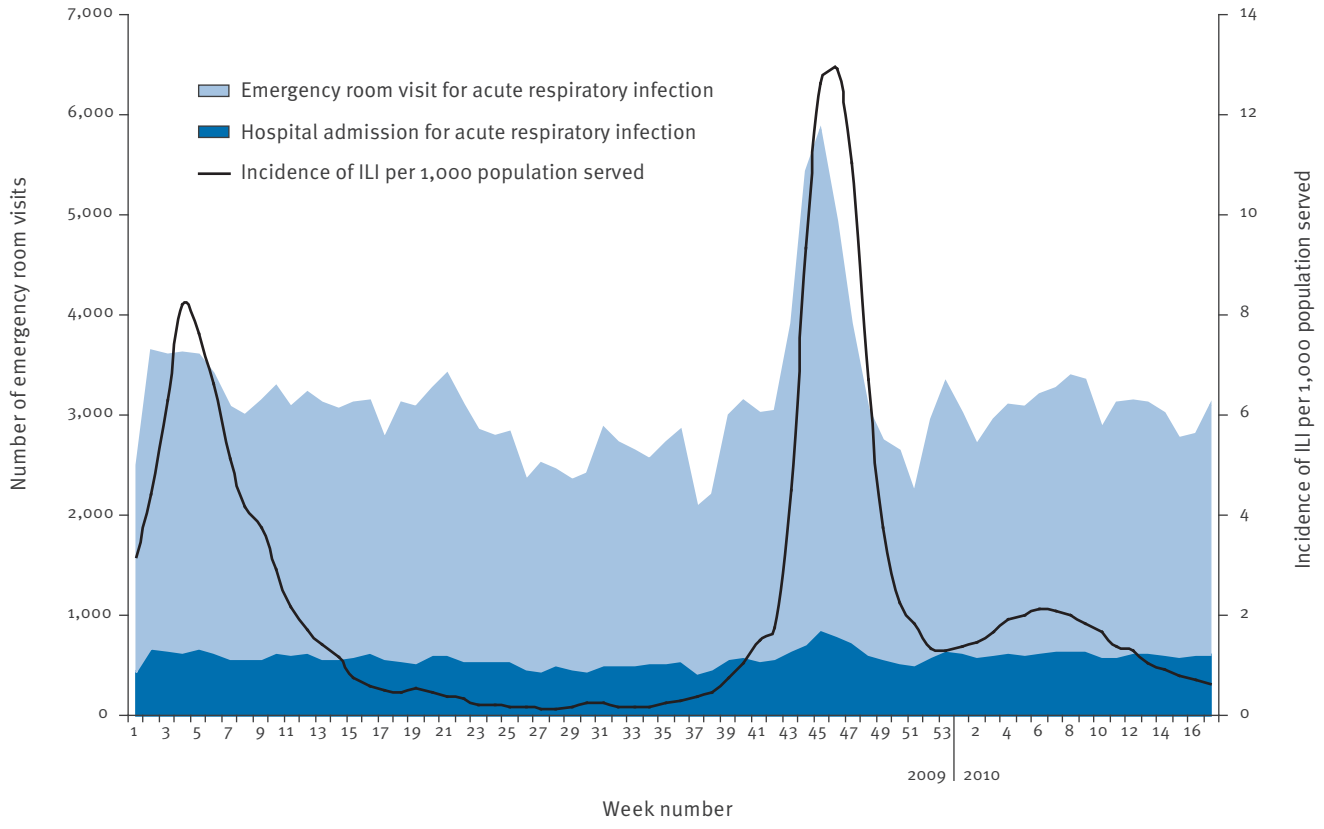
Lessons learned

When the pandemic virus emerged in late April 2009, reliable epidemiological data on the new circulating virus were limited and not available in a timely manner [13]. Consequently, uncertainty regarding the pathogenicity and severity of the pandemic virus, at the very beginning of its appearance, led advisors of decision-makers to consider the worst-case scenario. The combination of uncertainty and urgency to implement containment and mitigation measures in a short time made it difficult to fine-tune measures already included in the 2006 National Preparedness and Response Plan and to produce real-time modelling analysis with different scenarios of the possible impact of the mitigation measures. The WHO 11 June 2009 pandemic level 6 declaration supported the worst-case scenario approach. Therefore, on the basis of epidemiological data available in April 2009, only the actions listed in the 2006 Plan that were considered relevant to the situation at that time were performed. Among the activities undertaken, planning and coordination, situation monitoring and assessment, and containment and mitigation measures appeared to be efficient in the first containment phase (April- July 2009), in accordance with modelling results [8]. In fact, our experience suggests that the early response phase may have contributed to delaying and reducing the impact of the pandemic during spring and summer. This was facilitated also by school closure from early June to mid-September.

By contrast, the communication strategy adopted in Italy turned out to be a major problem. While at the beginning, the fast worldwide spread of the pandemic generated among the general population the feeling of a threat that was able to disrupt social life. Given the WHO pandemic level-6 declaration in June 2009, it was quite clear that the 2009–10 pandemic was caused by a virus able to spread effectively between humans. The uncertainty of the data (regarding disease severity and real number of affected individuals and of deaths) between April and October 2009 caused a high degree of disconcertion among healthcare workers and the public. This heavily influenced the vaccination campaign, in which the communication strategy plays a crucial role. The low vaccination uptake led to coverage

Figure 4

Influenza-like illness incidence[a] and emergency room visits for acute respiratory infections, Italy, week 1 of 2009 to week 17 of 2010



ILI: influenza-like illness.

[a] Source: INFLUNET.

of only 4% of the target population: 15% of the healthcare personnel and 1.5% of the general population [10].

In addition, the pandemic vaccines used during the 2009 pandemic were licensed by the European Medicines Agency (EMA) based on a mock-up vaccine procedure and were used on the basis of clinical data supporting the safety and effectiveness of vaccines developed using the influenza A(H5N1) strain, which had been thought would cause the next pandemic [14]. The way in which the pandemic vaccines were licensed was one of the main reasons of concern among healthcare workers and the general population. Another reason for concern was that this vaccine was a vaccine containing an adjuvant (MF59-squalene) and was recommended for risk groups (such as children and pregnant women) that differed from those included in the seasonal vaccination recommendations (elderly people and persons with underlying conditions older than 18 years) [15]. Concern was also raised by media regarding the risk of Guillain–Barré syndrome, related to the pandemic vaccine that was associated with 'swine influenza' vaccine that was administered in the United States in 1976–77 [16,17]. However, surveillance of adverse effect of pandemic influenza vaccination in Italy showed no particular evidence with respect to previous years [18].

These issues were mainly of concern to healthcare workers (e.g. general practitioners, paediatricians, specialists and nurses), who were supposed to liaise between the national and regional health authorities and the community. An Italian survey conducted in October 2009 among physicians and nurses, which investigated attitudes and behaviours towards preventive measures against the pandemic influenza, showed that: 70% of the 1,360 females (mainly nurses) in the sample and 51% of the 600 males would not get vaccinated against pandemic influenza [19].

Given this, many general practitioners and paediatricians were not able to disseminate the correct message, not even to the risk groups. Healthcare workers should have been timely informed about vaccine safety and involved in specific health education programmes in order to correctly inform the general population, but it was impossible to set up specific training before the end of December 2009, due to the overload of activities to be carried out during the pandemic. Indeed, concerns about vaccine safety should have been addressed first with general practitioners, using specific educational communication programmes. The fact that pandemic vaccine recommendations and prioritisation were based on risk rather than age strategies, coupled with the shortage of pandemic vaccines before the pandemic peak, vaccine dosage uncertainties, and the milder impact of the epidemic, concurred in discouraging the population to seek vaccination and probably had an important role in the failure of the vaccination campaign. This was the unfortunate consequence of the high level of uncertainties that informed most decisions during the period from July to September 2009.

As a result of the low vaccination coverage at national level, vaccine stock levels at the Ministry of Health warehouse remained high. In December 2009, a vaccine order was revised, 2,4 million doses were donated to WHO for developing countries, but the one-year validity of the vaccine doses forced the government to recall the doses and they will probably be discarded [20].

Enhanced epidemiological surveillance implemented in Italy during the pandemic substantially improved the quality and completeness of the epidemiological data collected. The integration of different data sources (i.e. incidence, mortality, severe cases, hospitalisation, emergency room visits, drugs purchases, pandemic vaccine coverage), allowed a weekly description of the burden of the 2009 pandemic influenza. This weekly epidemiological report (available also in English), disseminated through various official websites (Ministry of Health, Istituto Superiore di Sanità/National Centre for Epidemiology Surveillance and Health Promotion (Epicentro) and ECDC), has been a useful tool in informing and updating the media and health workers about the pandemic in Italy.

The intrinsic unpredictable characteristics of an influenza pandemic made every attempt of preparedness difficult and required flexibility in decision-making. However, the surveillance efforts made during this pandemic have provided a unique opportunity to validate influenza integrated surveillance, at both regional and national level. This surveillance, together with the established INFLUNET sentinel surveillance, will be maintained during the next influenza seasons. The underestimation of deaths could have been a weakness of the enhanced surveillance system adopted, because not all cases were laboratory confirmed.

The communication problems experienced during the pandemic also turned out to be valuable in generating a constructive discussion and building awareness of the importance of the active involvement of all health professionals (at local, regional and national level) in influenza pandemic preparedness.

In Italy responsibility for public health is shared between health authorities at national and regional level. Because of the threat posed by the pandemic, the regional health authorities implemented local pandemic plans. Thus, logistics issues, especially those concerning the distribution of vaccines within each region, as well as the strategy for the vaccinations at vaccination services or at the practices of general practitioners, were designed locally. Therefore, the response to the pandemic threat in Italy may have not been uniform and homogeneous, but it has strengthened the collaboration between central and peripheral levels.

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Electronic real-time surveillance for influenza-like illness: experience from the 2009 influenza A(H1N1) pandemic in Denmark

K M Harder (katjaharder@gmail.com)[1], P H Andersen[1], I Bæhr[1], L P Nielsen[2], S Ethelberg[1], S Glismann[1], K Mølbak[1]
1. Department of Epidemiology, Statens Serum Institut, Copenhagen, Denmark
2. Department of Virology, Statens Serum Institut, Copenhagen, Denmark

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To enhance surveillance for influenza-like illness (ILI) in Denmark, a year-round electronic reporting system was established in collaboration with the Danish medical on-call service (DMOS). In order to achieve real-time surveillance of ILI, a checkbox for ILI was inserted in the electronic health record and a system for daily transfer of data to the national surveillance centre was implemented. The weekly number of all consultations in DMOS was around 60,000, and activity of ILI peaked in week 46 of 2009 when 9.5% of 73,723 consultations were classified as ILI. The incidence of ILI reached a maximum on 16 November 2009 for individuals between five and 24 years of age, followed by peaks in children under five years, adults aged between 25 and 64 years and on 27 November in senior citizens (65 years old or older). In addition to the established influenza surveillance system, this novel system was useful because it was timelier than the sentinel surveillance system and allowed for a detailed situational analysis including subgroup analysis on a daily basis.

Introduction

In most industrialised countries, surveillance for influenza-like illness (ILI) is carried out by networks of sentinel general practitioners or clinics. Data from sentinel surveillance, in combination with virological data, constitute the basis for influenza surveillance, and has for many years proven to be of value [1]. However, the sentinel surveillance systems have limitations. In most countries, participation in the system is voluntary and it requires time and commitment for a general practitioner to report on a regular basis. Due to a limited number of active sentinel practitioners, analysis of trends and differences by subgroups such as age or geography may also be imprecise. Furthermore, reporting from sentinel practitioners is often done on a weekly basis and only during the influenza season. Finally, the Danish sentinel system, as organised at the present, has delays due to mail delivery from the sentinel practices to the surveillance institute and other practicalities [2,3].

To enhance influenza surveillance, a year-round simple electronic reporting system was established in Denmark in collaboration with the Danish medical on-call service (DMOS). Nearly real-time surveillance of ILI was achieved by a simple checkbox for ILI inserted in the electronic health record. This system was first established in 2006 and covered the entire country in 2008. This paper describes the DMOS surveillance system and reports data from the influenza A(H1N1)2009 pandemic from May 2009 to January 2010 where this surveillance system allowed a risk assessment of ILI trends on a daily basis.

Methods

DMOS is a national public medical service replacing the function of the general practitioners after opening hours. On weekdays, this service is open for attendance from 4 pm to 8 am, and during weekends and national holidays on a 24-hours basis. The service is staffed by physicians, mainly general practitioners. DMOS can only be contacted by telephone. The duty officer will either give advice on the phone, make an appointment for a consultation (at the nearest public clinic staffed by DMOS or a home visit, depending on the circumstances), or refer for admission to hospital.

All contacts are registered in a single national computer system. In the electronic health record, demographic data are registered in a structured format, but the medical history, diagnosis and actions taken are recorded in a free text format. In agreement with the on-call physicians and the Danish Medical Association, the computer system was in 2006 modified when a checkbox for ILI was added in the userinterface of the data system. It has a 'mouse-over' function presenting the ILI definition. When the ILI checkbox is marked, the following text with the ILI definition is automatically entered in the unstructured text field: 'Influenza-like illness (ILI): sudden onset of fever, muscle pain, headache and respiratory symptoms'. The cursor is placed after this text, and the physician may enter additional clinical information. With this simple improvement it

became possible to obtain structured data on ILI without interfering with the routines of the physicians. In our definition of ILI all three symptoms must be present in order to increase the specificity of the diagnosis.

On a real-time basis, data are transferred to a common external server. On working days, a surveillance data extract is transferred daily to the national public health institute for infectious diseases (Statens Serum Institut). Data are available before 1 pm. The file uploaded on Monday includes activities from Friday, 4 pm to Monday, 8 am.

The data file contains the following information on each contact: time of contact, ILI (yes/no), age in months, sex, residence of patient (postal code), geographical region of the reporting DMOS physician, type of contact: call, followed by consultation, doctor's visit to the home of the patient, or hospital admission. When a patient contacts the on-call service more than once during one working period, only one record is generated and the information on action taken is the last action taken (e.g. visit to a clinic or admission to hospital). No personal information on individuals is transferred through this system.

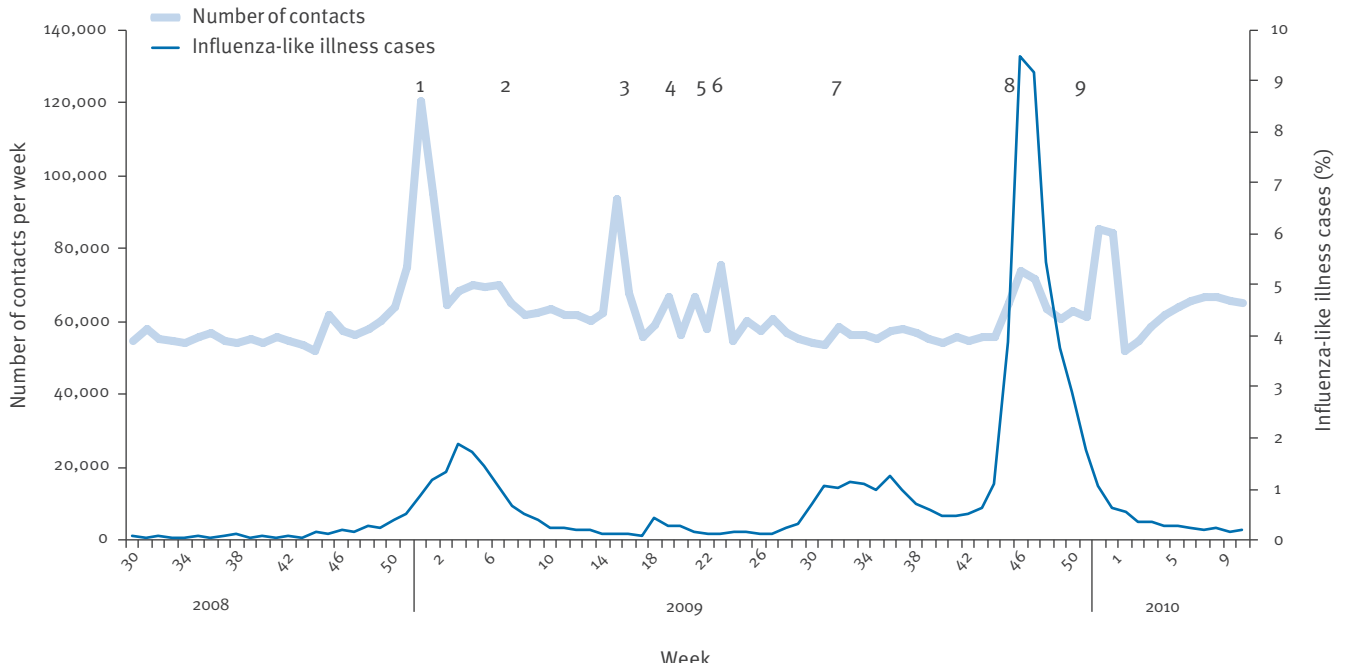
At Statens Serum Institut, data are stored in a SQL database and analysed to obtain the incidence rate of ILI and the proportion of patients with ILI of all patients managed (consultation percentage). The results are analysed by age group and geographical region. During the peak influenza period, a seven-day moving average was presented daily on the website of Statens Serum Institut. Furthermore, a weekly report based on data aggregated over a full week were presented along with data from sentinel surveillance and virological data from the weekly influenza bulletin published every Wednesday on the Statens Serum Institut website. Because the system was recently implemented, we have not yet established a historical baseline and epidemic thresholds for these outcome measures.

The data were compared by visual inspection with national data of laboratory-confirmed influenza A(H1N1)2009 and with data from the sentinel surveillance which during the autumn comprised information from approximately 250 general practitioners. We calculated the number of calls that were followed by referral to a consultation (defined as consultation at a public clinic, doctor's visits to patients' homes, or hospital admission), and compared the proportion of calls that resulted in a consultation between ILI registered during the periods of influenza A(H1N1)2009 transmission and seasonal influenza in the season 2008/09 ('referral rates'). Because patients were younger in the influenza A(H1N1)2009 pandemic than in seasonal influenza, the referral rates were adjusted for age by Poisson regression (age in five-year groups as categorical variables). We used the GENMOD procedure of the SAS statistical software (SAS institute, Cary, NC, United States of America).

We developed an application available on the website of Statens Serum Institut showing the spatial distribution of ILI in Denmark and the timeline of the pandemic [4]. A geographic information system (GIS) was

Figure 1

Contacts to the on-call medical service and influenza-like illness cases, per week, Denmark, 2008-2010



1: Christmas 2008; 2: Seasonal influenza 2008/09; 3: Easter 2009; 4-6: Other public holidays; 7: Summer wave of the influenza A(H1N1)2009 pandemic; 8: Autumn wave of the influenza A(H1N1)2009 pandemic; 9: Christmas 2009.

applied to show the temporal-spatial development of ILI cases as well as the proportion of consultations with ILI diagnosis. Graduated colours of regions were used to show the proportion of consultations based on DMOS location and proportional circles were used to indicate the number of cases per geographic unit (post districts) based on the home address of the patients. The ILI activity monitored by the DMOS was reported to the public on the website of Statens Serum Institut and the Danish public service broadcasting company (Danmarks Radio) on a weekly basis with ILI incidence graphics and maps of ILI incidence in different regions of Denmark. Geographic maps were produced with ArcGIS 9.3, ESRI and the time graphic with Emprise JavaScript ChartsTM, Emprise Corporation.

In this paper, we report data from calendar week 30 of 2008 (starting on 21 July 2008) to week 15 of 2010 (last day included is 18 April 2010). The dataset contained information on about 5.7 million contacts over 91 weeks.

Results

The median weekly number of contacts to the DMOS was 60,029 corresponding to 1,089 contacts per 100,000 population. Peak activities were seen around winter holidays (with a maximum of 120,535 contacts in week 52 of 2008 and 95,080 in week 1 of 2009), Easter (96,586 contacts in week 13 of 2009) and in the Danish public holidays that follow Easter (Figure 1).

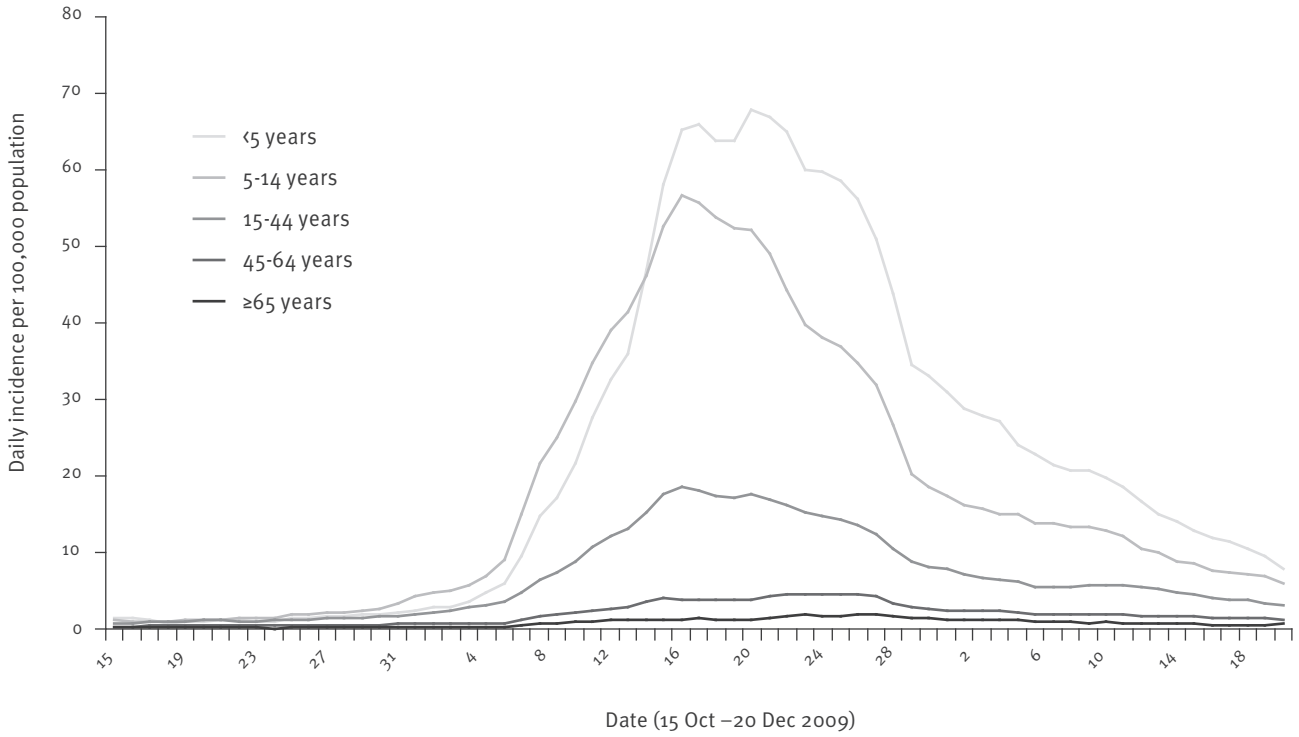
The proportion of cases with ILI ranged from 0.05% in week 30 of 2008 to 9.5% in week 46 of 2009, which coincided with the peak of the autumn wave of the influenza A(H1N1) 2009 pandemic. In the peak week, 6,987 of 73,723 contacts were classified as ILI. Increase in the proportion of ILI cases was additionally seen during periods with seasonal influenza in the beginning of 2009 (maximum 1.9% in week 3, 2009). A peak in ILI activity was also noted in the late summer of 2009 when cases of influenza A (H1N1)2009 were imported to Denmark, but only limited domestic transmission occurred. In this summer wave, a maximum activity of 1.3% was observed in week 36 of 2009.

Figure 2 shows the daily age specific incidence (seven-day moving average) of ILI in the period from 15 October to 20 December 2009. Age specific peaks appeared from 16 to 27 November 2009 (weeks 47 and 48).

In children aged between five and 14 years, the incidence increased from 0.9 per 100,000 population (n=6) on 17 October to a peak of 57 per 100,000 population (n=387) on 16 November 2009. On the same day, there was a peak in the incidence of cases among individuals aged between 15 and 24 years (18 per 100,000 population, n=396). The incidence in children under five years of age peaked on 20 November (68 per 100,000 population, n=222), in adults aged between 25 and 64 years on 24 November (5 per 100,000 population, n= 68), and persons aged 65 years or more on 27 November (2 per 100,000 population, n=17).

Figure 2

Age-specific incidence of influenza-like illness cases per day, medical on-call service, Denmark, 15 October – 20 December 2009



Table

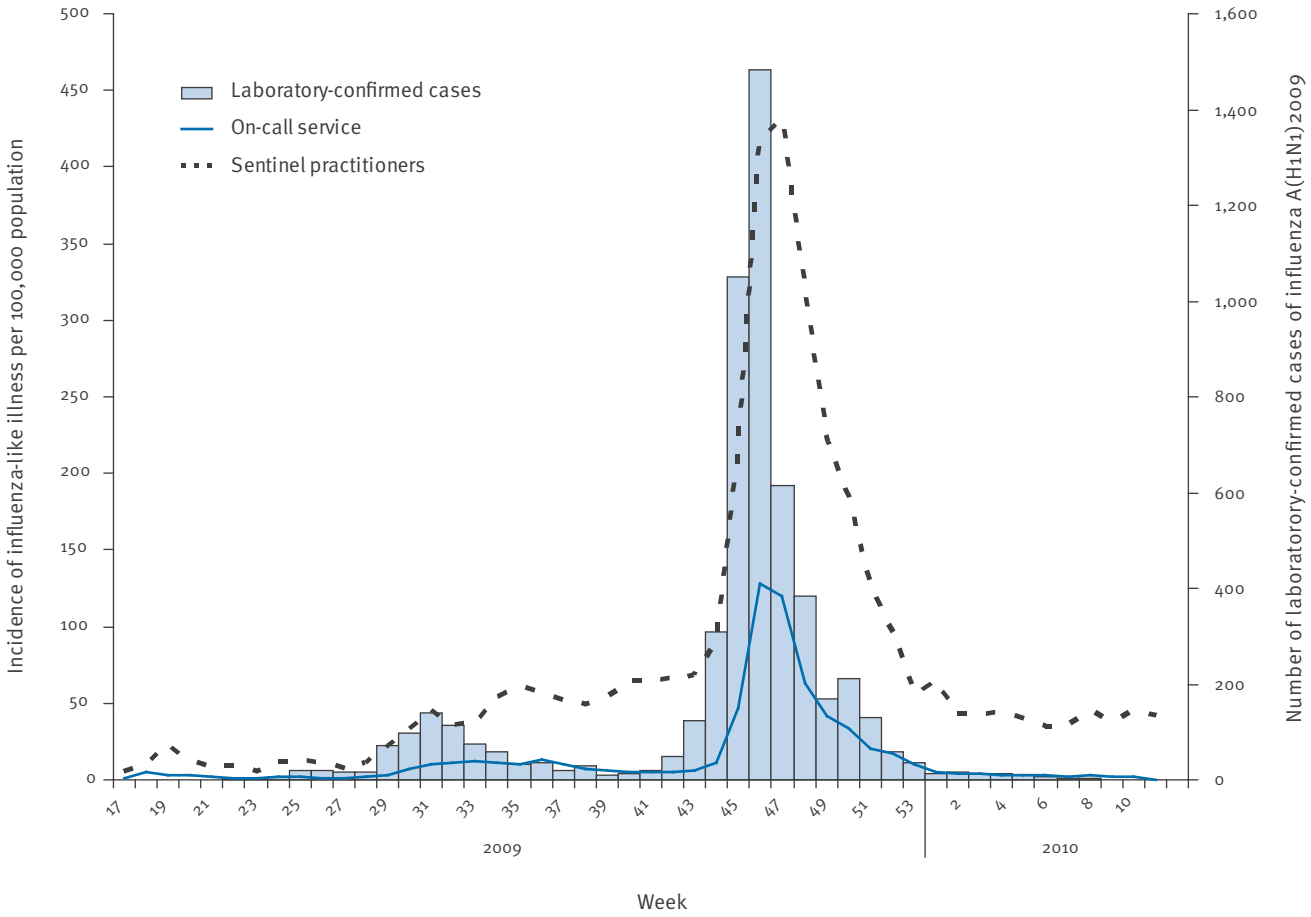
Referral of patients with influenza-like illness to consultation at a clinic or hospital during seasonal influenza 2008/09 and summer and autumn waves of influenza A(H1N1)2009, Denmark, 2008–2010

Period	Patients with influenza-like illness		Relative risk (95% CI) [d]
	Total	Referred to consultation, Number (%)	
Seasonal influenza[a]	9,158	4,321 (47)	1 (reference)
Summer wave [b]	6,094	1,599 (26)	0.57 (0.54 to 0.61)
Autumn wave[c]	29,735	8,390 (28)	0.62 (0.60 to 0.64)

CI: confidence intervals.
[a] 8 December 2008 to 15 March 2009.
[b] 13 July to 11 October 2009.
[c] 12 October 2009 to 18 April 2010.
[d] Adjusted for age by Poisson regression analysis.
Source: Danish medical on-call service.

Figure 3

Weekly incidence of influenza-like illness cases, Denmark, 2009–2010



The left y-axis represents cases recorded by the Danish medical on-call service.
The right y-axis represents the number of laboratory-confirmed infections with influenza A(H1N1)2009 virus.

In order to examine referral rates, the data were analysed according to three time periods determined according to influenza transmission: seasonal influenza (8 December 2008 to 15 March 2009), influenza A (H1N1)2009 summer wave (13 July to 11 October 2009), and autumn wave (from 12 October 2009 to 18 April 2010) (Table).

Referral rates were highest for seasonal influenza (47%), whereas only 26% and 28% were referred for consultation during the two pandemic waves. Patients were younger in the autumn wave of the pandemic than in the seasonal influenza period: median age (interquartile range) was 27 years (11 to 41 years) in the seasonal influenza period, 27 years (15 to 40 years) in the summer peak and 15 (6 to 32 years) in the autumn peak. We therefore adjusted for age by Poisson regression and time period remained independently associated with referral rate (Table).

Figure 3 shows overall incidence of ILI in the sentinel practices (adjusted for number of reporting sentinel practices), incidence of ILI in DMOS as well as the number of laboratory-confirmed cases of influenza A(H1N1)2009 reported to the Department of Virology, Statens Serum Institut.

The incidence of ILI was higher in the sentinel system than in the DMOS. In both systems, marked increases in incidence were observed in week 45 and the peak appeared a week earlier in the DMOS compared with the sentinel surveillance. Thus, the peak incidence in DMOS was in week 46 of 2009 with 128 cases per 100,000 population whereas the peak incidence in the sentinel system was 432 cases per 100,000 population in week 47. The latter estimate was based on 1,864 reports from 288 practices extrapolated to the total of 3,655 general practitioners in Denmark. For comparison, the incidence of laboratory-confirmed cases of influenza A(H1N1)2009 peaked in week 46 with 1,472 cases (27 cases per 100,000 population).

Discussion

During the 2009 pandemic, the DMOS provided valuable real-time and detailed information on ILI-incidence in different age groups and geographical areas. The surveillance data were updated each week. However daily updates were used during the autumn wave of the pandemic, as illustrated in Figure 2. This enabled us to provide timely data to policy makers and health authorities. In particular, they were able to get an overview of the influenza activity during the previous day whereas the sentinel system had more than a week delay. To our knowledge, this is the first year-round, real-time electronic syndromic influenza surveillance system with national coverage that is based on reports provided by physicians. The surveillance system had several advantages among which the automatic data transfer and the daily reporting were the most important. The fact that it was added to an existing administrative system, made it simple to establish and maintain and can therefore be considered as an efficient approach to syndromic surveillance.

Other systems for influenza surveillance, including traditional surveillance for consultation of general practitioners for ILI or acute respiratory infections within their working hours, ambulance dispatches [5,6] and hospital admissions [7,8], may in emergencies or in times of lack of resources become 'saturated'. It is obvious that such systems have limited capacity (for instance, the number of ambulance dispatches will be limited by the number of ambulances and ambulance drivers, and people will find alternative ways to get to hospital during crisis). General practitioners often have a very busy schedule of planned visits and may only have a small number of slots open for acute illnesses. By contrast, the public on-call service is more flexible. There are by definition no planned visits and capacity may be increased by calling in standby medical doctors and adding more telephone lines. This may be one of the reasons that the signal from the on-call service came earlier than in the sentinel surveillance (Figure 1). However, it is also possible that there are differences in the characteristics of the patients (including age) who use the two systems and that this contributes to a later peak in the sentinel system. Importantly, we were able to demonstrate that the peak in the virological surveillance corresponded well with the peak in the DMOS system.

Another possible useful source for influenza surveillance are web queries [9,10]. Web queries have the advantage of being cost-effective and timely and may serve as an early indication of unusual activity. However, since they are based on lay reporting, data are more subjective than the present system which has both the advantage of being very timely and automated while still based on evaluation by medical staff. An interesting development of influenza surveillance is Gripenet and related surveillance schemes consisting of cohorts of volunteers reporting ILI cases on a regular basis on the Internet [11]. Gripenet is a fast and flexible monitoring system whose uniformity allows for direct comparison of ILI rates between countries and is useful for assessing the burden of illness. However, it requires more commitment from administrative staff and participants than does DMOS system and cases are not evaluated by medical staff.

Nevertheless, the DMOS system has its limitations. As opposed to the sentinel system, there are no virological data from the on-call physicians. Therefore, it cannot replace the sentinel system. Furthermore, sentinel doctors are committed to influenza surveillance, whereas the on-call service is staffed by a larger group of physicians with different knowledge and attitude towards influenza surveillance. Although the novel system was promoted in the regions that administer the DMOS, we have no formal evaluation of its use and the completeness of reporting.

The emergence of influenza A(H1N1)2009 outside the normal 2009/10 influenza season, the high morbidity, the high burden of illness in children and young adults, and the occurrence of several waves are all characteristics of a pandemic [12]. The system described here was sufficiently sensitive to be able to detect different peaks for different age groups, and we hope that such detailed data will be of value to obtain more detailed knowledge on the pandemic. As shown in the Table, patients with pandemic influenza were less frequently referred to consultation or admitted to hospital than patients with seasonal influenza in the 2008/09 season. This confirms that in most patients, the clinical presentation in the 2009 pandemic was mild [13-15], but may also reflect that the public may have been concerned with the situation and that the threshold for contacting the healthcare system was lower than in periods with seasonal influenza, with the on-call physicians being the most accessible professionals. From July 2009, the Danish National Board of Health advised the public to use the telephone for getting in contact with the healthcare system and to restrict physical consultations in order to limit the spread of influenza A(H1N1)2009. A relatively low referral rate may reflect that this advice was often followed [16].

In conclusion, we established a simple, yet comprehensive and timely, system that allowed us to follow the incidence and consultation percentage of ILI during the autumn of 2009 when pandemic influenza peaked in Denmark. The system allowed for a detailed situational analysis and was useful for the health authorities' response to the pandemic, including risk communication. We propose that other countries explore the possibility of establishing such a system which may also be of relevance for other public health threats.

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Early spread of the 2009 infuenza A(H1N1) pandemic in the United Kingdom – use of local syndromic data, May–August 2009

S Smith (sue.smith@hpa.org.uk)[1], G E Smith[1], B Olowokure[2], S Ibbotson[1], D Foord[3], H Maguire[4], R Pebody[5], A Charlett[4], J Hippisley-Cox[6], A J Elliot[1]

1. Real-time Syndromic Surveillance Team, Health Protection Agency, Birmingham, United Kingdom
2. West Midlands Regional Epidemiology Unit, Health Protection Agency, Birmingham, United Kingdom
3. NHS Direct, Linford Wood East, Milton Keynes, United Kingdom
4. Health Protection Agency London, Regional Epidemiology Unit, London, United Kingdom
5. Health Protection Agency, Centre for Infections, London, United Kingdom
6. Division of Primary Care, School of Community Health Sciences, University of Nottingham, Nottingham, United Kingdom

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Following the confirmation of the first two cases of pandemic influenza on 27 April 2009 in the United Kingdom (UK), syndromic surveillance data from the Health Protection Agency (HPA)/QSurveillance and HPA/NHS Direct systems were used to monitor the possible spread of pandemic influenza at local level during the first phase of the outbreak. During the early weeks, syndromic indicators sensitive to influenza activity monitored through the two schemes remained low and the majority of cases were travel-related. The first evidence of community spread was seen in the West Midlands region following a school-based outbreak in central Birmingham. During the first phase several Primary Care Trusts had periods of exceptional influenza activity two to three weeks ahead of the rest of the region. Community transmission in London began slightly later than in the West Midlands but the rates of influenza-like illness recorded by general practitioners (GPs) were ultimately higher. Influenza activity in the West Midlands and London regions peaked a week before the remainder of the UK. Data from the HPA/NHS Direct and HPA/QSurveillance systems were mapped at local level and used alongside laboratory data and local intelligence to assist in the identification of hotspots, to direct limited public health resources and to monitor the progression of the outbreak. This work has demonstrated the utility of local syndromic surveillance data in the detection of increased transmission and in the epidemiological investigation of the pandemic and has prompted future spatio-temporal work.

Introduction

The first two cases of pandemic influenza in the United Kingdom (UK) were confirmed in Scotland on 27 April 2009 [1]. Initially UK policy was to contain the spread of the virus and during the early stages the main focus of surveillance was on virologically confirmed cases. This containment policy continued until 2 July when the Government announced that due to further spread of the disease the UK was moving to a treatment (mitigation) phase [2]. A key factor in this decision was the presence of sustained community transmission. Data from a range of national surveillance systems, including syndromic surveillance data, were used during the pandemic to assess when the change from sporadic cases to more widespread community transmission occurred.

Syndromic surveillance systems monitor generic symptoms and/or clinically diagnosed disease in order to provide timely information at an earlier stage of illness (compared to laboratory-confirmed diagnosis) [3]. Data are captured electronically, often using information collected for other purposes, to create large datasets that can be analysed rapidly, some systems being able to provide daily data. Some systems are well established, for example the Royal College of General Practitioners Weekly Returns Service has many years of historical data that can be used to monitor longer-term disease trends [4,5]. Syndromic surveillance can provide early warning of, for example, seasonal rises in influenza and norovirus infections and can trigger appropriate public health action but can also be used to alert to unexpected events such as an unusual rise in illness that could indicate an outbreak [6,7].

This paper describes the early spread of influenza-like illness (ILI) at Primary Care Trust (PCT) level during the first phase of the 2009 influenza pandemic using data from national syndromic surveillance systems, with a particular focus on West Midlands and London, the areas initially most affected, in order to identify the point when sustained community transmission began.

Methods

HPA/NHS Direct surveillance system

NHS Direct is a 24-hour nurse-led telephone helpline that provides health information and advice to the general public [8]. To handle the calls, nurses use a computerised clinical decision support system that uses symptom-based clinical algorithms. Nurses assign the call to the most appropriate algorithm and the patient's symptoms determine the questions asked and the action to be taken following the call, which could be guidance on self-care or referral to their general practitioner (GP) or advice to attend a hospital emergency department. Anonymised data on the number of calls for key algorithms are sent to the Health Protection Agency (HPA) Real-time Syndromic Surveillance Team every day for surveillance purposes. As the number of daily calls to NHS Direct varies, indicators are expressed as the percentage of calls for that algorithm using all NHS Direct calls as the denominator. The algorithms for cold/flu, cough, fever, and difficulty breathing were monitored during the 2009 influenza pandemic on a daily basis. Due to the increasing number of calls received by NHS Direct an additional 'swine flu' algorithm was introduced, which was included in the cold/flu calls in order to capture all pandemic related calls.

Call data for cold/flu were mapped by postcode district in the West Midlands region, following an outbreak of pandemic influenza A(H1N1)2009 in a primary school [9], and also in London following an increase in the number of cases in early June.

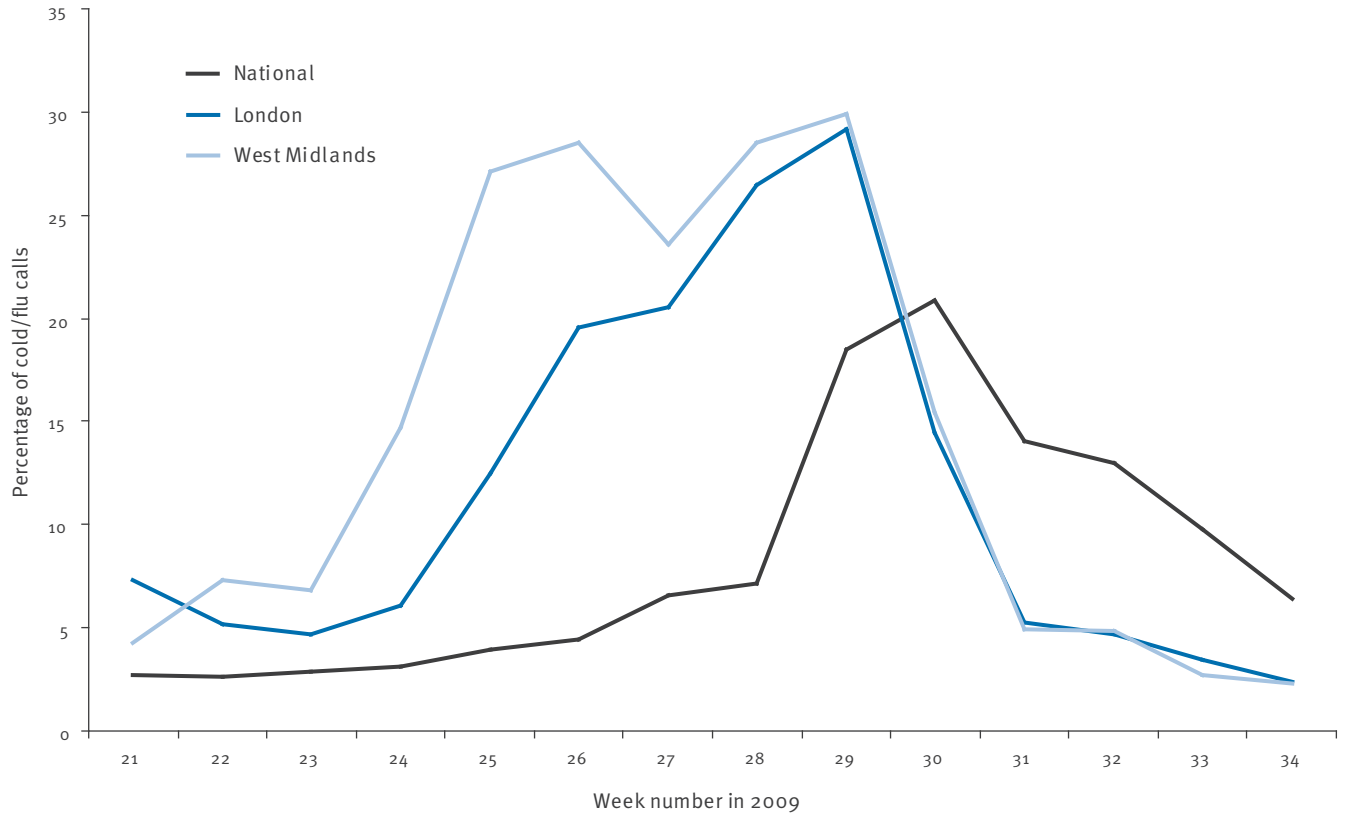
HPA/QSurveillance system

The HPA/QSurveillance system was set up by the University of Nottingham and Egton Medical Information Systems (EMIS; a supplier of general practice computer systems) in collaboration with the HPA [10,11]. Over 3,400 general practices with over 23 million patients submit data to the QSurveillance database, covering about 38% of the UK population. Aggregated data on GP consultations for a range of indicators are automatically uploaded daily from GP practice systems to a central database. Consultation data are based on clinical diagnoses that are recorded as codes on the practice system. Indicators, for example ILI, are defined as collections of clinical diagnosis codes. The surveillance system usually produces weekly reports, but daily reports were also provided throughout the pandemic period. Data are available at national, regional and PCT level.

Daily data for ILI, pneumonia, upper respiratory tract infection (URTI), lower respiratory tract infection (LRTI), ILI with antiviral drugs prescribed, and pneumonia with antibiotics prescribed were monitored during the pandemic. Daily ILI data were mapped by PCT, initially only for the West Midlands and London regions, and later also for other regions when the local ILI rates increased. Weekly mapping at PCT level was later extended to all PCTs in England and continued through the second pandemic wave during the winter of 2009/10.

Figure 1

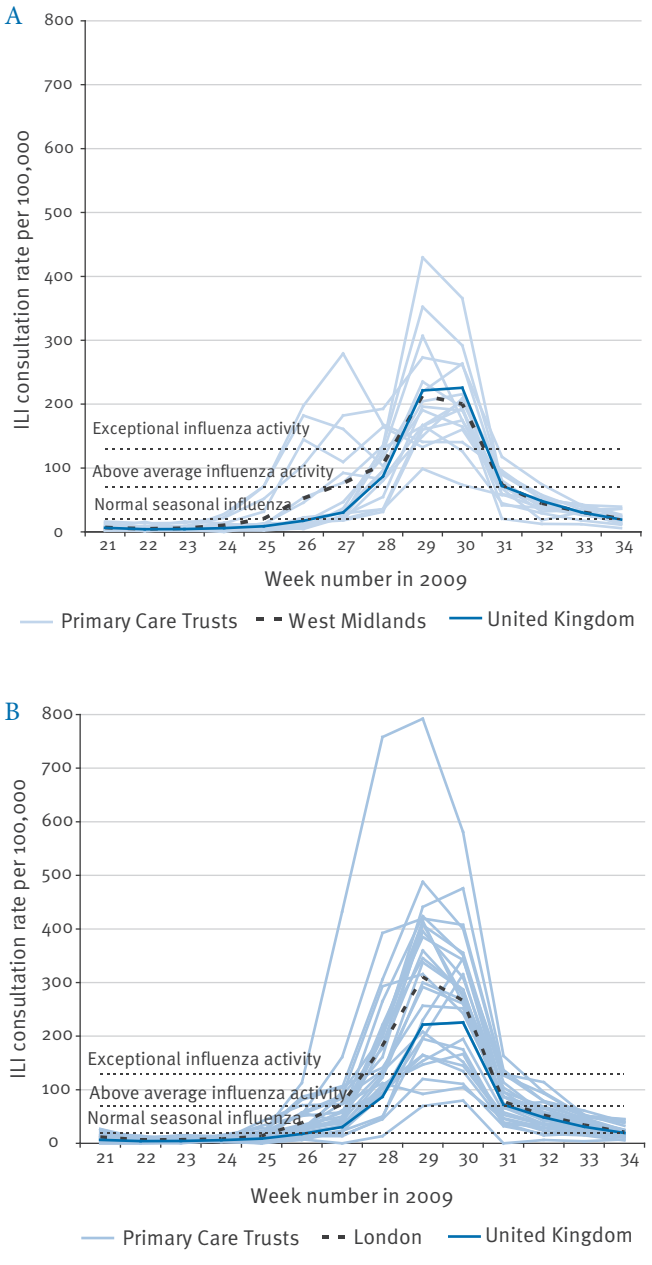
NHS Direct cold/flu calls for West Midlands and London, summer 2009



The ILI indicator is a group of clinical diagnosis codes recorded by GPs during routine consultations and is widely used as a proxy for community-based influenza activity [12,13]. In order to compare ILI rates with the seasonal influenza activity experienced in a normal winter season estimated thresholds for daily and weekly HPA/QSurveillance data were developed and used to interpret ILI data included in surveillance bulletins and PCT maps [11]. All maps were drawn using MapInfo Professional version 9.5. In this paper data are presented from week 21 in 2009 (week commencing 18 May), when the first school outbreak occurred in Birmingham, to week 34 in 2009 (week commencing 17 August), when UK ILI rates returned to baseline activity, to demonstrate the progression of the first wave of the influenza pandemic in the UK. This period coincides with the treatment only phase of the outbreak that began on 2 July (in week 27, the week commencing 29 June).

Figure 2

HPA/QSurveillance general prctitioner consultation rate for influenza-like illness in Primary Care Trusts in the West Midlands (A) and London (B), summer 2009



HPA: Health Protection Agency; ILI: influenza-like illness.

▪▪▪▪▪▪▪ Indicative estimated thresholds for QSurveillance weekly influenza-like illness data in the United Kingdom

HPA/QSurveillance system influenza-like illness thresholds [11]: baseline influenza activity: below 20 per 100,000; normal influenza activity: 20-70 per 100,000; above average influenza activity: 70-130 per 100,000; exceptional influenza activity: ≥130 per 100,000

The HPA routinely analyse and monitor syndromic data throughout the year. From the start of the pandemic the HPA Real-time Syndromic Surveillance Team used daily outputs from the HPA/NHS Direct and HPA/QSurveillance systems to monitor a range of indicators that might suggest wider community transmission of pandemic influenza A(H1N1)2009, and were also used, along with laboratory data and local intelligence, to help identify hotspots, areas of particularly high influenza activity and of rapid increase in influenza rates. Data at national, regional (Strategic Health Authority), local health district (PCT), and postcode district level were included in daily bulletins distributed to the HPA, the Department of Health, the National Health Service (NHS) and the Government.

Results

The first suggestion of community spread was seen in the West Midlands region following an outbreak in a primary school in the Heart of Birmingham PCT where the first case of pandemic influenza A(H1N1)2009 was confirmed during week 21, 2009 [9]. The cold/flu call data from the HPA/NHS Direct system and the PCT level data from the HPA/QSurveillance system showed two distinct peaks of pandemic influenza activity in the West Midlands (Figures 1 and 2). NHS Direct cold/flu calls for the West Midlands showed an early rise in calls that peaked in week 26 (week commencing 22 June). There was a second peak in both systems in week 29 (week commencing 13 July). These peaks were respectively four weeks and one week ahead of the national peak in week 30 (week commencing 20 July). In the HPA/QSurveillance system, GP consultation rates for ILI showed that the early increase was accounted for by four PCTs: Heart of Birmingham, where the initial school outbreak occurred, and the three surrounding PCTs, Birmingham East and North, Sandwell, and South Birmingham. By week 26, all four had reached exceptional levels of influenza activity (above 130 consultations per 100,000) except South Birmingham which reached this level in week 27.

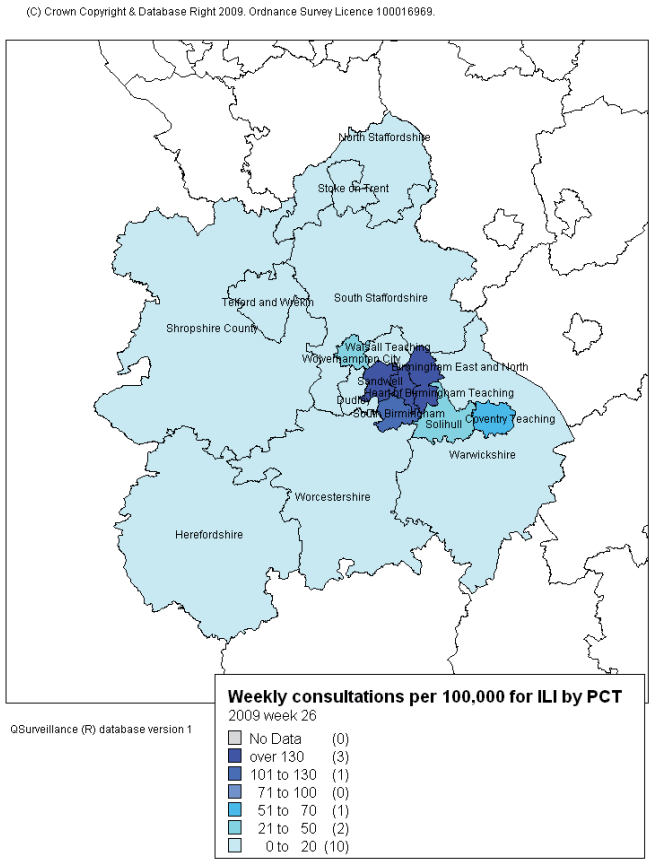
Community transmission in London started slightly later and showed a different pattern, with HPA/NHS Direct and HPA/QSurveillance systems both showing a single peak in week 29, the same week as the West Midlands peak, one week ahead of the national peak (Figures 1 and 2). HPA/QSurveillance ILI rates reached exceptional levels in the Tower Hamlets PCT and the City and Hackney PCT in week 27, and the majority of

Figure 3

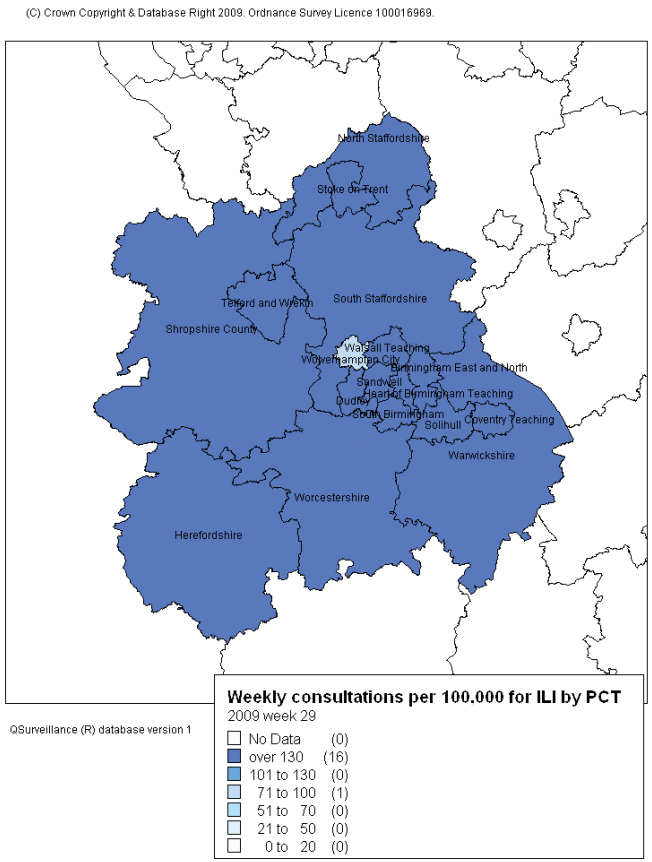
Weekly HPA/QSurveillance consultation rates for influenza-like illness by PCT and cold/flu calls to the HPA/NHS Direct Syndromic Surveillance System by postcode district for West Midlands and London, summer 2009

West Midlands, QSurveillance

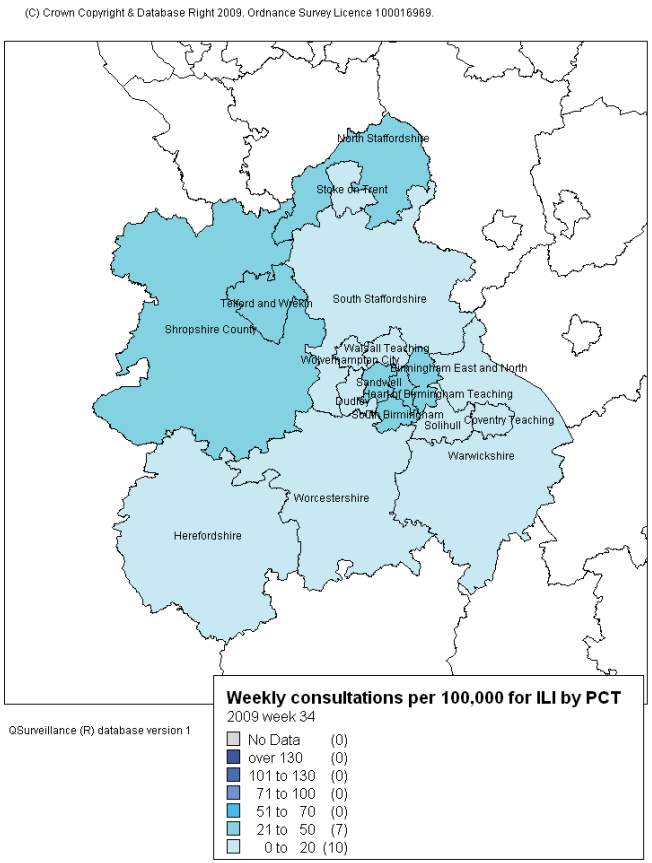
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)

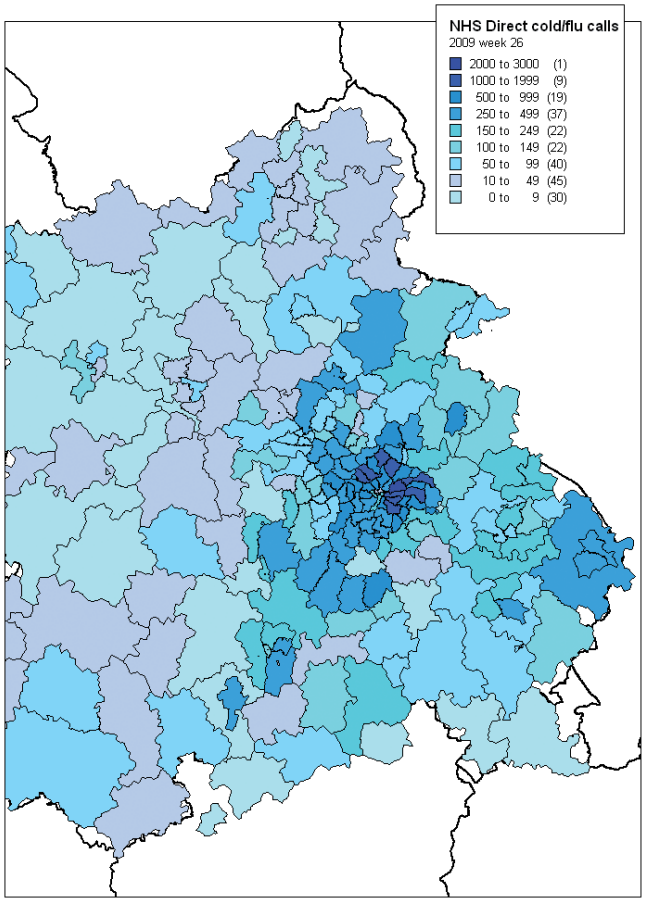


Week 34 (17-23-August 2009)

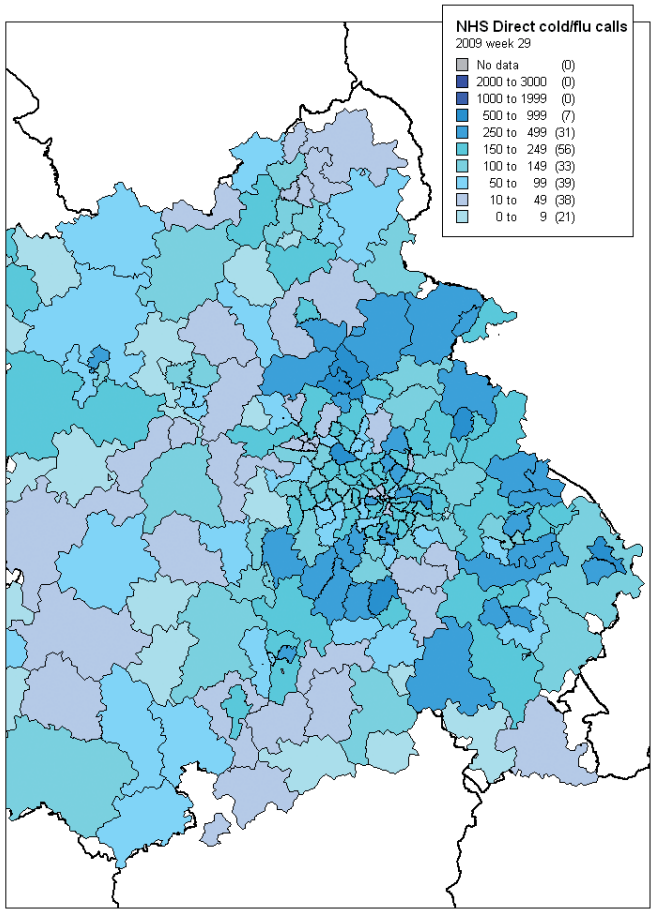


West Midlands, NHS Direct

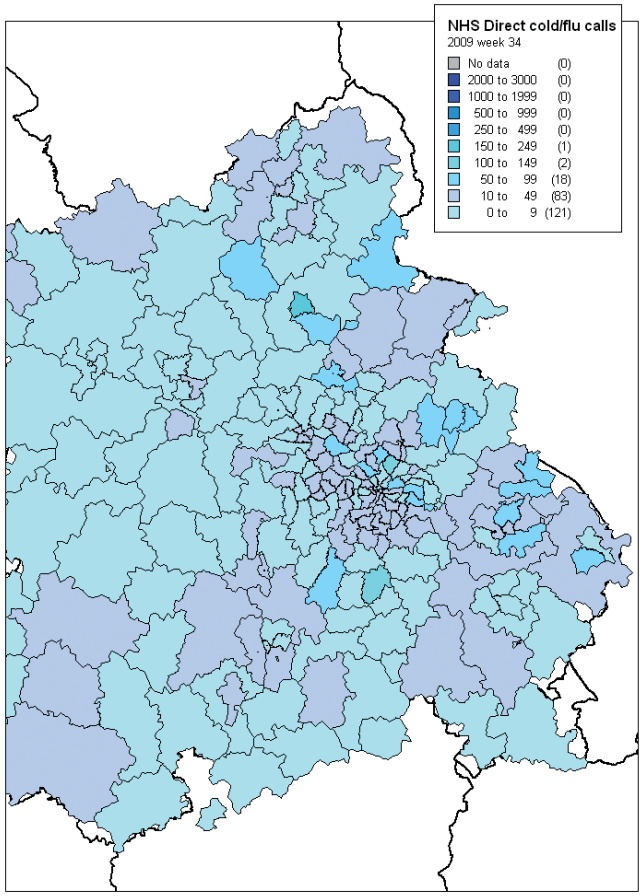
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)

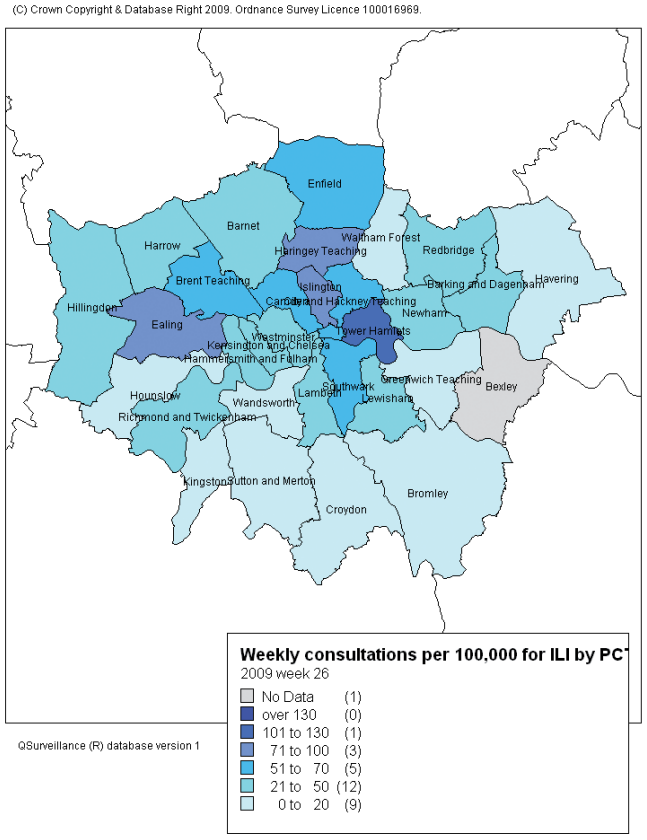


Week 34 (17-23-August 2009)

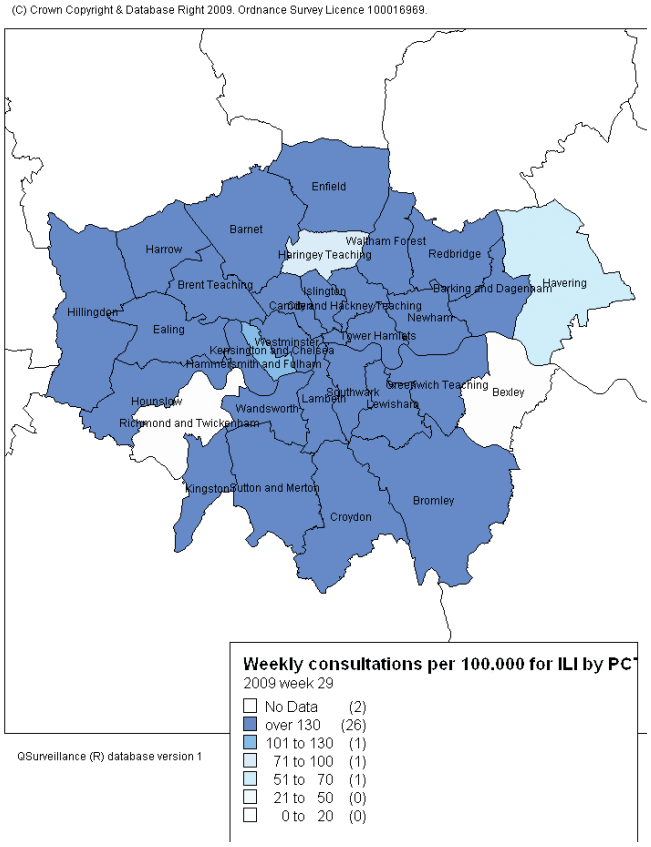


London, QSurveillance

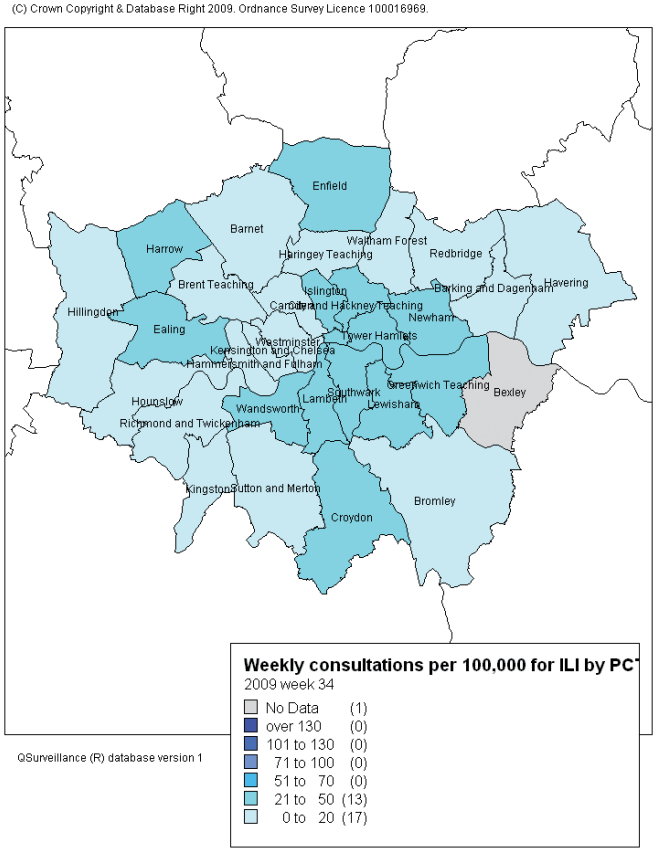
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)

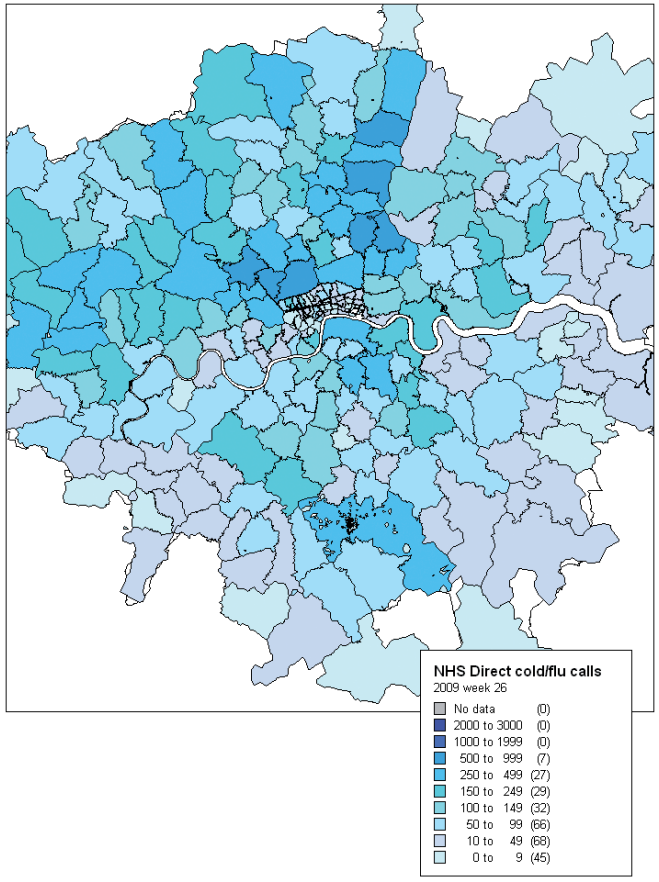


Week 34 (17-23-August 2009)

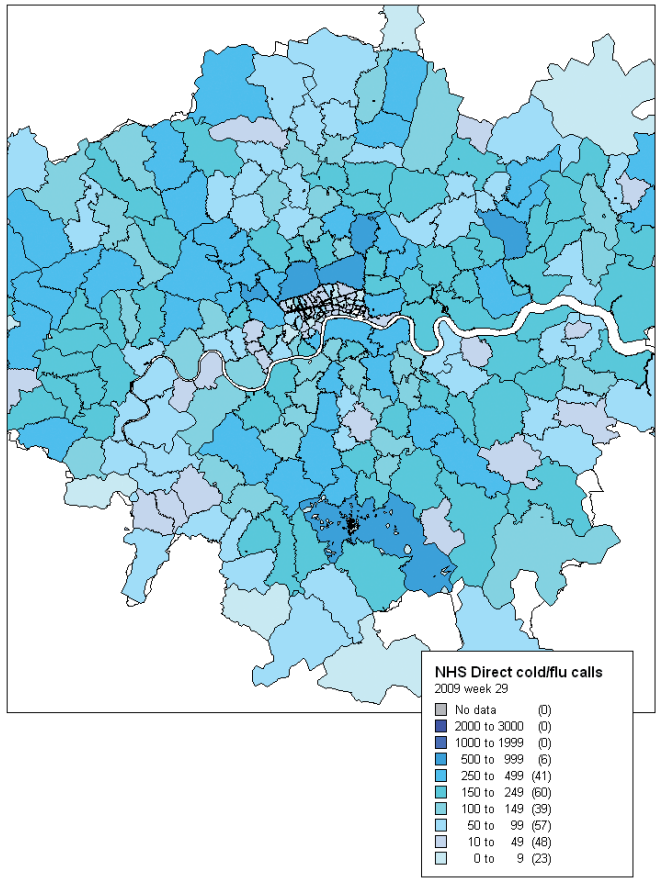


London, NHS Direct

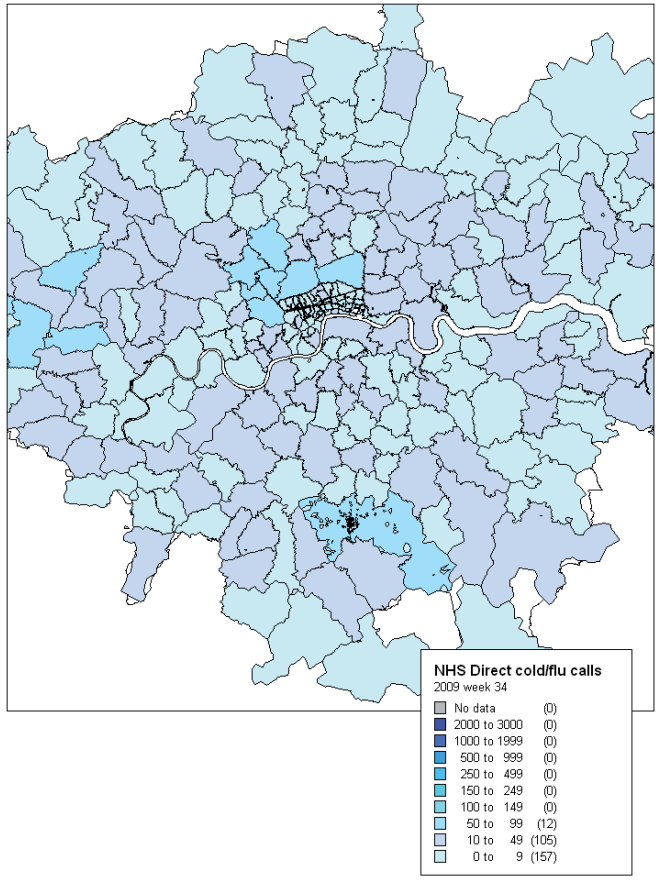
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)



Week 34 (17-23-August 2009)



HPA: Health Protection Agency; PCT: Primary Care Trust.

HPA/QSurveillance system influenza-like illness thresholds [11]: baseline influenza activity: below 20 per 100,000; normal influenza activity: 20-70 per 100,000; above average influenza activity: 70-130 per 100,000; exceptional influenza activity: ≥130 per 100,000.

London PCTs simultaneously peaked in week 29. The peak ILI rates in London were generally higher than those seen in the West Midlands, with the highest ILI rates recorded in the Tower Hamlets PCT (792.4 per 100,000 in week 29).

HPA/NHS Direct cold/flu calls were mapped by postcode and HPA/QSurveillance ILI data were mapped by PCT to monitor the geographical spread of the outbreak, in order to assist in the identification of hotspot areas and in the outbreak management, and in directing public health resources (Figure 3). On 19 June 2009 sustained community transmission was declared in the PCTs Birmingham East and North, Heart of Birmingham, South Birmingham, and Sandwell due to high numbers of confirmed cases that were predominantly not travel-related [11], school absenteeism, high GP consultation rates (HPA/QSurveillance system) and high numbers of calls to NHS Direct.

Discussion

We used syndromic surveillance systems to track the progress of pandemic influenza A(H1N1)2009 in the UK on a daily basis and were able to show the early stages of community transmission at a local level in the West Midlands and London. These systems were key in defining the start of community transmission. The first evidence of sustained community transmission was seen in the West Midlands. Influenza activity in the West Midlands and London peaked a week ahead of the rest of the UK. Although this hasn't been formally analysed, we can say empirically that there was considerable agreement between data from the HPA/NHS Direct and HPA/QSurveillance systems, however NHS Direct call data showed an increase a week earlier than the GP consultation data in the HPA/QSurveillance system, confirming the usefulness of NHS Direct as an early warning of outbreaks [6].

HPA/NHS Direct call data were mapped at postcode level and HPA/QSurveillance data were mapped at PCT level. Such maps were used by those managing the incident at national, regional and local levels. Syndromic surveillance data from both systems, along with laboratory data and local intelligence, helped identify hotspots in the early stages of community transmission, and monitor the progress of the outbreak at local level. The data were included in surveillance bulletins and thus influenced the local management of the pandemic.

Limitations of the data

Although the HPA/QSurveillance system has good coverage in England, there are variations in coverage at local level. The QSurveillance database only collects data from GP practices that use the EMIS practice information system; the coverage at PCT level can therefore vary depending on the number of practices that use that system. Data at PCT level are suppressed if fewer than three practices report to the system in order to preserve the anonymity of patients and practices; data were unavailable for one PCT in London for this reason.

It has been shown that older people and ethnic minorities are less likely to use NHS Direct [14]. While this does not substantially affect the usefulness of regional and national data, this would be important at postcode level and could potentially be a cause of under-reporting for example in a district with a high ethnic minority population. In the context of our study, age was considered a less important limitation because pandemic influenza A(H1N1)2009 predominately affected younger age groups [15].

The peak of the first wave of the pandemic in the UK in week 30 coincided with the launch of the National Pandemic Flu Service on 23 July 2009, which was established to authorise antiviral drugs for patients who met the clinical criteria for pandemic influenza A(H1N1)2009 and thereby remove the pressure from GP practices and NHS Direct. It is likely that this explains at least partly the observed reduction in GP consultation rates for ILI and NHS Direct cold/flu calls in week 31 in 2009 [11]. The highest rates of pandemic influenza A(H1N1)2009 were seen in school-aged children. During week 30 in 2009 schools closed for the summer holidays, which would have interrupted transmission in that age group and contributed to decreased consultation rates in week 31 of 2009 [16,17].

Conclusion

This work has demonstrated the usefulness of local mapping of syndromic surveillance data for the detection of increasing transmission and for the epidemiological description of the pandemic. We detected early rises of pandemic influenza A(H1N1)2009 in the West Midlands and London using these systems. It has prompted further spatio-temporal work to describe in more detail the determinants of the initial spread.

Acknowledgements

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Two waves of pandemic influenza A(H1N1)2009 in Wales – the possible impact of media coverage on consultation rates, April – December 2009

M Keramarou (maria.keramarou@wales.nhs.uk)[1,2], S Cottrell[1], M R Evans[1,3], C Moore[4], R E Stiff[1], C Elliott[1], D R Thomas[1], M Lyons[5], R L Salmon[1]

1. Communicable Disease Surveillance Centre, Public Health Wales, Cardiff, United Kingdom
2. European Programme on Intervention Epidemiology Training (EPIET)
3. Department of Primary Care and Public Health, Cardiff University, United Kingdom
4. Public Health Wales Microbiology, Cardiff, United Kingdom
5. Health Protection Services, Public Health Wales, Cardiff, United Kingdom

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In the United Kingdom, the influenza A(H1N1)2009 pandemic had a distinct two-wave pattern of general practice consultations for influenza-like illness (ILI). We describe the epidemiology of the influenza pandemic in Wales between April and December 2009 using integrated data from a number of independent sources: GP surveillance, community virology surveillance, hospital admissions and deaths, and media enquiries monitoring. The first wave peaked in late July at 100 consultations per 100,000 general practice population and attracted intensive media coverage. The positivity rate for the A(H1N1)2009 influenza did not exceed 25% and only 44 hospitalisations and one death were recorded. By contrast, the second wave peaked in late October and although characterised by lower ILI consultation rates (65 consultations per 100,000 general practice population) and low profile media activity, was associated with much higher positivity rates for pandemic influenza A(H1N1)2009 (60%) and substantially more hospital admissions (n=379) and deaths (n=26). The large number of ILI-related consultations during the first wave in Wales probably reflected the intensive media activity rather than influenza virus circulating in the community. Data from community surveillance schemes may therefore have considerably overestimated the true incidence of influenza. This has implications for the future interpretation of ILI surveillance data and their use in policy making, and underlines the importance of using integrated epidemiological, virological and hospital surveillance data to monitor influenza activity.

Introduction

The media are major sources of health information. They can generate awareness of health issues and play key roles in health behaviour change [1]. Studies suggest that media reports are the main source of most parents' information about health problems [2]. The media can also influence the behaviour of healthcare professionals, for example by increasing awareness and reporting of communicable diseases especially during outbreaks [3,4].

In mid-April 2009, a new strain of influenza A(H1N1) was identified in the United States (US). The same strain was identified in Mexico and Canada and later elsewhere. By late April the virus, then named novel influenza A/H1N1, had spread worldwide [5]. Within Europe, the United Kingdom (UK) and Spain were the countries initially most affected [6]. On 11 June 2009, after confirming community transmission of influenza A(H1N1)2009 virus in two of its regions, the World Health Organization (WHO) declared an influenza pandemic [7].

On 29 May 2009, the first confirmed case of influenza A(H1N1)2009 was diagnosed in Wales (a man returning from the US with a respiratory illness). In response, measures were taken in Wales to strengthen case finding and reporting of influenza-like illness (ILI) among travellers returning from affected areas [8]. All suspected cases were tested for the virus by specific real-time reverse transcription – polymerase chain reaction (RT-PCR) and confirmed by sequence analysis. All household contacts were given antiviral prophylaxis, oseltamivir, as part of an initial containment strategy.

On 6 July 2009, the Welsh Assembly Government announced a move from containment to mitigation after community transmission of influenza A(H1N1)2009 had been confirmed in several parts of Wales [9]. Active case finding and routine diagnostic testing for influenza were discontinued and tracing and prophylaxis of contacts ceased. All patients who were diagnosed clinically with influenza A(H1N1)2009 by a GP were given antiviral treatment and diagnostic laboratory testing was confined to suspected influenza cases admitted to hospital or presenting to a network of sentinel general

practices. Thereafter, influenza activity in the general population was monitored using a variety of community surveillance systems.

In England, the National Pandemic Flu Service (NPFS) was introduced in mid-July 2009 in order to relieve pressure on primary care services [10]. Patients with influenza symptoms were advised not to consult their general practitioner (GP), but to contact the NPFS either online or by telephone in order to obtain antiviral drugs. This meant that GP surveillance data no longer provided a reliable indicator of influenza activity in England. However, in Wales, no change was made to usual arrangements for clinical influenza diagnosis and antiviral prescribing by GPs.

We investigated the impact of media coverage of the influenza pandemic in Wales between April and December 2009 on surveillance systems using integrated data from a number of independent sources.

Methods

We examined data on ILI consultation rates generated by NHS Direct Wales, two independent GP surveillance systems (GP sentinel surveillance of infection and rapid automated GP surveillance) in conjunction with laboratory data (community virology surveillance), hospital admissions and deaths in order to define the epidemic period of influenza and the distribution of other circulating viruses. We also analysed media interest in influenza A(H1N1)2009 over the same time period. The data sources used are detailed below.

NHS Direct Wales

This is a nurse-led telephone helpline that provides health information and advice to callers. Anyone may call the helpline at any time and symptoms are classified based on a series of clinical algorithms. Call data can be used for syndromic surveillance and symptoms that correspond to the influenza/colds algorithm provide the basis for real-time, daily monitoring of ILI in the community [11].

GP sentinel surveillance of infection

Influenza activity is reported to Public Health Wales according to the GPs' clinical diagnosis of the patients' ILI symptoms (upper respiratory tract symptoms, fever, chills, myalgia and cough). The resulting data is reported on a weekly basis by 44 volunteer, sentinel general practices, approximately 9% of practices in Wales, covering some 356,000 people. Weekly clinical consultation rates are calculated per 100,000 general practice population by age group. The scheme has operated since 1985 with no change in case definition or reporting procedure, thus allowing historical comparisons to be made.

Laboratory-based surveillance

Virological surveillance was carried out to monitor the circulation of seasonal respiratory viruses. A volunteer subset of sentinel practices collected dry nasal/ throat swab samples from the first patients presenting with ILI symptoms each week (maximum five samples per week). These specimens were sent to the regional virus laboratory and tested for influenza A, influenza B, respiratory syncytial virus (RSV) and rhinovirus using real-time molecular techniques. All influenza A positive samples were subtyped as A(H1N1)2009 or seasonal H1 or H3 viruses using real-time RT-PCR.

Rapid automated GP surveillance

Around 400 general practices across Wales (approximately 80% of practices in Wales) report clinical diagnoses of ILI, classified according to Read codes [12], on a daily basis using an automated computer system called Audit+ (Informatica Systems Ltd [13]. We used these data to calculate ILI consultation rates per 100,000 general practice population. Rates were calculated as rolling weekly rates based on the seven day period leading up to and including the report submission date. This scheme started in late April 2009 specifically to monitor the influenza pandemic in Wales.

Hospital admissions and deaths

All acute hospitals were asked to report admissions and deaths in hospital of people with laboratory-confirmed influenza A(H1N1)2009. GPs were asked to report any deaths from suspected influenza occurring outside hospital and post-mortem testing was carried out to confirm the diagnosis.

Media coverage of pandemic influenza

Google News captures articles from printed press, television, radio and internet sources. The keyword 'swine flu' was used to search Google News for media references between 1 January and 30 December 2009. Searches were conducted on a worldwide, UK, and Wales basis. A record of influenza-related media enquiries received by Public Health Wales was also maintained throughout the pandemic. These include only a fraction of media coverage of the influenza A(H1N1)2009 pandemic in Wales, but they tend to reflect levels of media coverage nationally.

Results

Surveillance of ILI-related calls to NHS Direct Wales

NHS Direct in Wales recorded a small peak in the percentage of calls related to influenza in early May 2009 about 25% of total calls), followed by a rapid rise to a peak of more than 50% of calls by mid-July. A second peak occurred in mid-October 2009 (30% of calls). This level of influenza calls to NHS Direct Wales was higher than at any time during the previous four years (January 2006-December 2009), superseding the peak in December 2008 (28% of calls).

Surveillance of ILI consultations by the GP schemes

The GP sentinel surveillance scheme detected an increase in ILI consultations that exceeded the threshold for normal seasonal activity by mid-July 2009

(week 29) (Figure 1). The first wave of ILI lasted from weeks 27 to 34 and reached a peak of nearly 100 consultations per 100,000 general practice population at the end of July (weeks 30–31). This was followed by a period of quiescence during August before the development of a second wave of ILI in the autumn, which started in early September (week 38), peaked in late October (week 42) and receded at the end of December (week 52). The second wave was more prolonged than the first, with a lower peak in consultation rate of 65 consultations per 100,000 general practice population. Neither of the waves exceeded an ILI rate of 100 consultations per 100,000 general practice population, the threshold used by the scheme for higher than average seasonal activity. During both waves, rates were recorded well below those in winter 1999/2000, the last winter season when substantial influenza activity occurred in Wales.

ILI consultation rates by sex were similar for both waves with females accounting for 58% of consultations in the first wave and 56% in the second. The mean age for ILI consultations was 32.1 years (standard deviation 19.9 years) and 75% of consultations were in people under 45 years of age. There was a difference in the age distribution of patients consulting with ILI during the two waves (Figure 2). In the first wave, consultation rates were highest in children aged 0-4 years and lowest in the 5-19 age group, while in the second wave rates were highest in the 10-14 age group.

Virological surveillance of GP sentinel samples

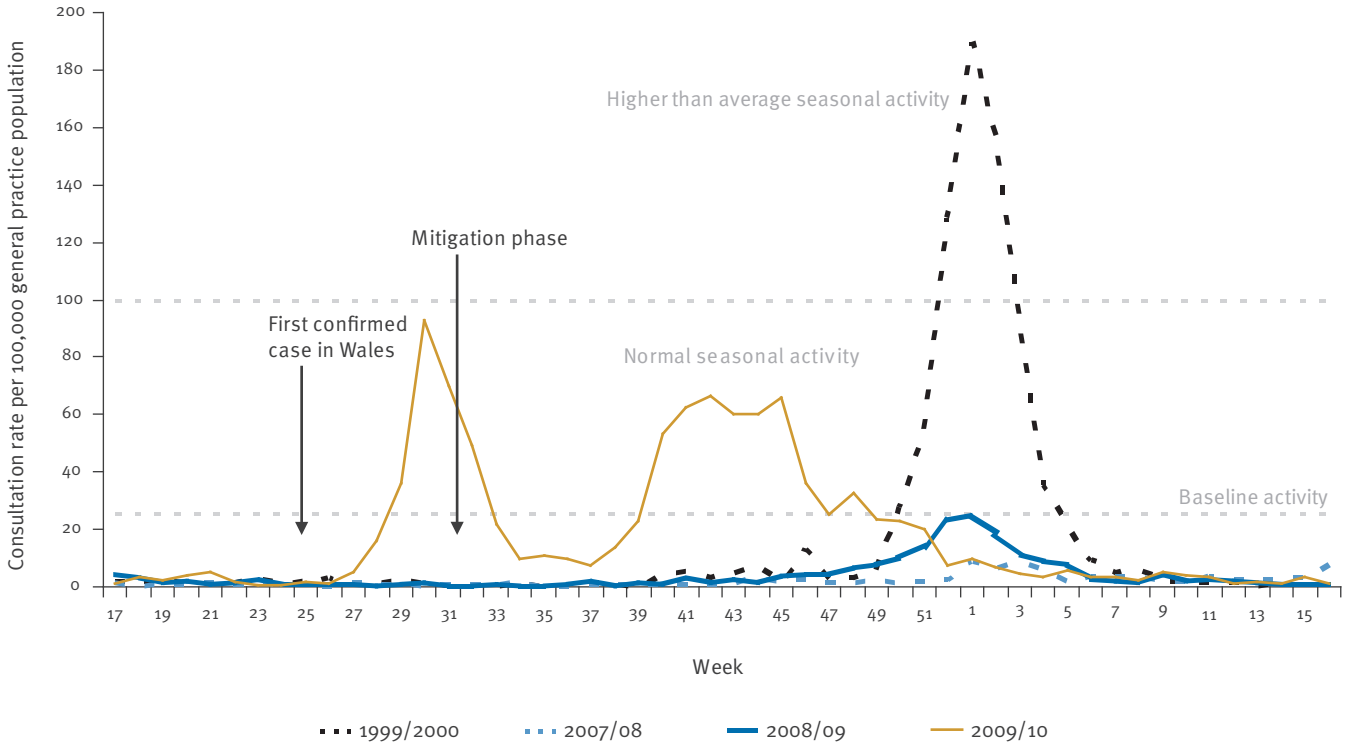
The two waves of ILI activity also differed with respect to a number of other epidemiological characteristics. Both the number of people being tested and the proportion testing positive for influenza A(H1N1)2009 were much higher during the second wave than the first (Figure 3). The proportion testing positive remained below 25% during the first wave, but reached almost 60% at the peak of the second wave (week 43). Neither of the two waves was associated with substantial numbers of positive tests for other respiratory viruses, and the influenza A(H1N1)2009 virus was the only influenza strain identified. During the first wave, samples were as likely to test positive for rhinovirus as influenza A(H1N1)2009. However, from early October (week 40) the majority of positive tests were for influenza A(H1N1)2009, until late November (week 48) when RSV became the dominant virus identified (Figure 3).

Surveillance of hospitalisations and deaths

During the first wave, there were 44 hospital admissions and one patient died from confirmed influenza A(H1N1)2009. By contrast, the second wave resulted in substantially more hospital admissions (n=379), despite lower ILI consultation rates in GP, including

Figure 1

Weekly consultation rates for influenza-like illness per 100,000 general practice population in Wales, United Kingdom, 1999/2000 and 2007/08-2009/10[a]



[a] Key events in 2009/10 are shown on the graph.

Source: Public Health Wales (general practitioner sentinel surveillance scheme).

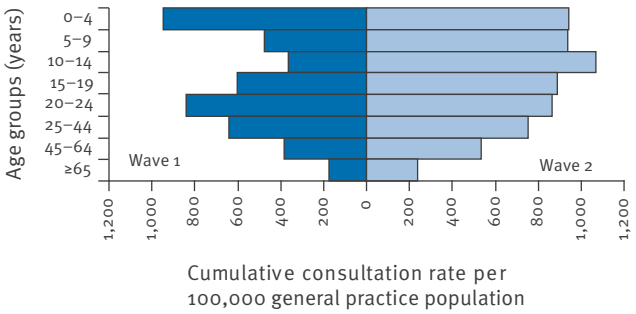
over 60 admissions to intensive care units and 26 deaths (Figure 4).

Surveillance of media reports and enquires

The Google News search for news articles showed that the highest concentration of media reports on pandemic influenza occurred during May 2009 with 34,300 reports internationally and 2,560 in the UK. The second highest month for articles in the UK was July 2009 with 2,330 reports.

Figure 2

Consultation rates by age group during the first and the second pandemic influenza A(H1N1)2009 wave, Wales, United Kingdom, weeks 27–52, 2009



Source: Public Health Wales (Rapid general practitioner surveillance of influenza using Audit+).

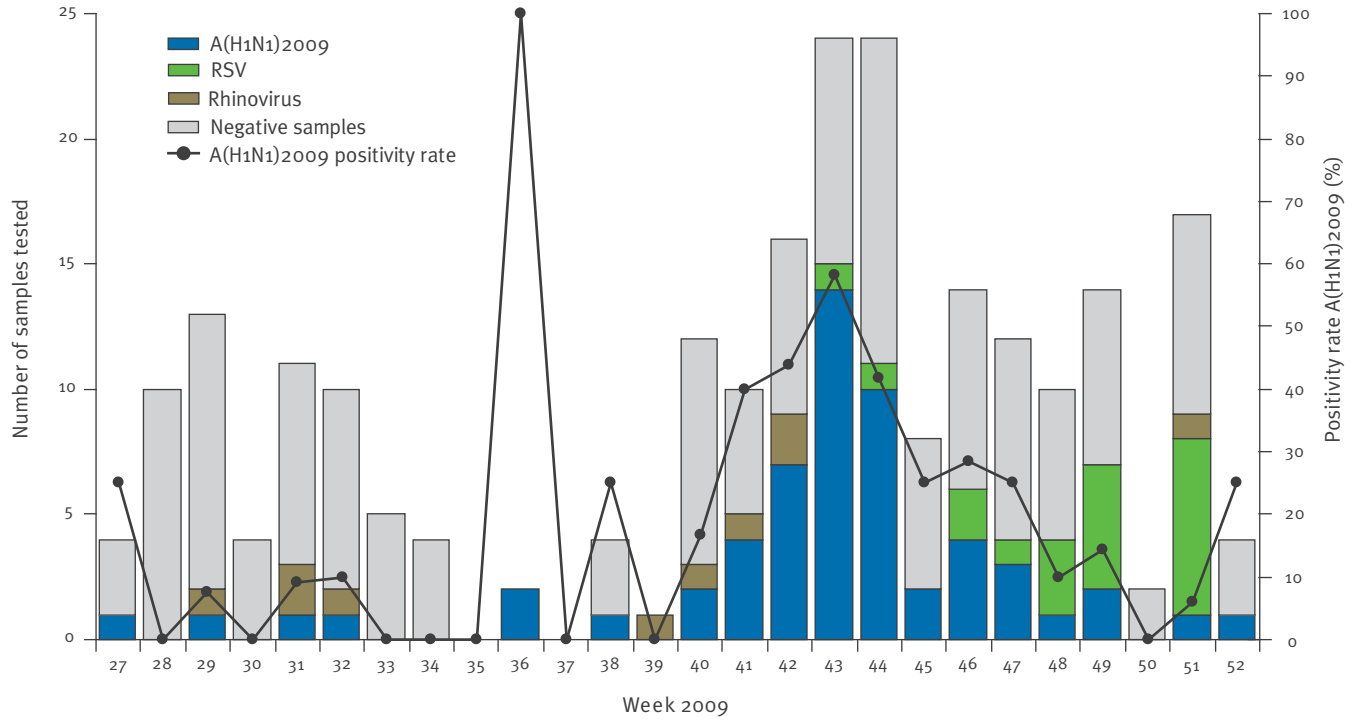
Public Health Wales received 344 influenza-related media enquiries between April and December 2009. Of these, 172 came from print media, 92 from radio, 76 from television, and four from other sources. The highest peak in media coverage was recorded in week 18 when WHO raised the level of influenza pandemic alert to phase 4 and later to phase 5 (Figure 5). Media interest dropped considerably after this week. Another wave of media interest began in week 26, preceding the first wave. A third period of media activity occurred at the end of October and beginning of November, coinciding with the launch of influenza A(H1N1)2009 vaccine in the UK.

Discussion

The influenza A(H1N1)2009 pandemic in Wales was characterised by two waves in ILI consultation rates that peaked in late July and late October 2009 respectively. However, the two waves were strikingly different in their epidemiological features. During the first wave, the highest ILI rates were in preschool children and the lowest rates in school children. During the second wave, the highest ILI rates were in school children. The first wave was also characterised by a much lower proportion of confirmed infections, and far fewer hospital admissions and deaths. These findings led us to question whether the first wave of ILI consultations in Wales was a genuine reflection of large numbers of infected people or mainly a consequence of extensive

Figure 3

Community virological surveillance showing tests for respiratory viruses and proportion positive for influenza A(H1N1)2009, Wales, United Kingdom, weeks 27–52[a], 2009



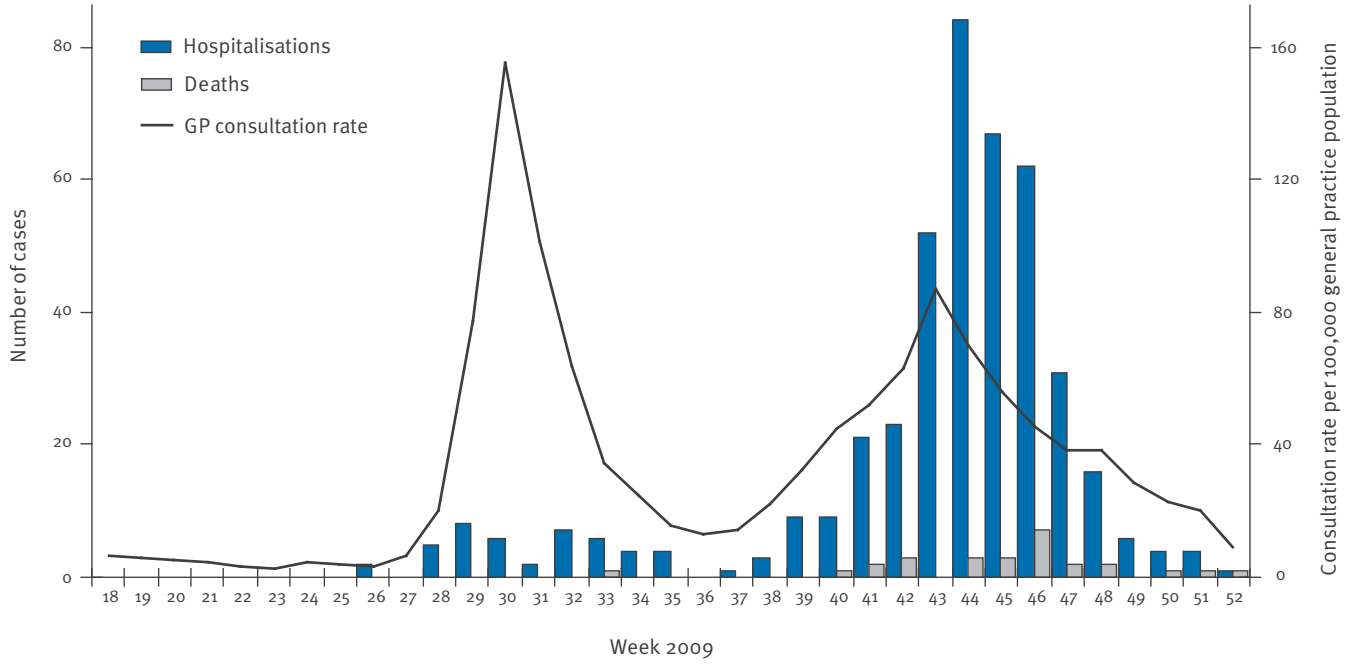
RSV: respiratory syncytial virus.

[a] In week 36 only two samples were tested, both were positive.

Source: Public Health Wales (regional virus laboratory).

Figure 4

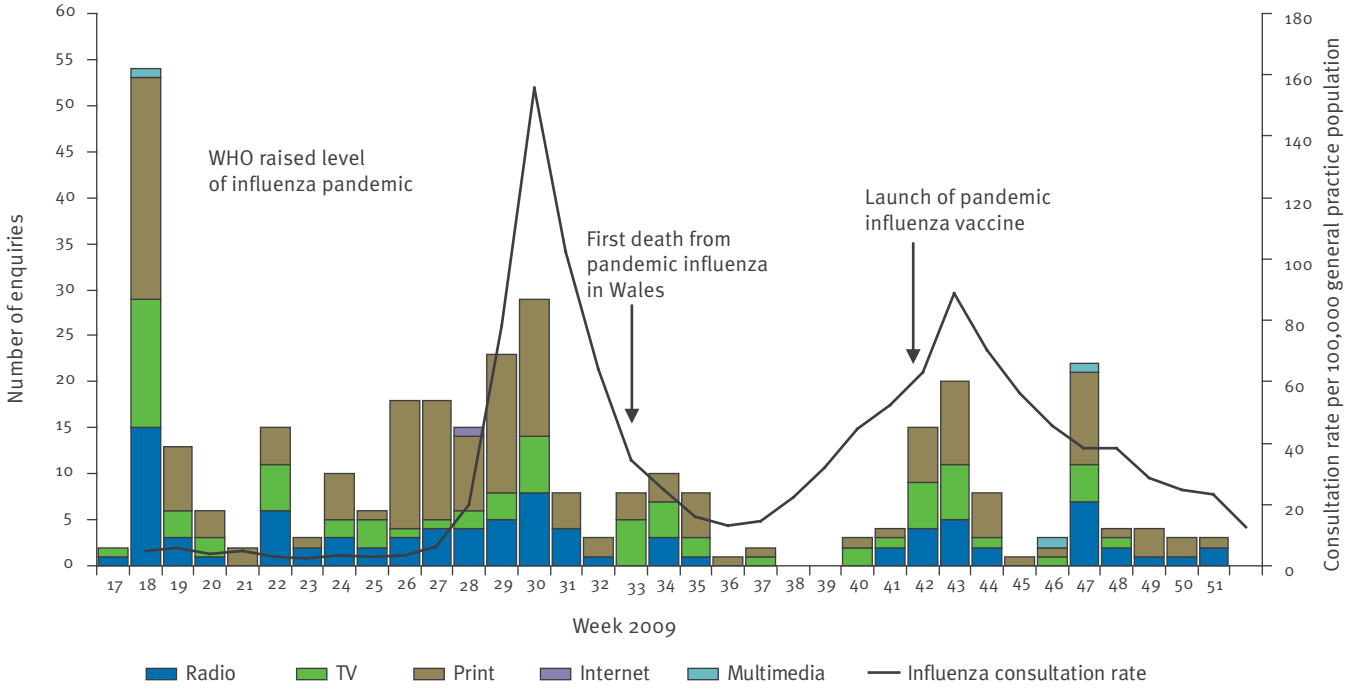
Consultation rates for influenza-like illness, and admissions to hospital and deaths from influenza A(H1N1)2009, Wales, United Kingdom, weeks 18–52, 2009



Source: Public Health Wales (Health Protection Services and Audit+).

Figure 5

Media enquiries about influenza A(H1N1)2009 received by Public Health Wales, April - December 2009



TV: television; WHO: World Health Organization.
Source: Public Health Wales (Communications team and Audit+).

media coverage. A number of possible explanations for the differences observed between the two waves are considered below.

Firstly, there may have been a lower threshold for contacting NHS Direct or consulting a GP during the first wave. This may have been influenced by extensive media coverage early in the pandemic, also observed in other countries [14,15], and perhaps by general public anxiety and fear of the unknown. Additionally, the public health message delivered by the public health authorities to consult promptly in order to obtain medical advice and treatment with antiviral medication may have led patients with minor upper respiratory infections, who would not normally consult, to seek medical care [16]. This would account for the low positivity rate for influenza A(H1N1)2009 in community samples in the first wave.

Secondly, GPs may have had been more likely than usual to suspect influenza in patients presenting with non-specific respiratory symptoms, particularly since public health authorities encouraged a low diagnostic threshold as part of the case-finding approach used during the initial stages of the pandemic Moreover, GPs may have also been influenced by the extensive media coverage. As a result they may have obtained samples from patients with mild respiratory symptoms, accounting for the low proportion of positive tests.

Thirdly, the difference between the two waves may be an artefact of surveillance. However, unlike in England where the introduction of the NPFS substantially altered the pattern of GP consultation (and hence make it difficult to interpret GP sentinel surveillance data), no such changes were made in Wales. New diagnostic codes were introduced for influenza A(H1N1)2009 by some GP software providers but similar patterns in ILI rates were recorded by both GP surveillance systems in Wales even though they operate independently and used different methods: one based on a weekly return of cases meeting a clinical case definition and the other based on automated extraction of coded diagnoses from general practice computers. Triangulation of data from both GP surveillance schemes and from NHS Direct Wales shows synchronous timing in the peaks, indicating that the three data sources were recognising the same phenomenon.

Fourthly, there may have been other respiratory viruses giving rise to ILI symptoms circulating at the time of the first wave. Some virological specimens were positive for other viruses, particularly rhinovirus which accounted for half of the samples testing positive during the first wave. It is possible that viral interference could have affected the spread of influenza A(H1N1)2009 virus during the first wave in Wales, as occurred elsewhere in the autumn [17,18]. However, this rhinovirus activity is more likely to represent background levels rather than a coincident epidemic, though there are no historical Welsh data from the summer months available for comparison as community samples are normally only tested during the influenza season. During the second wave, influenza A(H1N1)2009 was the predominant virus identified until the onset of the RSV season in late November.

Fifthly, influenza A(H1N1)2009 may have been underestimated during the first wave because of false negative laboratory tests. The reliability of virological testing depends on the timing of the sample (negative tests are more likely five or more days after symptom onset), the quality of the sample, and the sensitivity and specificity of the test [19]. Sample quality might be affected if primary care staff improved their sampling technique as the pandemic progressed. However, sample quality is routinely checked by the laboratory using a housekeeping gene probe to confirm the presence of human RNA and there was no change in the proportion of samples with inadequate cells. This explanation is therefore unlikely.

Finally, the much higher number of hospital admissions and deaths of people with confirmed influenza during the second wave might be due to a change in the virulence of the virus or to a change in hospital testing policy. There is no evidence for increased virulence of the influenza A(H1N1)2009 virus during the second wave and hospital testing policy remained consistent throughout the pandemic. The simplest explanation is that there were higher levels of influenza A(H1N1)2009 circulating in the community during the second wave in Wales, as demonstrated by the much higher influenza positivity rate in community samples.

There are several strengths as well as limitations to our study. We used a number of independent data sources to analyse the two waves of influenza A(H1N1)2009 in Wales, and all reflect the same phenomenon. Health service arrangements for clinical diagnosis and treatment of influenza remained consistent in contrast to England where the NPFS was introduced partway through the pandemic. Virological surveillance was also carried out consistently throughout the pandemic with participating practices instructed to send a maximum of five specimens per week from patients meeting the ILI case definition.

The main limitation of the study is the absence of detailed information on the symptoms of the patients consulting with ILI. The GP surveillance schemes rely either on an imprecise clinical case definition of ILI or automated extraction of relevant Read codes, neither of which capture subtle changes in presenting symptoms. Virological surveillance was restricted to five viruses, (influenza A, influenza B, influenza A(H1N1)2009, RSV and rhinovirus), so we cannot tell if some ILI consultations were due to other respiratory viruses, such as parainfluenza virus or adenovirus.

In conclusion, Wales experienced two waves of pandemic influenza during mid-summer and mid-autumn

2009 respectively. Each wave presented a different epidemiological profile. The first wave had a lower proportion of ILI cases confirmed as influenza and fewer hospital admissions and deaths compared with the second. These differences are most likely to be due to the different thresholds for contacting a GP that existed during the period of the pandemic and the different risk perceptions of the population over time. This was probably triggered by changes in media coverage throughout the pandemic and especially the high media profile during the initial stages of the pandemic, causing public anxiety. What is clear is that most patients presenting with ILI during the first wave in Wales do not appear to have had influenza and therefore did not require antiviral treatment. This has implications for the interpretation of surveillance data on ILI and on its use in policymaking. Above all, our study underlines the importance of using integrated epidemiological, virological and hospital surveillance data to routinely monitor influenza activity.

Acknowledgements

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Oseltamivir-resistant influenza viruses circulating during the first year of the influenza A(H1N1)2009 pandemic in the Asia-Pacific region, March 2009 to March 2010

A C Hurt (aeron.hurt@influenzacentre.org)[1], Y M Deng[1], J Ernest[1], N Caldwell[1], L Leang[1], P Iannello[1], N Komadina[1], R Shaw[1], D Smith[2], D E Dwyer[3], A R Tramontana[4], R T Lin[5], K Freeman[6], A Kelso[1], I G Barr[1]

1. WHO Collaborating Centre for Reference and Research on Influenza, North Melbourne, Victoria, Australia
2. PathWest Laboratories, Perth, Western Australia, Australia
3. Centre for Infectious Diseases and Microbiology, ICPMR, Westmead Hospital, New South Wales, Australia
4. Peter MacCallum Cancer Centre, Melbourne, Australia
5. National Public Health Laboratory, Communicable Diseases Division Ministry of Health, Singapore
6. Centre for Disease Control, Darwin, Australia

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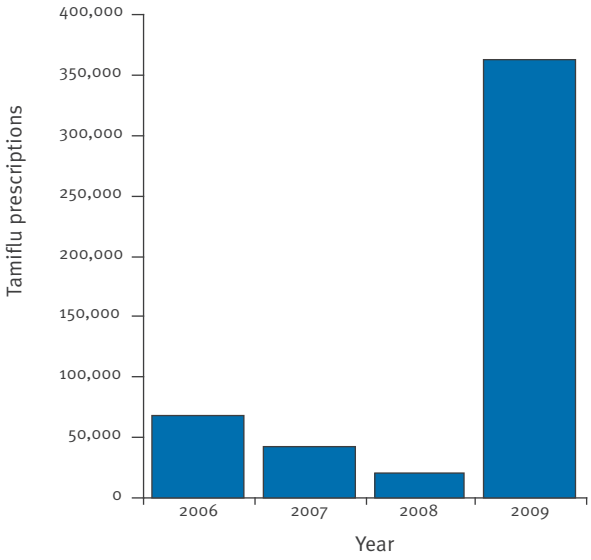
During the first year of the influenza A(H1N1)2009 pandemic, unprecedented amounts of the neuraminidase inhibitors, predominantly oseltamivir, were used in economically developed countries for the treatment and prophylaxis of patients prior to the availability of a pandemic vaccine. Due to concerns about the development of resistance, over 1,400 influenza A(H1N1)2009 viruses isolated from the Asia-Pacific region during the first year of the pandemic (March 2009 to March 2010) were analysed by phenotypic and genotypic assays to determine their susceptibility to the neuraminidase inhibitors. Amongst viruses submitted to the World Health Organization Collaborating Centre for Reference and Research in Melbourne, Australia, oseltamivir resistance was detected in 1.3% of influenza A(H1N1)2009 strains from Australia and 3.1% of strains from Singapore, but none was detected in specimens received from other countries in Oceania or south-east Asia, or in east Asia. The overall frequency of oseltamivir resistance in the Asia-Pacific region was 16 of 1,488 (1.1%). No zanamivir-resistant viruses were detected. Of the 16 oseltamivir-resistant isolates detected, nine were from immunocompromised individuals undergoing oseltamivir treatment and three were from immunocompetent individuals undergoing oseltamivir treatment. Importantly, four oseltamivir-resistant strains were from immunocompetent individuals who had not been treated with oseltamivir, demonstrating limited low-level community transmission of oseltamivir-resistant strains. Even with increased use of oseltamivir during the pandemic, the frequency of resistance has been low, with little evidence of community-wide spread of the resistant strains. Nevertheless, prudent use of the neuraminidase inhibitors remains necessary, as does continued monitoring for drug-resistant influenza viruses.

Introduction

Neuraminidase inhibitors (NAIs) are specifically designed to bind to the conserved neuraminidase (NA) enzymatic site of all influenza A and B viruses, inhibiting the normal function of the enzyme and preventing virus release from the host cell following replication [1]. The NAIs oseltamivir (Tamiflu, Hoffmann-La Roche) and zanamivir (Relenza, GlaxoSmithKline) have been

FIGURE 1

Number of Tamiflu prescriptions filled in Australia between 2006 and 2009



All data derived from IMS Health kindly provided by F. Hoffmann-La Roche Ltd. IMS Rx data represents prescription data, and not necessarily consumption data. Some prescriptions were given based on clinical diagnosis and therefore may include individuals with diseases other than influenza. Data from other countries in the region were not available.

available throughout the world for the treatment and prevention of influenza infections since 1999. Another NAI, peramivir (Biocryst), that has been under investigation as a parenteral formulation, was given emergency use authorisation in some countries such as the United States (US) and Australia during 2009, and in early 2010 was approved for use in Japan for the treatment of both uncomplicated and severe influenza infections [2,3]. In previous years the use of these drugs for the treatment of typical seasonal influenza has been greatest in Japan and the US, but has been very low in other parts of the world such as Australasia, south-east Asia and the South Pacific [4]. Despite their relatively low usage for seasonal influenza and unknown effectiveness against potential pandemic strains, in the last decade many economically developed countries began stockpiling NAIs for use in the event of an influenza pandemic [5,6]. The influenza A(H1N1)2009 pandemic was the first influenza pandemic to have occurred since the NAIs became available.

Early analysis of the pandemic influenza A(H1N1)2009 strain revealed that it was susceptible to the NAIs but was resistant to the adamantanes, an older class of anti-influenza drugs that inhibit the M2 ion channel [7]. In the early months of the pandemic and prior to the production and availability of a specific vaccine, the NAIs were the only specific pharmaceutical intervention available for the treatment or prevention of infection with this novel strain. In economically developed countries such as Australia, significantly increased amounts of oseltamivir were prescribed during the 2009 pandemic compared to previous years (Figure 1), whereas less economically developed countries in the region used little or no NAIs during the pandemic.

Prior to 2007, only sporadic cases of NAI resistance had been detected, even in Japan and the US where large quantities of the drugs were used. However in late 2007, high frequencies of oseltamivir-resistant seasonal influenza A(H1N1) viruses began to be detected in untreated individuals in Europe and the US [8,9] and by the middle of 2008 these viruses had

Table 1

Frequency of oseltamivir-resistant influenza A(H1N1)2009 viruses from different countries, Asia-Pacific region, 17 March 2009 to 17 March 2010 (n=1,488)

Region / country	Isolates tested by NA enzyme inhibition assay			Clinical specimens tested by pyrosequencing[a]		Total frequency of oseltamivir resistance
	No. tested	No. oseltamivir-resistant[b]	No. zanamivir-resistant	No. tested	No. with H275Y mutation[c]	
Australasia	808	5	0	312	7	1.1% (12/1,120)
Australia	649	5	0	312	7	1.3 % (12/961)
New Zealand	159	0	0	0	-	0
South-east Asia	252	4	0	3	0	1.6% (4/255)
Brunei	12	0	0	0	-	0
Cambodia	10	0	0	0	-	0
Malaysia	64	0	0	0	-	0
Philippines	32	0	0	0	-	0
Singapore	128	4	0	0	-	3.1% (4/128)
Thailand	6	0	0	0	-	0
Other[d]	0	0	0	3	0	0
South Asia and east Asia	24	0	0	0	-	0% (0/24)
Sri Lanka	3	0	0	0	-	0
Macau	21	0	0	0	-	0
South Pacific	62	0	0	27	0	0% (0/89)
Fiji	17	0	0	1	0	0
Guam	5	0	0	5	0	0
New Caledonia	12	0	0	6	0	0
Tahiti	28	0	0	1	0	0
Other[e]	0	-	-	14	0	0
Total	**1,146**	**9**	**0**	**342**	**7**	**1.1% (16/1488)**

NA: neuraminidase.

[a] None of the 342 clinical specimens had a corresponding isolate, therefore each one of the 1,488 samples tested (isolates and clinical specimens) represents an individual patient.

[b] Viruses were considered resistant if the IC50 exceeded 200 nM. All oseltamivir-resistant strains detected in NA enzyme inhibition assay were confirmed to contain the H275Y mutation.

[c] Only includes specimens that contained at least 50% of the H275Y mutation according to allele quantitation pyrosequencing analysis.

[d] Papua New Guinea (n=2), East Timor (n=1).

[e] Nauru (n=1), Palau (n=1), Kosrae (n=4), Yap (n=3), Chuuk (n=3), Pohnpei (n=2).

spread to many parts of the Asia-Pacific region [10]. By 2009 virtually all seasonal influenza A(H1N1) viruses circulating globally were oseltamivir-resistant [11], indicating that the mutant viruses were of equivalent or greater fitness than the previous oseltamivir-sensitive strain, thus dismissing the theory that all viruses with NAI-resistance mutations have a reduced viral fitness [12]. The oseltamivir-resistant seasonal influenza A(H1N1) strains all contained an H275Y mutation in the NA (equivalent to residue 274 based on N2 numbering) [10], a substitution that has previously been detected in other oseltamivir-resistant viruses containing an N1 neuraminidase, such as highly pathogenic influenza A(H5N1) viruses [13]. Therefore, the emergence of the N1-containing 2009 pandemic virus raised concerns that oseltamivir-resistant variants with the H275Y NA mutation (or with other mutations that confer NAI resistance) may emerge and spread throughout the world. Here we report on the frequency of oseltamivir and zanamivir resistance observed in influenza A(H1N1)2009 viruses from the Asia-Pacific region during the first year of the pandemic and describe virological and epidemiological properties of the resistant viruses detected.

Materials and methods

Viruses

Isolates and clinical specimens from Oceania, Asia and Africa were received at the World Health Organization Collaborating Centre for Reference and Research on Influenza (WHO CC), Melbourne, Australia, as part of the WHO Global Influenza Surveillance Network. No recommendations were made regarding the number and type of specimens or isolates sent by submitting laboratories, and the specimens were received from institutes with varying analytical capacity. Some of the samples submitted to the WHO CC may have been biased towards severe or hospitalised cases. Of those confirmed to be the novel influenza A(H1N1)2009 subtype, 1,146 cultured influenza isolates were tested for NAI susceptibility using a functional NA inhibition assay, and a further 342 clinical specimens were tested using molecular techniques for the presence of the H275Y amino acid mutation (Table 1). None of the 342 clinical specimens had a corresponding isolate, therefore each one of the 1,488 samples tested (isolates and clinical specimens) represents an individual patient. All 1,488 samples were taken from patients infected with the influenza A(H1N1)2009 virus within the first year of the pandemic (17 March 2009 to 17 March 2010). The NAI treatment status of patients was not known for the majority of samples received at the WHO CC, although this information was retrospectively obtained for the viruses detected as resistant.

Neuraminidase inhibition assay

All viruses were isolated in Madin-Darby canine kidney (MDCK) cells using standard techniques described previously [14]. Oseltamivir, zanamivir and peramivir susceptibility was measured using a NA inhibition assay that utilises the fluorescent product 4-methylumbelliferone from the substrate

Table 2

Patient and virological details for oseltamivir-resistant H275Y mutant influenza A(H1N1)2009 viruses, Asia-Pacific region, 17 March 2009 to 17 March 2010 (n=16)

Patient details						NAI susceptibility of isolates (mean ± standard deviation)		
Patient number	Location	Immunological status	Oseltamivir treatment	Specimen date	Known duration of shedding	Oseltamivir IC_{50} (nM)	Peramivir IC_{50} (nM)	Zanamivir IC_{50} (nM)
1	Singapore	Competent	Yes	30 May 09	27–30 May 09	374.1± 37.3	41.6 ±12.2	0.3 ± .04
2	Melbourne, Australia	Compromised	Yes	25 June 09	16–25 June 09	-	-	-
3	Sydney, Australia	Compromised	Yes	20 July 09	–20 July 09	-	-	-
4	Melbourne, Australia	Compromised	Yes	22 July 09	30 June–22 July 09	-	-	-
5	Melbourne, Australia	Compromised	Yes	24 July 09	20–24 July 09	-	-	-
6	Perth, Australia	Compromised	Yes	28 July 09	Unknown	306.7 ± 21.2	33.3 ± 3.4	0.31 ± 0.03
7	Sydney, Australia	Compromised	Yes	10 Aug 09	20 July–10 Aug 09	279.1 ± 44.9	42.0 ±11.9	0.25 ± 0.05
8	Perth, Australia	Compromised	Yes	12 Aug 09	24 July–24 Aug 09	296.7 ± 20.0	37.8 ± 3.7	0.28 ± 0.02
9	Singapore	Compromised	Yes	14 Aug 09	3–14 Aug 09	462.3 ± 74.3	32.0 ± 5.3	0.32 ± 0.07
10	Perth, Australia	Competent	Yes	14 Aug 09	9–14 Aug 09	292.6 ± 25.2	32.5 ± 5.6	0.23 ± 0.02
11	Sydney, Australia	Compromised	Yes	18 Aug 09	Unknown	312.5 ± 39.0	32.1 ± 5.0	0.30 ± 0.05
12	Darwin, Australia	Competent	No	29 Dec 09	Unknown	-	-	-
13	Melbourne, Australia[a]	Competent	No	15 Jan 10	Unknown	-	-	-
14	Melbourne, Australia[a]	Competent	No	15 Jan 10	Unknown	-	-	-
15	Singapore	Competent	Yes	21 Jan 10	17 Jan–1 Feb 10	295.5 ± 32.1	29.1 ± 2.1	0.26 ± 0.03
16	Singapore	Competent	No	1 Feb 10	Unknown	378.5 ± 67.0	30.6 ± 3.1	0.31 ± 0.03

NAI: neuraminidase inhibitor; IC50: inhibitory concentration reducing 50% of neuraminidase NA activity).

- indicates that the H275Y mutant virus could not be cultured and therefore no isolate was available for NAI susceptibility analysis.

[a] Patients were related.

2-(4-methylumbelliferyl)-a-D-N-acetylneuraminic acid (MUNANA) (Sigma, Australia) as a measure of NA activity [15] following a previously published protocol [14]. Oseltamivir carboxylate, the active form of the ethyl ester prodrug oseltamivir phosphate, was kindly provided by Hoffmann-La Roche Ltd, Switzerland, and zanamivir was kindly provided by GlaxoSmithKline, Australia. Peramivir was kindly provided by BioCryst, Birmingham, US, and was used to test strains with reduced oseltamivir susceptibility. IC_{50} values (the concentrations required to inhibit 50% of NA activity) were calculated using a logistic curve fit programme 'Robosage' kindly provided by GlaxoSmithKline, UK.

RT-PCR, sequencing and pyrosequencing

The NA and haemagglutinin (HA) genes were amplified by RT-PCR and sequenced using standard techniques [16]. Pyrosequencing followed previously published methods [17] and relative proportions of wild-type and mutant genes were determined using the Pyromark ID v1.0 software following allele quantitation analysis. Neighbour-Joining phylogenetic trees of the HA and NA genes were constructed using the PAUP (V4.0) plugin on Geneious [18,19]. Bootstrap values were calculated from 1,000 NJ replicates. FigTree v1.3.1 was used to display the trees.

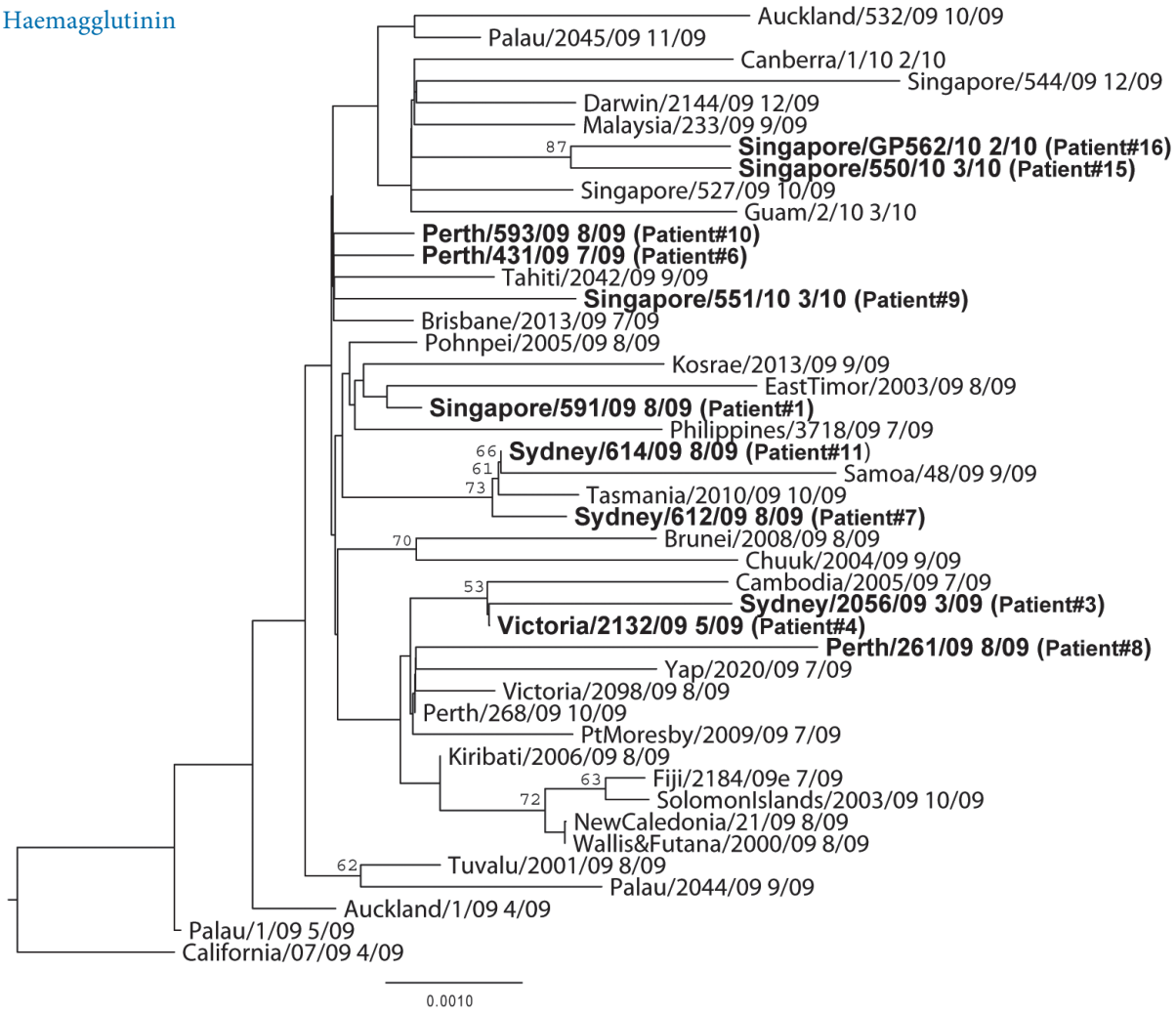
Results

Of the 1,146 cell culture-grown influenza A(H1N1)2009 influenza isolates tested for NAI susceptibility, nine demonstrated resistance to oseltamivir and none was resistant to zanamivir (Table 1). The mean IC_{50} ± standard deviation for the fully susceptible influenza A(H1N1)2009 isolates was 0.3 ± 0.2 nM for zanamivir (n=1,146), 0.5 ± 0.4 nM for oseltamivir (n=1,137) and 0.2 ± 0.1 nM for peramivir (n=94). In comparison, the nine oseltamivir-resistant influenza A(H1N1)2009 isolates had mean oseltamivir IC_{50} values ranging from 279 nM to 462 nM (Table 2), at least 550-fold higher than the mean oseltamivir IC_{50} value for susceptible wild-type influenza A(H1N1)2009 strains. The oseltamivir-resistant strains remained fully susceptible to zanamivir, but had peramivir IC_{50} values ranging from 30.6 nM to 42.0 nM, demonstrating an approximate 170-fold increase

Figure 2

Phylogenetic relationships of (A) haemagglutinin and (B) neuraminidase gene sequences for oseltamivir-resistant H275Y mutants and oseltamivir-sensitive influenza A(H1N1)2009 viruses, Asia-Pacific region, 17 March 2009 to 17 March 2010 (n=11 patients)

A. Haemagglutinin



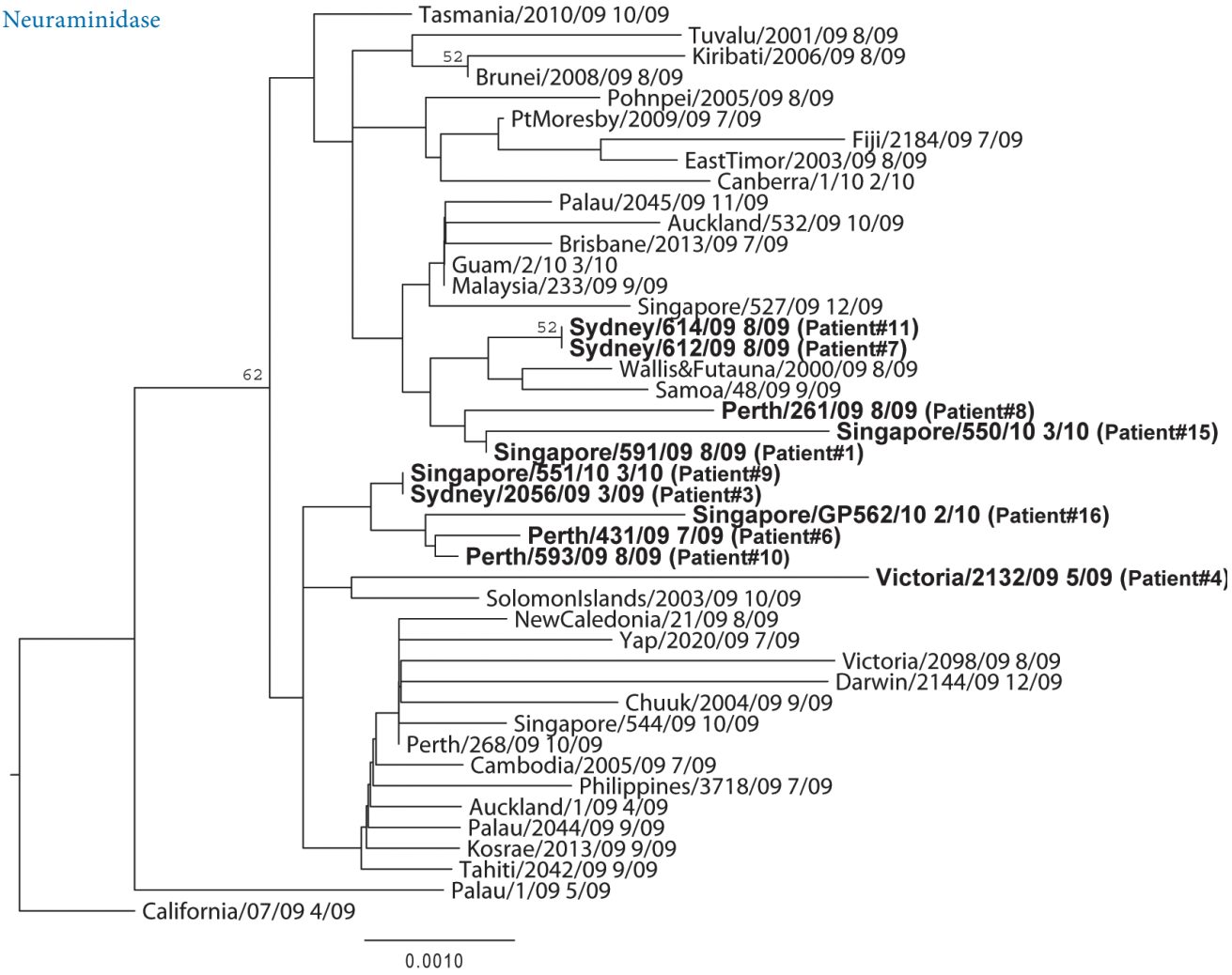
compared to the mean peramivir IC_{50} for fully susceptible influenza A(H1N1)2009 isolates (Table 2). Sequence analysis of the oseltamivir-resistant strains revealed that they all contained the H275Y NA mutation.

Of the nine oseltamivir-resistant H275Y mutant isolates detected in the NA enzyme inhibition assay, five were from Australia and four were from Singapore (Table 1). Pyrosequencing analysis of clinical specimens that could not be cultured (n=342) detected a further seven Australian viruses with the H275Y mutation (Table 1). Apart from these seven strains, an additional five Australian clinical specimens were found to contain the H275Y mutation, but analysis revealed the presence of the mutant virus at a proportion lower than 50% (ranging from 5% to 34 %) and therefore these samples were not included in the count of oseltamivir-resistant strains. In comparison, the seven Australian clinical specimens that were classified as oseltamivir-resistant contained the H275Y mutant at a proportion of 89% to 100% of the viral population.

By combining the data from the functional NA inhibition assay and the pyrosequencing assays, the overall frequency of oseltamivir-resistance in the Australian influenza A(H1N1)2009 viruses submitted to the WHO CC was 1.3% (12/961), while the frequency was slightly higher in the Singaporean influenza A(H1N1)2009 viruses (4/128; 3.1%) (Table 1). As oseltamivir-resistant viruses were not detected among samples from any other countries, the overall frequency of oseltamivir-resistance in influenza A(H1N1)2009 viruses detected in the Asia-Pacific region was 1.1% (16/1,488) (Table 1).

Of the 16 cases in whom oseltamivir resistance was detected, nine patients were considered immunocompromised and were receiving oseltamivir treatment at the time the specimens yielding resistant virus were collected. These patients were ill during the southern hemisphere winter period in the early months of the first pandemic wave and some of them were shedding virus for over three weeks whilst receiving multiple courses of single and double-dose oseltamivir treatment (Table 2). Eight of these patients were undergoing

B. Neuraminidase



Full haemagglutinin (HA) and neuraminidase (NA) gene sequences derived from influenza A(H1N1)2009 oseltamivir-resistant H275Y mutant strains (in bold) are compared phylogenetically with oseltamivir-sensitive viruses. Specimen dates (month/year) are included after the strain name. Patient numbers have been included in parentheses after the designation of oseltamivir-resistant viruses to allow cross referencing with case details in Table 2. Culture of virus from Patients 2, 5, 12, 13 and 14 was attempted but was not successful, as such analysis of the original specimen was undertaken but sequence data was not of sufficient quality or length to be included in the phylogenetic trees. Only bootstrap values >50 are shown.

chemotherapy for cancer, including treatment for multiple myeloma (Table 2, Patient 2), prolymphocytic leukaemia (Table 2, Patient 4) and aplastic anaemia (Table 2, Patient 5), as reported in detail previously [20]. One immunosuppressed patient had undergone a renal transplant seven weeks prior to their influenza infection (Table 2, Patient 8). Following infection with an oseltamivir-sensitive influenza A(H1N1)2009 virus, Patient 8 shed both oseltamivir-sensitive and -resistant viruses over a period of nine weeks whilst undergoing 36 days of single- or double-dose oseltamivir treatment together with shorter periods of nebulised and intravenous zanamivir treatment (a full case study on this patient has been reported previously [21]).

Seven patients who had an infection with oseltamivir-resistant virus were otherwise healthy and immunocompetent. Of these seven patients, three were receiving oseltamivir treatment at the time of recovery of resistant virus, including a case from Singapore of an American patient initially infected in New York (Table 2, Patient 1). This case represents the earliest oseltamivir-resistant influenza A(H1N1)2009 virus reported in this study (30 May 2009). Importantly, four of the immunocompetent patients from whom oseltamivir-resistant virus was recovered were not being treated with oseltamivir or any other influenza antiviral drug and had no known contact with other individuals receiving oseltamivir treatment. Each of these four cases occurred between 29 December 2009 and 1 February 2010, well after the main pandemic periods in Australia (late May to early October 2009) [22] and Singapore (late June to early October 2009) [23].

HA and NA gene sequence analysis was conducted on all of the oseltamivir-resistant viruses that were successfully cultured. Phylogenetic trees drawn from sequences derived from this study showed that oseltamivir-resistant and -sensitive strains were distributed throughout different parts of the tree, with bootstrap values showing less than 50% support for the majority of branches (Figure 2). The low bootstrap values are a result of the lack of divergence in the influenza A(H1N1)2009 viruses since their emergence, and as a consequence the genetic data is neither able to support nor disprove the epidemiological conclusions that these strains arose independently and not as part of an emergent group of related variants.

Discussion

Characterisation of the first influenza A(H1N1)2009 viruses from the pandemic revealed that the strains were resistant to the older class of influenza antivirals, the adamantanes [7], similar to the other swine influenza viruses concurrently circulating in North America [24]. Therefore the NAIs were the only class of influenza antiviral drug available for the treatment and prophylaxis of the novel pandemic strain, and were particularly important before the availability of a specific vaccine. The studies published to date indicate that oseltamivir usage in patients was significantly greater than zanamivir usage during the first year of the pandemic [25-27], and was associated with a lower risk of intensive care admission or death in hospitalised patients if commenced within two days of symptom onset [28].

Although increased amounts of oseltamivir and, to a lesser extent, zanamivir were used during the 2009 influenza A(H1N1) pandemic, only 267 oseltamivir-resistant viruses were reported globally from over 10,000 samples during the first year of the pandemic [29]. In this study, oseltamivir-resistant viruses were detected in Australia and Singapore, but not in samples from the South Pacific, New Zealand, Kenya, south Asia and east Asia, although it is of note that only a relatively small number of viruses were available for testing from the regions where resistance was not detected, and that analysis of a greater number of samples may have revealed a low proportion of resistance. Due to insufficient samples it was not possible to determine if oseltamivir resistance was more prevalent in children than in adults, as has been reported previously for seasonal influenza [30]. It is most likely that the higher apparent frequency of resistance in Australia and Singapore was a reflection of the amount of oseltamivir used there during the pandemic. The frequency of oseltamivir resistance in Australia (1.3%) and Singapore (3.1%), as determined in this study, was no higher than that reported among oseltamivir-treated adult patients infected with seasonal influenza viruses in clinical trials (1-4%) [31,32] but was higher than that observed in community surveillance studies before 2007 [33-35]. However, care should be taken in drawing conclusions about the frequency of resistance either in treated individuals or in specific patient groups (e.g. immunocompromised) as detailed clinical and epidemiological information was unavailable for the majority of the NAI susceptible cases tested in this study. In addition, it should be noted that samples submitted to the WHO CC (and therefore tested in this study) may be biased towards unusual isolates or hospitalised patients, and therefore the actual frequency of oseltamivir resistance in some countries may be lower than reported here.

Before 2007, there was little evidence of community spread of oseltamivir-resistant viruses and resistant strains in untreated patients were only occasionally detected [16,35], presumably due to impaired viral growth and infectivity of the resistant viruses [36-39]. However the global spread of oseltamivir-resistant seasonal influenza A(H1N1) viruses with the H275Y NA mutation during and after 2008 demonstrated the ability of these resistant strains to replicate and transmit efficiently in the absence of drug selective pressure. It is thought that two permissive mutations in the NA, V234M and R222Q, that occurred in seasonal influenza A(H1N1) viruses shortly before the emergence of the H275Y mutant enabled the virus to tolerate the resistance mutation with no impact on viral fitness [40]. To date, neither of these compensatory mutations

have been detected in any influenza A(H1N1)2009 viruses (including those reported in this current study), although the majority of influenza A(H1N1)2009 viruses actually possess N at residue 222 rather than R [41]. Nevertheless, future close monitoring of gene sequences is necessary as these, or other, permissive mutations may enable influenza A(H1N1)2009 H275Y mutant viruses to easily transmit throughout the community. In the current study we identified four patients (Table 2, Patients 12,13,14 and 16) who were shedding oseltamivir-resistant viruses even though they were not undergoing oseltamivir treatment, and all were detected during a period of low influenza activity in the southern hemisphere (December 2009 to February 2010). It is unknown if these patients were infected directly by oseltamivir-treated individuals shedding resistant virus, or whether low level transmission of resistant strains is occurring sporadically in the community. Previous studies have shown that H275Y oseltamivir-resistant influenza A(H1N1)2009 viruses was transmitted from treated to untreated patients within a hospital in Wales [42], and between close contacts during a train journey in Vietnam [43], but there was no evidence of subsequent transmission to the wider community on either occasion.

Many of the specimens analysed in this study contained a mixed viral population of both oseltamivir-resistant and -sensitive viruses, indicating the need for diagnostic tests to detect small proportions of resistant virus in a mixture. The clinical significance of low-level populations of oseltamivir-resistant virus is uncertain, at least in otherwise healthy individuals. Because most oseltamivir-resistant viruses (including the H275Y mutant) remain fully susceptible to zanamivir, early detection of oseltamivir-resistant viruses in a mixed population can facilitate the use of alternative antivirals such as zanamivir, which have the potential to improve patient outcome.

Although the NAIs have been used in Japan and the US for many years, they have had relatively little use elsewhere. Therefore concern existed that sudden large-scale use of the NAIs in a pandemic, across many countries around the world, may result in the rapid and widespread selection of resistant viruses. Data collected during the first year of the 2009 influenza A(H1N1) pandemic has demonstrated that this has not occurred, with only 1.1% of strains from the Asia-Pacific region found to be oseltamivir-resistant and no detection of any zanamivir-resistant strains. Nevertheless, prudent use of the NAIs to treat infected individuals is encouraged to avoid selection of resistant viruses, which may in turn acquire the ability to transmit efficiently throughout the community, thereby reducing the available options for antiviral treatment.

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The second wave of 2009 pandemic influenza A(H1N1) in New Zealand, January–October 2010

D Bandaranayake (Don.Bandaranayake@esr.cri.nz)[1], M Jacobs[2], M Baker[3], D Hunt[2], T Wood[1], A Bissielo[1], M Macfarlane[2], L Lopez[1], G Mackereth[1], Q S Huang[1]

1. Institute of Environmental Science and Research, National Centre for Biosecurity and Infectious Disease, Upper Hutt, New Zealand
2. Ministry of Health, Wellington, New Zealand
3. Wellington School of Medicine and Health Sciences, University of Otago, Wellington, New Zealand

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This paper uses data from multiple surveillance systems to describe the experience in New Zealand with the second complete wave of pandemic influenza A(H1N1)2009 in 2010. Measures such as hospitalisation rates suggest the overall impact of influenza A(H1N1)2009 in 2010 was between half and two thirds that of the first wave in 2009. There was considerable regional and sub-regional variation with a tendency for higher activity in areas that experienced low rates in 2009. Demographic characteristics of the second wave were similar to those in 2009 with highest rates seen in children under the age of five years, and in indigenous Māori and Pacific peoples. Hospital services including intensive care units were not under as much pressure as in 2009. Immunisation appears to have contributed to the reduced impact of the pandemic in 2010, particularly for those aged 60 years and older.

Introduction

Between April and December 2009, New Zealand experienced the first wave of the influenza A(H1N1)2009 pandemic, with 3,211 laboratory-confirmed case notifications, 1,122 hospitalisations and 48 deaths [1]. The numbers from April to August 2009 have been documented in the literature [1-5]. Subsequently, a national seroprevalence survey confirmed that the true extent of infection from the pandemic was much greater than indicated by surveillance data, with an estimated cumulative incidence of over 780,000 infections (18.3% of New Zealanders) [6]. This survey utilised a randomly selected community-based sample from the New Zealand population aged over one year. It obtained 1,156 serum samples from populations enrolled in general practices in selected regions of the country and a further 527 samples from healthcare workers. In addition a baseline survey was conducted using 538 pre-pandemic samples collected for other reasons.

During the early months of 2010 the notifications of pandemic influenza A(H1N1)2009 cases dwindled to zero, until a few cases were notified in July. Influenza activity then increased and peaked in the middle of August 2010 with the pandemic influenza A(H1N1)2009 virus as the predominant strain [7]. The second wave of influenza A(H1N1)2009 again coincided with New Zealand's usual influenza season. This wave was of a similar duration with a lower peak than the first wave, but with significant regional variations – some areas that had relatively low influenza-like illness (ILI) activity or hospitalisations in 2009 experienced higher levels of influenza activity in 2010 [7]. For 2010, as of the middle of October we have seen 1,768 confirmed cases, including 732 hospitalisations and 15 confirmed deaths.

The eligibility policy for the 2010 trivalent influenza vaccine was extended to allow pregnant women, children under five years and obese individuals to receive subsidised vaccine. Individual's over 65 years and those with underlying health conditions were also eligible. A monovalent vaccine (CELVAPAN H1N1; Baxter) was made available for healthcare workers in February 2010. The trivalent (seasonal) vaccine became available in April. The uptake was low for the former while stocks had to be re-ordered for the trivalent vaccine in March 2010. The subsidised influenza immunisation programme ended on 30 September 2010. Since then, influenza vaccines have still been available for people who want to purchase them, but demand has been very low.

This report uses multiple surveillance sources to describe the second wave of pandemic influenza A(H1N1)2009 in New Zealand and compare it with the first wave. These sources are described in a previous publication reporting on the first wave of the pandemic [2]. The aims are to compare incidence and impact of infection as well as timing and shape of the epidemic curve, to identify whether there are persisting or divergent regional patterns and whether vulnerable age and ethnic groups have changed, to assess whether the virus has changed, and to analyse the extent and impact of immunisation. The overall aim is to identify

implications for minimising the public health impact of this virus, particularly for countries in the northern hemisphere in the future.

Methods and data sources

The following surveillance systems provide data on influenza disease burden, characteristics of the virus and immunisation coverage:

Surveillance of influenza-like illness by the Institute of Environmental Science and Research based on data from sentinel general practitioners

There are 90 volunteer sentinel general practitioner (GP) practices distributed throughout the country. Normally sentinel surveillance operates in the winter period, from May to September. However, due to the pandemic, the sentinel system operated continuously from May 2009 to September 2010. The sentinel system defines a case of ILI as *an acute respiratory tract infection characterised by an abrupt onset of at least two of the following: fever* [≥37 °C], *chills, headache, and myalgia* [8]. Each general practice records the daily number of consultations for ILI and also collects three respiratory samples (nasopharyngeal or throat swab) per week from each of the first ILI patient seen on Monday, Tuesday and Wednesday. Consultation numbers and samples were sent to the World Health Organization (WHO) National Influenza Centre at the Institute of Environmental Science and Research (ESR) in Wellington and other hospital laboratories. Sentinel ILI rates are expressed as per population and not per total numbers of consultations. This system has been described in detail previously [2,3].

Surveillance of influenza-like illness by Healthstat based on data from sentinel general practitioners

CBG Ltd, a privately owned company contracted by the New Zealand Ministry of Health (MoH), uses a core of 100 general practices throughout New Zealand to gather computerised information on ILI consultations on a weekly basis (Healthstat). Both the ESR and Healthstat surveillance use practices across the country, providing both a regional and national picture of ILI. However, samples for molecular analysis are not collected in the Healthstat system.

Healthline

Healthline is the national 24-hour triaged telephone health advice service provided by the MoH in New Zealand. All calls are answered by registered nurses with telenursing training and working within the Nursing Council's Professional Standards for Telenursing Practice [2]. The Healthline service uses a computerised triage algorithm for symptomatic callers and an electronic health topic library for general health information. Numbers of monitored ILI calls can be made available on a daily basis.

Notified cases

Influenza A(H1N1)2009 became a notifiable disease in New Zealand on 30 April 2009. Notifications include those made through direct laboratory notification which is a legal requirement in New Zealand. Other sources of notifications are from clinicians in both primary and secondary care. Data are entered into the national database for notifiable diseases (Episurv).
During 2010 and most of 2009, notification has largely been based on laboratory reporting of confirmed cases. Thus although notification data are useful for monitoring trends, they are a substantial underestimate of true community incidence of infection.

Virological surveillance

Virology swabs are collected through the ESR sentinel GP surveillance during the influenza season, as well as through year-round laboratory testing by the four regional virus diagnostic laboratories at Auckland, Waikato, Wellington and Christchurch Hospitals, and by the WHO National Influenza Centre at ESR. Laboratory identification methods include molecular detection by polymerase chain reaction or isolation of the virus [9]. Influenza viruses are typed and subtyped as influenza A, B, seasonal A(H1N1), seasonal A(H3N2), or A(H1N1)2009. Fluorometric neuraminidase inhibition assay is used for monitoring oseltamivir susceptibility [5].

Hospitalisations (including intensive care)

Hospitalisations among confirmed cases of influenza A(H1N1)2009 notified to EpiSurv were reviewed by ESR throughout the second wave. In addition, the National Minimum Data Set (NMDS) that collates all hospital discharges (with diagnoses) was also used. Hospitalisation rates give a good indication of incidence trends for more severe cases nationwide. Such rates, while representing only a small proportion of all cases give a more complete picture of the progression of the pandemic than notifications. Information on cases of influenza A(H1N1)2009 admitted to intensive care units (ICU) and ICU bed occupancy were also obtained directly from ICUs as additional surveillance measures of healthcare utilisation.

Deaths

Mortality data for influenza A(H1N1)2009 are obtained from the standard processes for death certification and case notification, and from deaths referred to the Coroner. In addition, a Pandemic Influenza Mortality Review Committee was established in 2009 to review all deaths linked to the influenza A(H1N1)2009 virus. A death associated with pandemic influenza A(H1N1)2009 was defined as *a person with confirmed pandemic influenza A(H1N1)2009 infection determined from ante-mortem or post-mortem specimens, and who died from a clinically compatible illness or complications attributable to that infection. There should be no period of complete recovery between illness and death, and no alternative agreed-upon cause of death* [10].

We estimated the case fatality and hospitalisation ratios for 2010 by first estimating the number of symptomatic influenza A(H1N1)2009 infections in 2010. The number of symptomatic cases due to influenza A(H1N1)2009 as estimated from the seroprevalence study was adjusted by the ratio of sentinel ILI activity for 2010 and 2009, and the proportion of viruses characterised as influenza A(H1N1)2009 in the two years. This gave an estimate of 176,308 symptomatic influenza A(H1N1)2009 cases in 2010.

School absenteeism

School absenteeism data represent numbers of pupils absent due to sickness or unexplained reasons. These are monitored on a daily basis by region through a database provided by the Ministry of Education using sentinel schools. The system commenced in 2010. 178 schools reported regularly, representing an average daily number of 64,911 students. Overall about 12% pupils are covered nationally. The data for 2010 are available for several regions. These results are not shown in this paper for reasons of brevity, lack of a valid baseline and the inability to compare with previous years.

Immunisation coverage

Estimations of total immunity prior to the onset of the second wave were based on the results of the seroprevalence study and estimated immunisation uptake levels [6]. These levels were taken as baseline levels for 2010, and estimated immunisation uptake levels were then included in the final estimate. Assuming that the immunisation uptake before the second wave was similar across age groups and independent of previous immune status, we estimated the age-specific immunity prior to the onset of the second wave as follows:
Total immune = Immune (following first wave) + Immune (vaccinated) – Immune (first wave and vaccinated)

Results

Epidemic curves

Following a substantial increase in July 2010, the number of influenza A(H1N1)2009 notifications peaked in mid-August and declined rapidly after that.

Figure 1 summarises the epidemic curves of the second wave of influenza A(H1N1)2009 in 2010 based on surveillance data from sentinel ILI, notifications, Healthline, hospitalisations and virological reporting systems in comparison with previous years. Results from these surveillance systems suggest that the pandemic in 2010 commenced one month later than in 2009 and had a significantly lower incidence.

Community surveillance of influenza-like illness (sentinel surveillance by the Institute of Environmental Science and Research)

The overall national ILI consultation rates in 2010 in the GP sentinel surveillance system show less influenza activity compared to 2009 (Figure 1a). As of the week 39 (ending 3 October 2010), the 2010 cumulative incidence rate of 1,019.9 per 100,000, was lower than that of 2,695.6 per 100,000 in 2009 (Table 1). The 2010 peak consultation rate of 152 per 100,000, which was lower than that of 284.0 per 100,000 in 2009, occurred in week 33 (ending 22 August), four weeks later than the 2009 peak.

During this period from May to 3 October 2010 the highest ILI consultation rates were recorded among children and young adults. ILI consultation rates per 100,000 were 1,982.2 for infants, 2,163.7 for children aged one to four years, and 1,092 for children aged five to 19 years.

Community surveillance of influenza-like illness (Healthstat)

Healthstat returns show some major differences compared to most other surveillance results. The epidemic curves for 2009 and 2010 in Figure 1b are of equal intensity. This might be a result of low sensitivity of the coding during 2009 (Table 1). It is known that in 2010 there was a concerted effort to improve the sensitivity of the data being collected with particular attention to coding by each of the practices involved.

Notified cases

Figure 1c shows the epidemic curves based on notifications for 2009 and 2010. These are all cases that have been notified and entered into the Episurv database from January to October 2010. The sharp increase in notifications during the second wave of influenza A(H1N1)2009 commenced four weeks later than during the first wave. Following a substantial increase in July 2010, the number of influenza A(H1N1)2009 notifications peaked in week 33 (ending 22 August) with 367 cases, and then declined to less than 10 per week by the first week in October 2010. From January to 24 October 2010, a total of 1,782 cases of influenza A(H1N1)2009 were notified, including 1,758 confirmed cases and 24 probable cases (Table1).

Healthline

The number of calls to Healthline for ILI during 2010 were lower than for 2009 (Figure 1d). The total number of triaged calls that were symptomatic for ILI gave the best indication of the impending second wave. Healthline calls increased in mid-June, two to three weeks before the other surveillance systems.

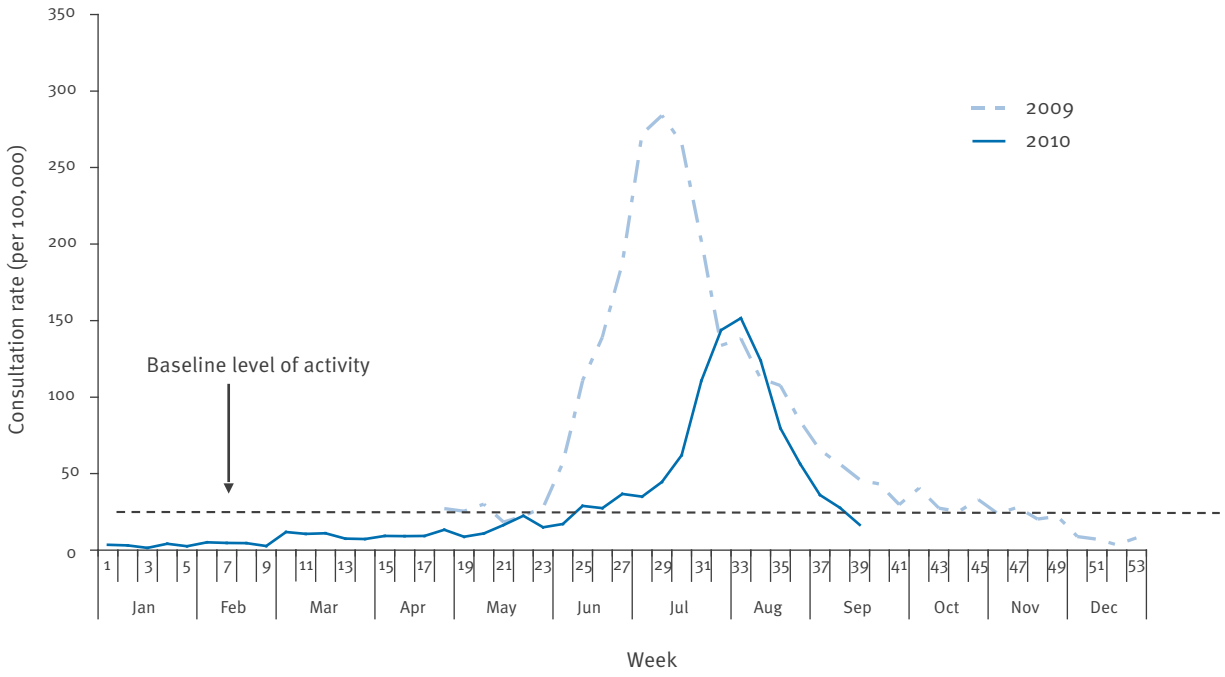
Hospitalisations and admissions to intensive care

Hospitalisation rates in 2010 were considerably below the peak national rates for 2009, and declined rapidly (Figure 1e). As of 15 October the total number of hospital admissions with confirmed influenza A(H1N1)2009 (n=732) was just over 72% of the total for the same period in 2009 (n=1,011) while the number of ICU admissions was 87.4% of 2009 admissions (n=104 and 119). The ICUs did not report unusually high levels of bed occupancy during the 2010 influenza wave. The hospitalisation ratio in 2010 (number hospitalised per symptomatic infections) was 415.2 cases per 100,000. This

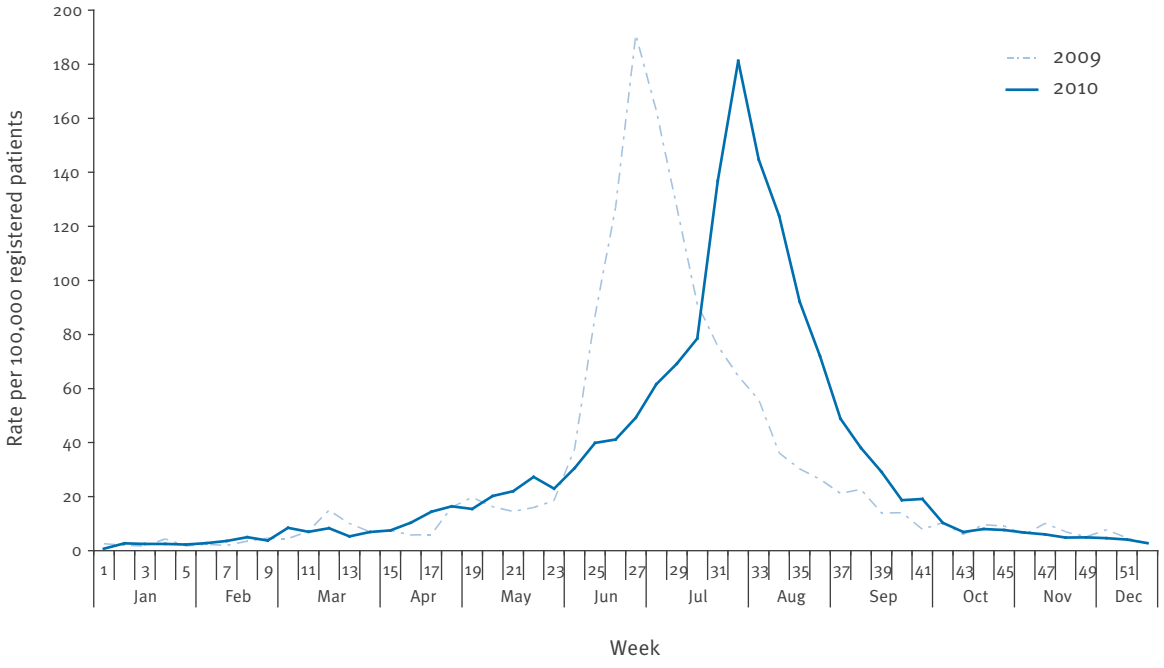
Figure 1

National influenza surveillance data, New Zealand, 2008–10

A. ILI consultation rates (ESR) 2008-10

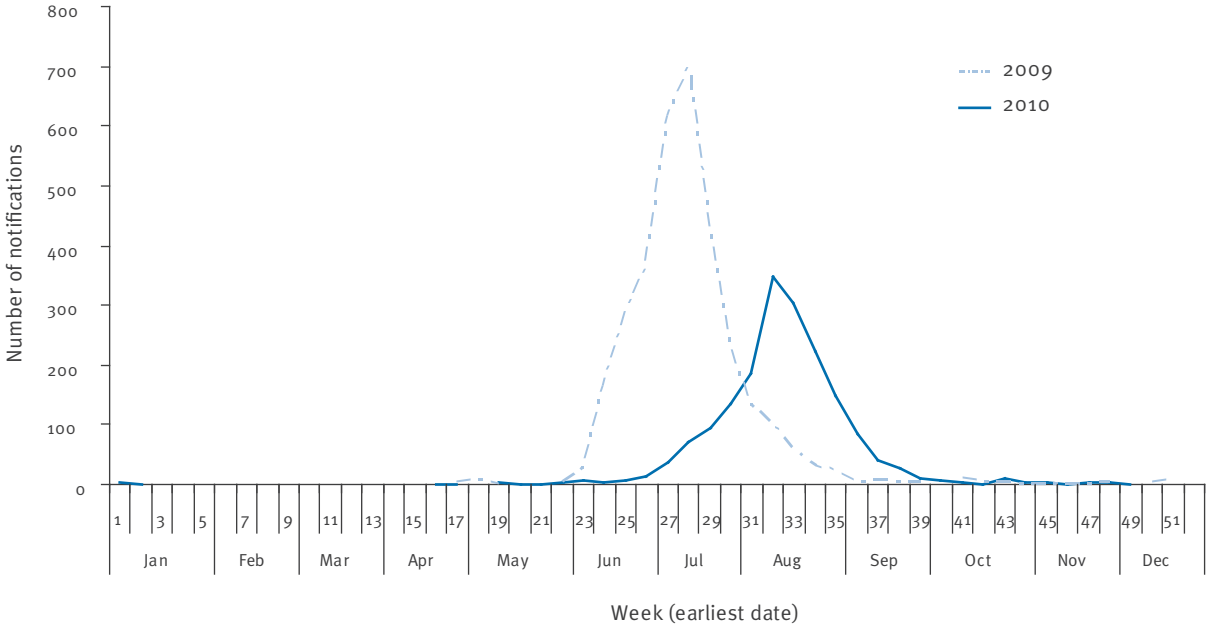


B. ILI consultation rates (Healthstat) 2008-10

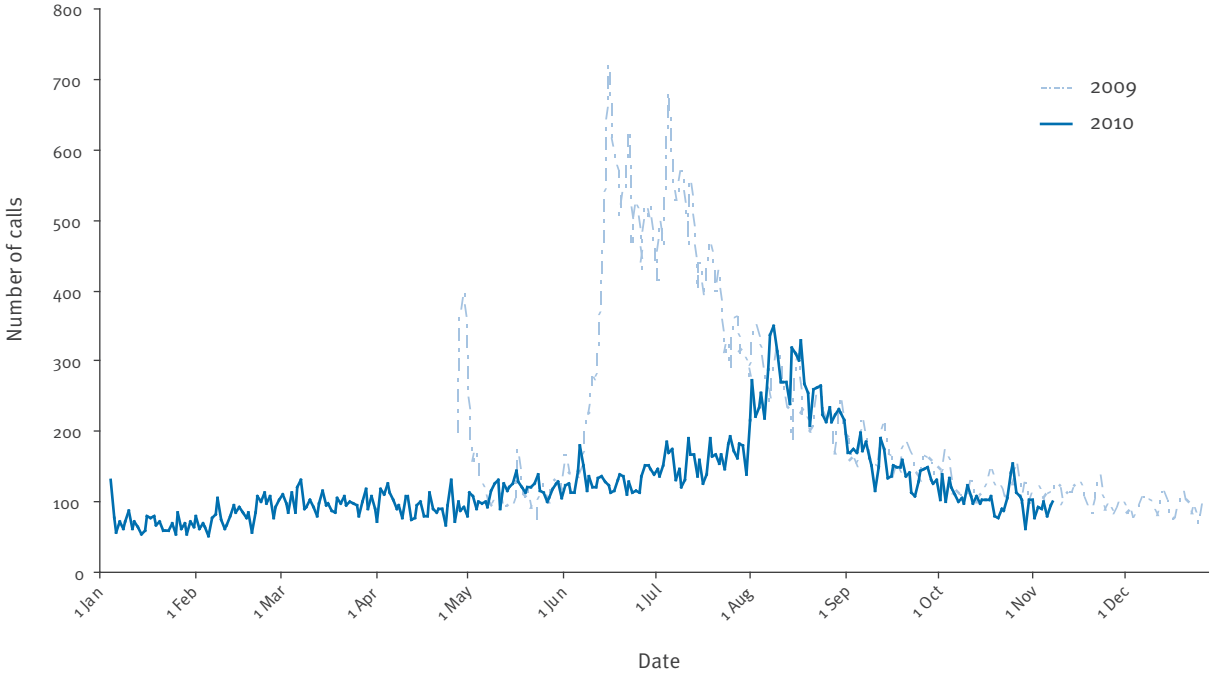


Data source: From responding practices of Original HealthStat GP practice panel.

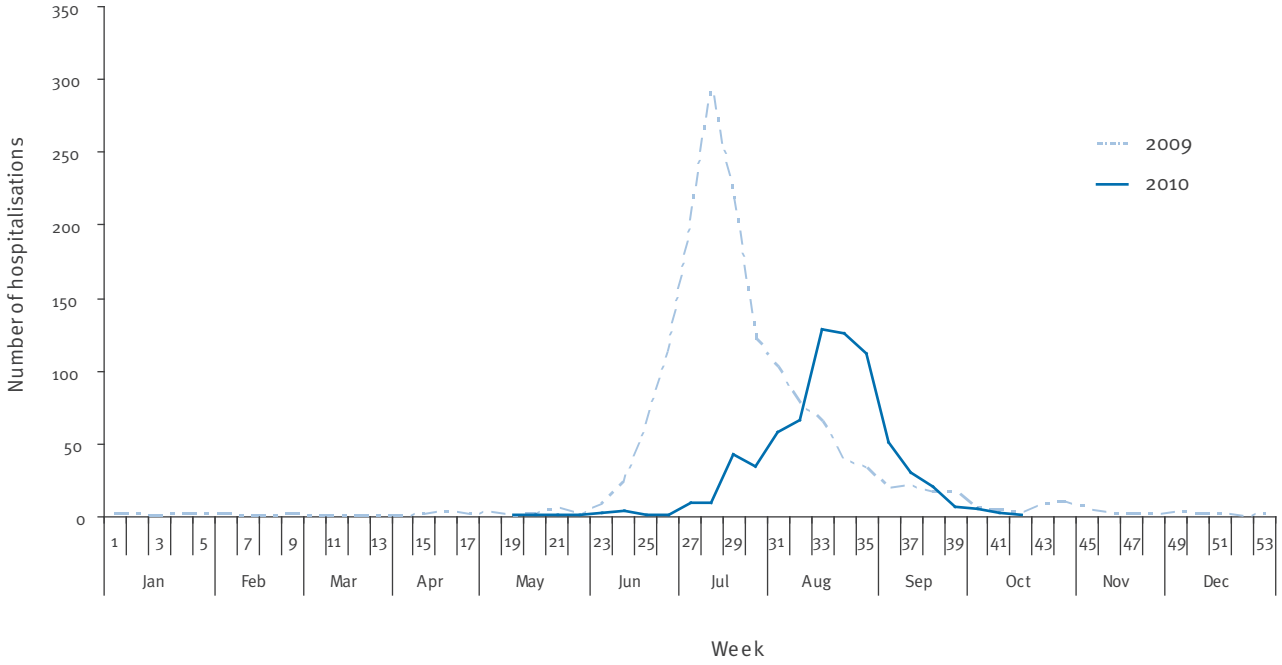
C. Influenza A(H1N1)2009 notifications 2009–10



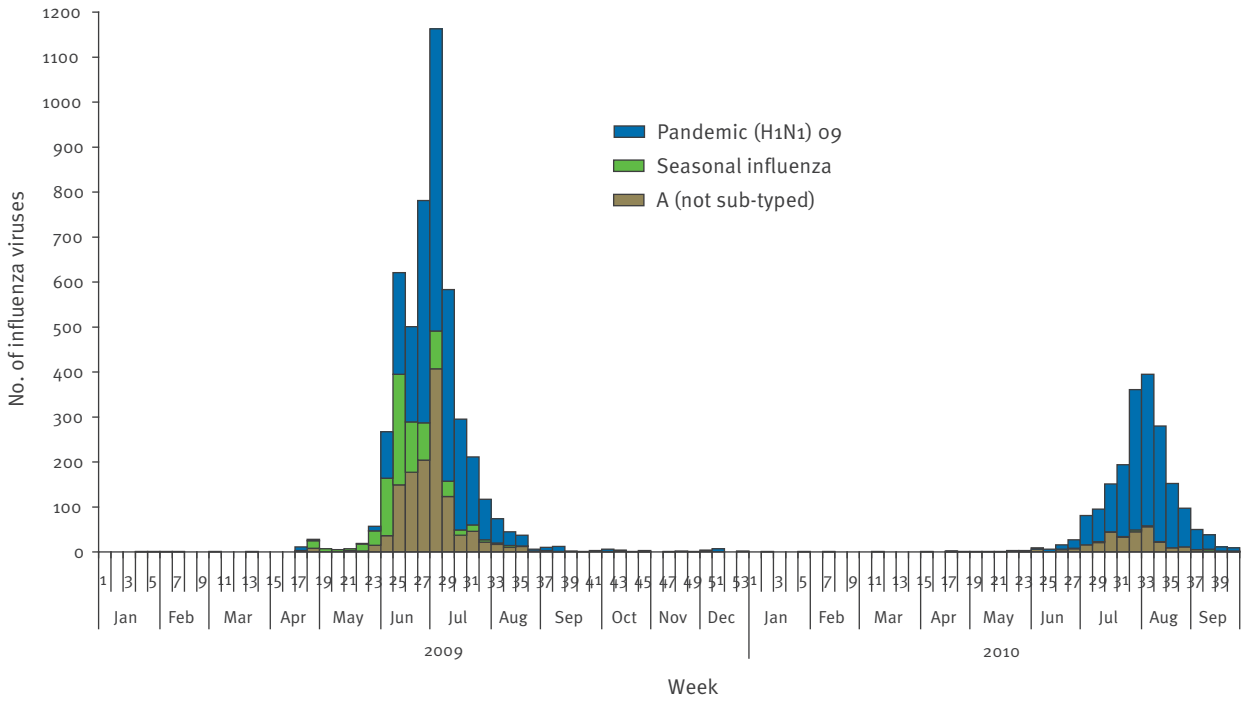
D. Healthline ILI calls, 2009–10



E. Hospitalisations 2009–10



F. Virological surveillance 2009–10



2010 data only up to week 39 (sentinel surveillance only).

ESR: Institute of Environmental Science and Research; ILI: influenza-like illness.

Table 1

Cumulative incidence of influenza-like illness and influenza A(H1N1)2009 cases, and viruses, New Zealand, 2009–10 (mid-October)

Surveillance system	Event	Cumulative incidence per 100,000 (number of cases)	
		2009	2010
Sentinel GP (ESR)[a]	ILI case	2,695.6	1,019.9
Sentinel GP (Healthstat)[a]	ILI case	462.9	521.9
Healthline	ILI call	987.9	820.4
Notifications[b]	Influenza A(H1N1)2009 case	74.5 (3,214)	40.4 (1,768)
Hospitalisations (notification data)[b]	Influenza A(H1N1)2009 case hospitalised	23.5 (1,016)	16.7 (732)[c]
Hospitalisations (NMDS)	Influenza A(H1N1)2009 case	26.0 (1,122)	16.4 (717)
ICU admission	Influenza A(H1N1)2009 case	2.8 (119)	2.4 (104)
Deaths (mortality reporting system)	Influenza A(H1N1)2009 case	1.1 (48)	0.34 (15)
Surveillance system	**Virus type**	**Percentage of total influenza viruses (number of viruses)**	
Virological surveillance – influenza A(H1N1)2009[d]	Influenza A(H1N1)2009 virus	63.6% (395)	75.9% (274)
Virological surveillance – seasonal influenza (A and B)[d]	A(H1N1) virus	15.8% (98)	0% (0)
	A(H3N2) virus	7.6% (47)	0.8% (3)
	B virus	0.5% (3)	0.3% (1)

ESR: Institute of Environmental Science and Research; GP: general practitioner; ICU: intensive care unit; ILI: influenza-like illness; NMDS: National Minimum Data Set.

[a] Data for surveillance week ending 6 May to week ending 30 September.

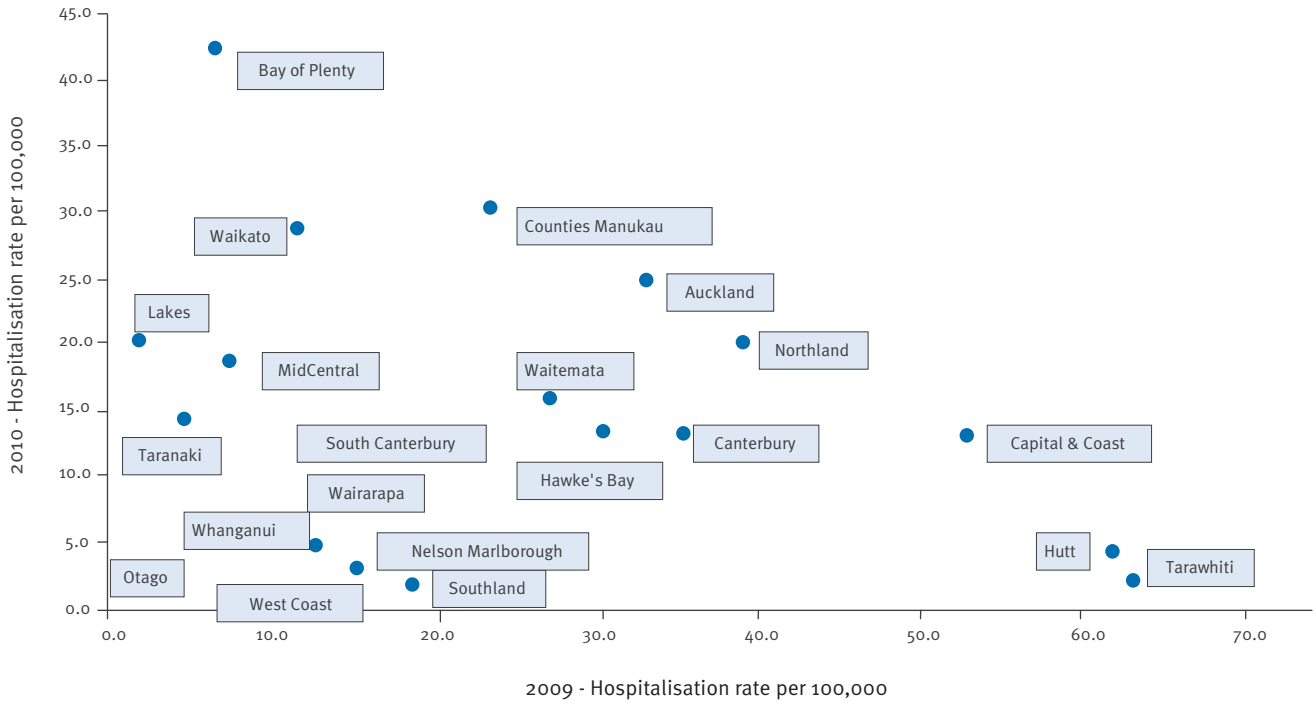
[b] Notified to Episurv for 2010 up to 15 October 2010.

[c] 65 hospitalised of 97 cases in pregnant women.

[d] The percentages represent proportions of the total number of viruses identified. These figures are ESR sentinel data, and do not include non-sentinel sources.

Figure 2

Laboratory-confirmed pandemic influenza A(H1N1)2009 hospitalisation rates per 100,000 by District Health Board of domicile, New Zealand, 2009 versus 2010[a]



[a] The full year 2009 (first pandemic wave) is compared with 2010 until 14 October (second pandemic wave).

was much higher than the ratio of 287 per 100,000 in 2009. Using total hospitalisations as the denominator from the NMDS, the ICU ratios in 2010 and 2009 were 14.5% and 10.6%, respectively, of all hospitalisations.

Deaths

From 1 January to 15 October 2010, 20 deaths were reported as *linked to* pandemic influenza A(H1N1)2009 [8]. Fifteen of these deaths have so far been confirmed as being *due to* influenza A(H1N1)2009. Most deaths occurred in the age group 20 years and older. The 15 confirmed deaths due to influenza A(H1N1)2009 in 2010 give a case fatality ratio of 8.5 per 100,000 (15 of 176,308). This is similar to the one calculated for 2009: 9.0 per 100,000. The median age of the fatal cases was 50 years in 2010 and 40 years in 2009.

Virological surveillance

Results of virological surveillance using samples from sentinel GPs and hospitals for 2010 and 2009 are shown in Figure 1e. As of the week ending 3 October 2010, pandemic influenza A(H1N1)2009 was the predominant strain (84.5%, 1,684 of 1,992) including 392 pandemic influenza A/California/7/2009(H1N1)-like strains, followed by not subtyped influenza A (n=290), influenza B (n=9) including four B/Brisbane/60/2008-like strains, and seasonal influenza A(H3N2) (n=9) including two A/Perth/16/2009 (H3N2)-like strains. No non-pandemic influenza A(H1N1) virus has been isolated in 2010, in contrast to 2009 when it was the dominant virus before influenza A(H1N1)2009 became established.

Most of the New Zealand isolates were antigenically and genetically closely related to the pandemic influenza A(H1N1)2009 vaccine candidate A/California/7/2009–like strain. In addition, 280 influenza A(H1N1)2009 isolates were subjected to the fluorometric neuraminidase inhibition assay and the results showed that they were all sensitive to oseltamivir.

Cumulative incidence of influenza A(H1N1)2009

Table 1 reports the cumulative incidence of ILI and influenza A(H1N1)2009 cases for 2010
up to the end of October and compares this with the total year 2009. Both periods cover the complete pandemic waves. The data show that the proportion of hospitalised cases admitted to ICUs has been higher in 2010 (14.5%) compared with 2009 (10.6%).

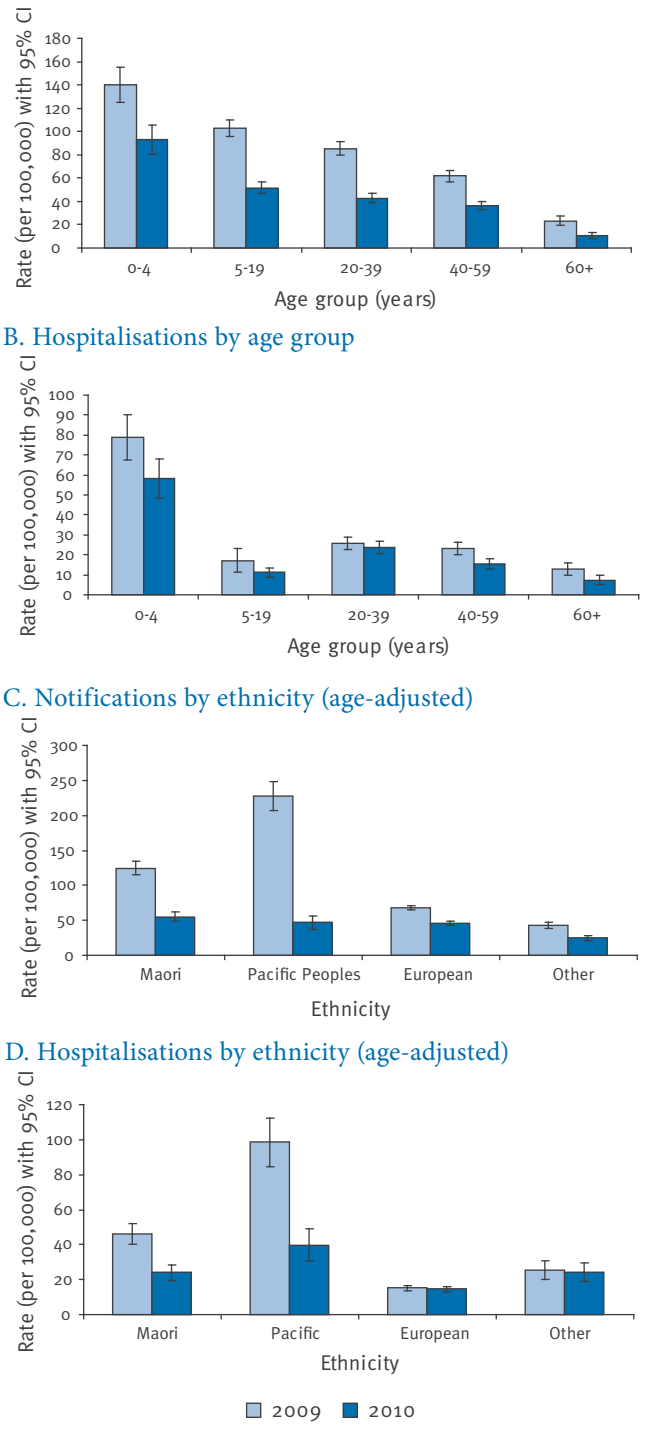
Regional patterns

We observed heterogeneous distribution of pandemic influenza A(H1N1)2009 among different geographical locations in New Zealand. In particular, some regions (mainly small urban and rural areas) that had relatively low ILI activity in 2009 experienced higher levels of activity during the second wave in 2010. For example, eight of the 20 District Health Boards (DHBs) reported weekly GP ILI consultation rates higher than those seen last year: Waikato, Bay of Plenty, Tairawhiti, Taranaki, Hawke's Bay, Wairarapa, West Coast and South Canterbury. Six DHBs hospitalised more cases with pandemic influenza A(H1N1)2009 this year than for the whole of the 2009 year: Counties Manukau, Waikato, MidCentral, Bay of Plenty, Taranaki and Lakes.

Figure 2 compares the DHBs' hospitalisation rates in 2010 with such rates in 2009. The scattergram gives

Figure 3

Notification and hospitalisation rates for influenza A(H1N1) by age group (A,B) and ethnicity (C,D), stratified by year, New Zealand, 2009 and 2010



CI: confidence interval.

a correlation coefficient of –0.20 indicating that in general DHB's with high rates in 2009 had low rates in 2010 and vice versa. The scattergram is included as a descriptive qualitative visual display only, with confidence intervals for each point not shown.

Notification and hospitalisation rates by age and ethnicity

Based on Episurv data, the age distribution of notifications and hospitalisations for influenza A(H1N1) infections in 2010 was very similar to 2009 (Figure 3). As in 2009, the highest cumulative rates of notification and hospitalisation were in children under five years of age (92.9 and 58.2 cases per 100,000 population respectively). The overall hospitalisation rates were about a third lower in 2010 compared with 2009. The overall notification rate in 2010 was just over half of the 2009 rate. Notification and hospitalisation rates declined from 2009 to 2010 in all age groups, with relatively greater reductions in the age group of 0-19 year-olds.

The ethnicity distribution of notifications and hospitalisations due to influenza A(H1N1)2009 infection in 2010 was markedly different from the one in 2009. Although highest rates in both years were seen in Pacific and Māori populations, their rates dropped relative to the groups European and Other (Figure 3). In comparison to the European ethnic group, the rate ratio for Pacific Peoples in 2010 was 1.6 (95% confidence interval (CI): 1.3–1.9) for hospitalisation and 1.0 (95% CI: 0.8–1.2) for notification. This is much lower than the hospitalisation rate ratio of 4.6 (95% CI: 4.2–5.1) and notification rate ratio of 3.4 (95% CI: 3.0–3.7) in 2009. The Māori hospitalisation rate ratio of 1.8 (95% CI: 1.6–2.0) and notification rate ratio of 1.2 (95% CI: 1.1–1.4) in 2010 showed a lesser reduction compared with those of 2.5 (95% CI: 2.3–2.7) and 1.8 (95% CI: 1.7–2.0) in 2009, respectively.

Immunisation coverage and immunity

Data are based on the results of the influenza A(H1N1)2009 seroprevalence study conducted in 2009–10 [6] and claims received by the Ministry of Health from GPs for immunisations given on the subsidised programme. These are likely to be underestimates as the number of claims yet to be received and the number of people who purchased the vaccine privately is unknown.

A minimum of 1,046,000 doses of the seasonal trivalent influenza vaccine were distributed in New Zealand in the 2010 season. Over 624,000 claims have been received up to end of October 2010 for the subsidised programme. In that year a considerable number of doses must have been purchased privately to explain that stocks were exhausted and had to be replenished. Table 2 shows numbers of persons with estimated levels of immunity and immunisation for five age groups.

Discussion

Impact of the 2010 influenza pandemic

The second year of pandemic influenza A(H1N1)2009 in New Zealand produced an epidemic curve similar in shape to the first wave, of about half to two thirds the size, and starting one month later in the winter. Multiple surveillance systems showed that the influenza A(H1N1)2009 incidence increased markedly in July 2010, peaked in mid-August and then declined. The national influenza wave lasted 15 weeks in 2009 as well as in 2010. It comprised multiple waves of activity at the district level that had a duration of about five weeks.

The second year of pandemic influenza A(H1N1)2009 again showed marked geographic heterogeneity. There was a weak negative correlation of infection rates in 2010 relative to 2009. This finding supports the hypothesis that areas that were more affected in 2009 were protected to a certain extent in 2010. If this was not the case, we would expect (as we see for most diseases) that rates from one year to the next would be highly positively correlated because patterns of vulnerability tend to persist. Regional variations of influenza A(H1N1)2009 infections were also observed in 2009 in clinical surveillance as well as an influenza A(H1N1)2009 serosurvey [2,3,6]. It is possible that this variability allowed areas (mainly rural and small urban areas) with low pandemic influenza A(H1N1)2009 activity to maintain more susceptible populations and to

Table 2

Influenza immunity levels by age group, New Zealand, 2010

Age group (years)	Baseline immunity[a] n (% of population)	Immunity following 2009 H1N1[a] n (% of population)	Immunisation 2010 (pre-second wave)[b] n (% of population)	Total immunity 2010[c] (pre-second wave)[b] n (% of population)
1-4	18,303 (6.1%)	88,515 (29.5%)	30,023 (10.0%)	109,818 (36.6%)
5-19	127,665 (14.0%)	425,853 (46.7%)	27,523 (3.0%)	440,443 (48.3%)
20-39	86,485 (7.5%)	255,995 (22.2%)	44,089 (3.8%)	290,589 (25.2%)
40-59	75,026 (6.5%)	233,159 (20.2%)	105,968 (9.2%)	317,419 (27.5%)
60+	169,401 (22.6%)	185,891 (24.8%)	416,832 (55.6%)	499,207 (66.6%)

[a] Seroprevalence study.

[b] Immunisation claims 2010.

[c] Estimated total immunity assuming vaccination independently distributed in age group.

sustain more influenza A(H1N1)2009 infections and transmission in 2010 than in 2009.

While the hospitalisation rates for influenza in 2010 (16.7 per 100,000) were lower than in 2009 (23.5 per 100,000), the proportion of hospitalised influenza cases was higher in 2010 than in 2009. In addition, the proportion of hospitalised cases admitted to ICUs was higher in 2010. The reasons for these differences are not clear. There has been no obvious change in the severity of pandemic influenza A(H1N1)2009 disease or the thresholds for hospital and ICU admission. However, there was less pressure on hospital and ICU bed availability this year. It is also possible that there was a greater awareness of pandemic influenza A(H1N1)2009 as a contributing factor to severe respiratory disease, and therefore higher likelihood of laboratory testing, hospitalisation and ICU admission.

The age distribution of influenza A(H1N1)2009 infections in 2010 was broadly similar to 2009 with highest rates in children under the age of five years. Hospitalisation rates declined significantly for most age groups, except for the 20-39-year-olds. This decline was particularly marked for children of 5-19 years although notification rates were still higher in children aged 5 19 years. This probably reflected a feature of the 2009 pandemic which caused relatively mild disease in children aged 5-19 years. By contrast, the ethnicity distribution of influenza A(H1N1) infections in 2010 changed markedly compared with 2009. Rates for Pacific and Māori populations remained significantly higher than for the groups European and Other, but the disparity was far less pronounced. These changes in the age and ethnicity distribution of the disease may reflect immunity from a combination of sources, including immunisation and natural infection (see impact of interventions below).

Reasons for ethnic differences in hospitalisation may include a higher incidence of infection in Pacific and Māori peoples, a higher prevalence of co-morbidities (such as asthma and diabetes), unfavourable environmental factors (such as household crowding and poor quality housing), behavioural differences in responding to influenza, differences in socio-cultural-economic status, differences in health service utilisation and increased genetic susceptibility [12]. Further study on the contributing factors to ethnic differences in the risk of influenza A(H1N1)2009 infection and severe disease is underway in New Zealand.

New Zealand experience compared with other southern hemisphere countries

When the experience with the 2010 winter influenza season in New Zealand was compared to other temperate southern hemisphere countries such as Australia, South Africa and South America, they shared the common features that the influenza season started later and overall influenza activity was lower in 2010 than in 2009, with regional variation observed [13].

Most of the New Zealand isolates were antigenically and genetically closely related to the pandemic influenza A(H1N1)2009 vaccine candidate A/California/7/2009–like strain. However, a genetic variant with the dual haemagglutinin mutations E391K and N142D emerged in Singapore in early 2010 and has subsequently spread through Australia and New Zealand in the 2010 winter period [11]. As of mid-October 2010, it appears that this genetic variant has not resulted in significant antigenic changes that would make the current vaccine less effective.

The pandemic influenza A(H1N1)2009 strain predominated with some seasonal influenza A(H3N2) and B viruses in New Zealand and Australia. In Chile, the most frequently detected virus has been seasonal influenza A(H3N2) and in South Africa influenza B.

Impact of interventions

Community-based interventions to reduce the impact of pandemic influenza A(H1N1)2009 included immunisation and continuing promotion of respiratory and hand hygiene. Parallel interventions included the provision of free antiviral drugs as well as asking sick persons to stay away from school or work and seek early medical advice. Uptake of the seasonal vaccine in 2010 was higher than in previous years although the proportions estimated to have been immunised remain low at around 24%. The age distribution of influenza A(H1N1)2009 in 2010 was consistent with estimated patterns of immunity in the population with higher disease rates in 20-39-year-old adults corresponding to their relatively low levels of immunity [14]. High levels of immunisation of those aged 60 years and older probably contributed to the large decline in disease rates in this age group in 2010 relative to their already low risk in 2009 [14]. The overall impact of these interventions requires further evaluation.

Implications for northern hemisphere

Many of the lessons from the first pandemic wave in the southern hemisphere in 2009 still apply[14] . While careful monitoring is required for emerging new antigenic variants the current circulating virus is now a familiar virus and we also have the benefits of an effective vaccine. The description of the second wave of the pandemic in New Zealand, a temperate southern hemisphere country, has some implications for the influenza season in the northern hemisphere. Although the second wave affected smaller numbers in New Zealand overall, it had a higher impact in some regions and populations with less immunity (from the first wave). Vulnerable populations continue to include indigenous people, the young, pregnant woman, and those with serious chronic health conditions [14]. There was no indication of a change in virulence of the virus.

The New Zealand experience also raises the question as to whether the phenomena we have seen with this virus in 2010 are best described as the second wave of a pandemic or the first year of a new seasonal

influenza virus. In past pandemics (certainly in 1918), the second and subsequent waves of infection were often characterised as out of season and with markedly higher virulence compared with seasonal viruses [15] The pandemic influenza A(H1N1)2009 virus has not shown those pandemic features in 2010. It appears to have completely displaced seasonal influenza A(H1N1) virus in 2010 in New Zealand.

Strengths and limitations of New Zealand surveillance data

The influenza surveillance systems in New Zealand provide information on disease, hazards, determinants and interventions related to this infectious agent [16] Several of these systems have been particularly effective at providing strategy-focused information to characterise the pandemic, notably GP sentinel surveillance (which includes virological surveillance), hospitalisation data, and the national serological survey. A full investigation is still needed to assess the overall adequacy of influenza surveillance in New Zealand, particularly control-focussed surveillance aimed at supporting the containment phase of pandemic management, but overall the systems stood up well to the challenges posed by the pandemic.

Acknowledgements

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Effectiveness of trivalent seasonal and monovalent influenza A(H1N1)2009 vaccines in population with major chronic conditions of Navarre, Spain: 2010/11 mid-season analysis

J Castilla (jcastilc@navarra.es)[1,2], J Morán[3], V Martínez-Artola[4], G Reina[5], I Martínez-Baz[1,2], M García Cenoz[1,2], N Alvarez[6], F Irisarri[1,2], M Arriazu[1,2], F Elía[3], E Salcedo[4]

1. Instituto de Salud Pública de Navarra (Public Health Institute of Navarre), Pamplona, Spain
2. CIBER de Epidemiología y Salud Pública (Biomedical Research Network of Epidemiology and Public Health)
3. Dirección de Atención Primaria, Servicio Navarro de Salud (Primary Health Care Department), Pamplona, Spain
4. Complejo Hospitalario de Navarra (Navarre Hospital Complex), Pamplona, Spain
5. Clínica Universidad de Navarra (University Clinic of Navarra), Pamplona, Spain
6. Servicio Navarro de Salud (Navarre Health Service), Pamplona, Spain

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We defined a cohort of people with major chronic conditions (152,585 subjects) in Navarre, Spain, using electronic records from physicians, to obtain 2010/11 mid-season estimates of influenza vaccine effectiveness. The adjusted estimates of the effectiveness of the 2010/11 trivalent influenza vaccine were 31% (95% confidence interval (CI): 20–40%) in preventing medically attended influenza-like illness, and 58% (95% CI: 11–80%) in preventing laboratory-confirmed influenza. Having received the monovalent influenza A(H1N1)2009 vaccine in the 2009/10 season had an independent preventive effect against medically attended influenza-like illness (17%, 95% CI: 1–30%), and having received both vaccines had 68% (95% CI: 23–87%) effectiveness in preventing laboratory-confirmed influenza.

Introduction

Because the influenza vaccine composition is adapted every season to the circulating viruses, its effectiveness varies. Estimates of the effectiveness of the vaccine during the influenza season help guiding health interventions aimed at reducing the impact of influenza in the population [1]. In the absence of randomised trials evaluating the efficacy of this vaccine, observational studies are of interest to verify if the expected effect has been achieved [1-3]. A multi-centre European study (I-MOVE: Influenza Monitoring Vaccine Effectiveness in Europe) was launched in 2008, including cohort and case-control studies in several settings. As part of this project, a cohort study is being conducted in Navarre, Spain [1].

During the early 2010/11 season, the influenza A(H1N1)2009 virus was the predominant circulating influenza virus [4]. It is therefore expected that both the trivalent 2010/11 seasonal vaccine, which includes this virus, [5] and the monovalent influenza A(H1N1)2009 vaccine [6] may provide some protection. Several studies have reported high effectiveness of the monovalent pandemic vaccine in preventing influenza A(H1N1)2009 during the 2009/10 season [7-11]. The aim of this study was to provide early estimates of the effectiveness of the 2010/11 seasonal vaccine and the influenza A(H1N1)2009 vaccine administered during the 2009/10 season in preventing medically attended influenza-like illness (MA-ILI) and laboratory-confirmed influenza during the 2010/11 season. The study was restricted to the population with major chronic conditions, since vaccination with both influenza vaccines was recommended for this group.

Methods

Study population and data collection

We conducted a prospective cohort study based on electronic records of physicians and laboratories and a nested case–control analysis of swabbed patients in the region of Navarre, Spain. This cohort included all non-institutionalised persons covered by the Regional Health Service (95% of the population of the region) with known pre-existing major chronic conditions (heart disease, lung disease, renal disease, cancer, diabetes, cirrhosis, dementia, stroke, immunodeficiency and body mass index of 40 or greater). The Navarre Ethical Committee for Medical Research approved the study protocol. The present study analysed the cases registered from 24 October 2010 (first week in which influenza virus was detected in the region) to 22 January 2011.

The seasonal influenza vaccination campaign took place from 11 October to 26 November 2010, although

a very small number of doses were still administered after that period. The trivalent inactivated non-adjuvanted vaccine (Sanofi Pasteur MSD) was used for all subjects. Monovalent influenza A(H1N1)2009 vaccine had been administered exclusively from November 2009 to January 2010, using the MF59-adjuvanted vaccine from Novartis (Focetria) for children up to the age of 17 years and for adults aged 60 years and older, the AS03-adjuvanted vaccine from GlaxoSmithKline (Pandemrix) in adults between 18 and 59 years of age, and the non-adjuvanted vaccine from Sanofi Pasteur (Panenza) for pregnant women. All these vaccines were offered free of charge to individuals with major chronic conditions and other populations with specific indications. Precise instructions for registering each dose were given to all vaccination points. For the present study, influenza vaccine status was obtained from the online regional vaccination register that is updated by the healthcare centres of the Regional Health Service. Subjects were considered to be protected 14 days after vaccine administration.

Influenza surveillance is based on automatic reporting of cases from all primary healthcare centres. Cases of MA-ILI are defined according to the International Classification of Primary Care version 2 (code R80) [12]. Two laboratories perform influenza testing in the region and provided the data for virological surveillance. All hospitalised patients with ILI or other acute respiratory diseases were swabbed for influenza virus testing. In addition, through a sentinel network composed of a representative sample of primary healthcare physicians covering 16% of the population, nasopharyngeal and pharyngeal swabs were taken from all patients

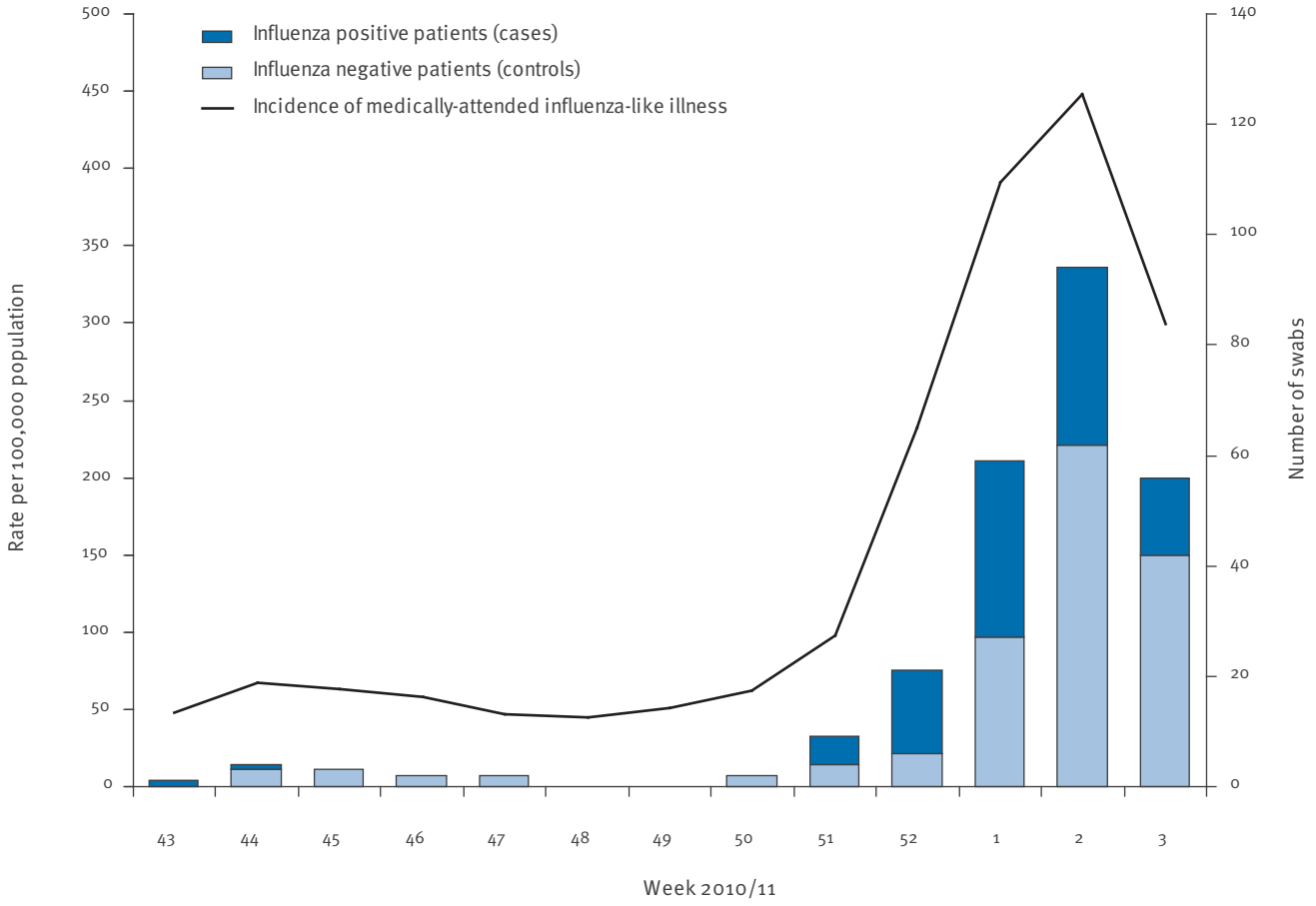
Table 1

Population with major chronic conditions included in the cohort study and vaccine coverage by age group, Navarre, Spain, 2010/11 (n=152,585)

Age group	Population (number)	Seasonal vaccine 2010/11 coverage (%)	Pandemic vaccine in 2009/10 coverage (%)	Both vaccines coverage (%)
1 to 59 years	81,407	11.3	7.7	4.2
≥ 60 years	71,178	60.0	26.2	22.5
Total	**152,585**	**34.0**	**16.4**	**12.7**

Figure 1

Weekly incidence of medically attended influenza-like illness and swabbed patients (n=253) according to influenza virus test result in the population with major chronic conditions, Navarre, Spain, 24 October 2010–22 January 2011



with MA-ILI, after obtaining verbal informed consent. Swabs were processed by RT-PCR assay and virus culture. Positive samples were characterised as influenza A (H1 and H3) and B virus using immunofluorescence and RT-PCR. Real-time RT-PCR for detection of the influenza A(H1N1)2009 virus was performed for all swabs.

From the electronic primary healthcare records we obtained the following baseline variables: sex, age, migrant status, district of residence, major chronic conditions, number of outpatient visits during the previous 12 months, and children in the household.

Study design and statistical analysis

In the cohort analysis, the incidence rates of MA-ILI in primary health care were compared in vaccinated and unvaccinated persons. Cox regression models were used to obtain MA-ILI-adjusted hazard ratios (HRs) for influenza vaccination status. Calendar time was used as the underlying time variable, with exit time as the

Table 2

Estimates of the effect of the 2010/11 seasonal influenza vaccine and influenza A(H1N1)2009 vaccine in preventing medically diagnosed influenza-like illness in the population with major chronic conditions, Navarre, Spain, 24 October 2010–22 January 2011 (n=152,585)

	Person-years	Cases	Crude hazard ratio (95% CI)[a]	Adjusted hazard ratio (95% CI)[b]
Analysis 1				
Seasonal vaccine 2010/11				
Yes	10,828	296	0.36 (0.32-0.42)	0.69 (0.60-0.80)
No	26,569	1,736	Reference	Reference
Pandemic vaccine 2009/10				
Yes	6,102	172	0.78 (0.66-0.92)	0.83 (0.70-0.99)
No	31,295	1,860	Reference	Reference
Analysis 2				
Seasonal and pandemic vaccines	4,108	100	0.30 (0.25-0.37)	0.59 (0.47-0.73)
Only seasonal vaccine 2010/11	6,720	196	0.35 (0.30-0.41)	0.69 (0.58-0.81)
Only pandemic vaccine 2009/10	1,994	72	0.72 (0.57-0.91)	0.81 (0.64-1.03)
Unvaccinated	24,575	1,664	Reference	Reference

CI: confidence interval.

[a] Cox regression model including vaccination status for 2010/11 seasonal and pandemic influenza A(H1N1)2009 vaccines.

[b] Cox regression model adjusted for sex, age group, major chronic conditions, outpatient visits during baseline period (tertiles within each age stratum), urban/rural residence, migrant status and children in the household, and stratified by age (1-14; 15-59; ≥60 years) and health district.

Table 3

Estimates of the effect of the 2010/11 seasonal influenza vaccine and influenza A(H1N1)2009 vaccine in preventing laboratory-confirmed influenza in the population with major chronic conditions, Navarre, Spain, 24 October 2010–22 January 2011 (n=253)

	Cases/controls	Crude odds ratio (95% CI)[a]	Adjusted odds ratio (95% CI)[b]
Analysis 1			
Seasonal vaccine 2010/11			
Yes	22 / 78	0.32 (0.17-0.60)	0.42 (0.20-0.89)
No	78 / 75	Reference	Reference
Pandemic vaccine 2009/10			
Yes	16 / 51	0.69 (0.33-1.41)	0.78 (0.35-1.73)
No	84 / 102	Reference	Reference
Analysis 2			
Seasonal and pandemic vaccines	10 / 43	0.22 (0.10-0.47)	0.32 (0.13-0.77)
Only seasonal vaccine 2010/11	12 / 35	0.32 (0.15-0.67)	0.45 (0.19-1.03)
Only pandemic vaccine 2009/10	6 / 8	0.70 (0.23-2.12)	0.88 (0.25-3.18)
Unvaccinated	72 / 67	Reference	Reference

CI: confidence interval.

[a] Logistic regression model including 2010/11 seasonal and pamdemic influenza A(H1N1)2009 vaccination status.

[b] Logistic regression analysis adjusted for sex, age (1-14; 15-59; ≥60 years), children in the household, urban/rural residence, healthcare setting (primary healthcare, emergency room, hospitalisation) and date (Week 43–49 2010; Week 50 2010–Week 1 2011; Week 2–3 2011).

date of MA-ILI diagnosis, death, or 22 January 2011 (end of this mid-season analysis), whichever came first. Vaccination status for the 2010/11 seasonal trivalent inactivated vaccine was included in the analyses as a time-dependent variable. The models were stratified by health district and age (1-14, 15-59, ≥60 years) because patients younger than 15 years are cared for by paediatricians and the vaccine coverage is higher among those aged 60 or older. Other potential confounders were adjusted for in the models, with age in intervals of 10 years and the number of outpatient visits categorised in tertiles within each age stratum.

From the cohort population, all outpatients and hospitalised patients who were swabbed during the study period were included in a case–control analysis that compared seasonal vaccination status in patients in whom any influenza virus was detected (cases) and those who were negative for influenza (controls). Crude and adjusted estimators of the effect were quantified by odds ratios (ORs) with their 95% confidence intervals (CI), calculated using logistic regression models.

The effects of the seasonal vaccine and the pandemic influenza A(H1N1)2009 vaccine were evaluated as independent variables in one model, and as a combined variable (unvaccinated, only seasonal vaccine, only pandemic vaccine, or both vaccines) in a different model. Vaccine effectiveness was estimated as a percentage: (1–HR)×100 or (1–OR)×100.

Results

Vaccine effectiveness in preventing medically attended influenza-like illness

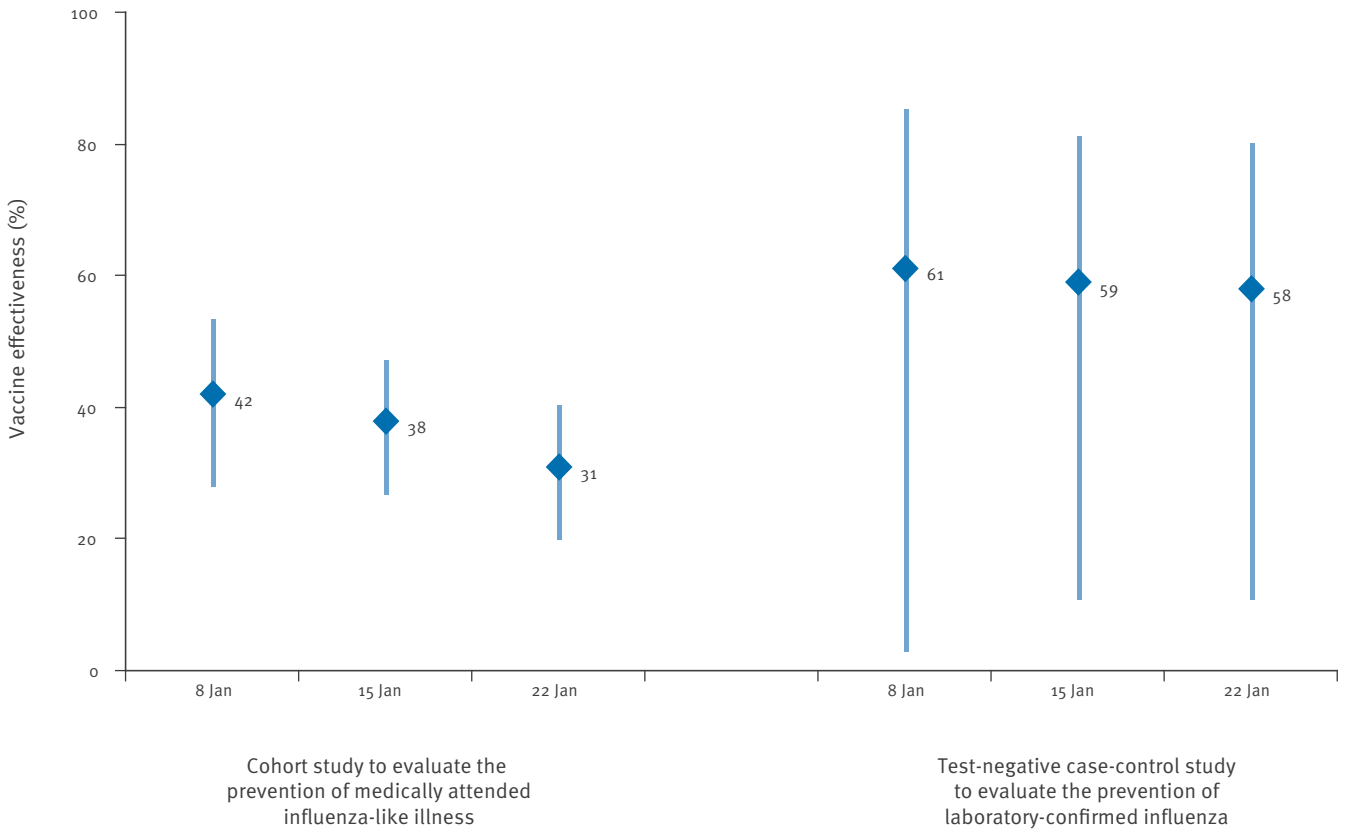
A total of 152,585 persons had major chronic conditions registered at baseline and were included in the cohort study, with 46.6% aged 60 years old or older. The seasonal influenza vaccine coverage for 2010/11 was 34.0%, and 16.4% had received the influenza A(H1N1)2009 pandemic vaccine in 2009/10 (Table 1).

From week 43 of 2010 (first influenza virus detection in the season) to week 3 of 2011, 2,032 cases of MA-ILI were diagnosed among the 152,585 cohort subjects in primary care centres, with the highest incidence in week 2 of 2011 (Figure 1). Eighty-nine of these patients were swabbed by sentinel physicians, and 51 (57%) of them were found positive for influenza virus.

The incidence rate was 27 per 1,000 vaccinated person-years with the seasonal vaccine as opposed to 65 per 1,000 unvaccinated person-years ($p<0.001$). In the adjusted Cox regression model the seasonal vaccine effectiveness against MA-ILI was 31% (HR=0.69; 95% CI: 0.60–0.80), and the effectiveness of the monovalent pandemic vaccine was 17% (HR=0.83; 95% CI:

Figure 2

Effectiveness of the 2010/11 seasonal influenza vaccine in preventing medically attended influenza-like illness and laboratory-confirmed influenza in the population with major chronic conditions, Navarre, Spain[a]



[a] Preliminary estimates obtained for the periods from 24 October 2010 to 8, 15 and 22 January 2011, respectively.

0.70–0.99). As compared with unvaccinated individuals, having received both vaccines provided a 41% reduction in the incidence of MA-ILI (HR=0.59; 95% CI: 0.47–0.73) (Table 2).

Vaccine effectiveness in preventing laboratory-confirmed influenza

During the study period swabs were analysed from 253 cohort patients who had MA-ILI (n=89) or were treated in hospitals for acute respiratory infection (n=164), and had major chronic conditions (Figure 1). A total of 100 cases (39.5%) were confirmed for influenza: 97 were positive for the influenza A(H1N1)2009 virus, one for influenza A(H3N2) and two for influenza B. There were 22 laboratory-confirmed cases in patients who had received the 2010/11 seasonal vaccine. Their mean age was 66 years (range: 52–84 years) and 10 of them had also been vaccinated with monovalent influenza A(H1N1)2009 vaccine. In the cases with vaccine failure the time from seasonal vaccination to diagnosis ranged 57 to 91 days. At baseline, 10 of these cases had lung diseases, nine had diabetes mellitus, seven had cardiovascular diseases, five had cancers, four had renal diseases and one had liver disease.

Compared with the influenza-negative controls, cases were less likely to have received the influenza seasonal vaccine (OR=0.32; 95% CI: 0.17–0.60). In the logistic regression analysis adjusting for sex, age (1-14; 15-59; ≥60 years), living with children, living in an urban/rural area, healthcare setting (primary healthcare, emergency room, hospitalisation) and date (Week 43–49 2010; Week 50 2010–Week 1 2011; Week 2–3 2011), seasonal influenza vaccination was associated with a 58% lower probability of a positive swab (OR=0.42; 95% CI: 0.20–0.89). The pandemic influenza vaccine showed a lower, not statistically significant, protective effect against laboratory-confirmed influenza (OR=0.78, 95% CI: 0.35–1.73). The interaction term between both vaccines was not significant (p=0.95). Compared with not being vaccinated, having received both vaccines provided 68% protection against laboratory-confirmed influenza (OR=0.32; 95% CI: 0.13–0.77) (Table 3).

Early estimates of influenza vaccine effectiveness

Effectiveness estimates made at the end of week 1 and 2 of 2011, when the numbers of influenza cases were still increasing, produced similar results (Figure 2). It is worth noticing the progressive decrease in the estimates of effectiveness in preventing MA-ILI, which coincides with a reduction in the percentage of swabs positive for influenza.

Discussion

The mid-season results of this study show a moderate protective effect of the 2010/11 seasonal influenza vaccine in preventing laboratory-confirmed influenza and MA-ILI during the 2010/11 seasonal period in a high-risk population. In these analyses, receipt of the monovalent influenza A(H1N1)2009 pandemic vaccine in the previous season also showed a small preventive effect. Influenza A(H1N1)2009 virus was found in 97% of the laboratory-confirmed influenza cases and was included in both vaccines, which is consistent with the observed protection. The greatest protective effect was seen in people who had received both vaccines, which could be interpreted as a dose-response effect. Similar findings have been reported in a mid-season analysis in the United Kingdom [13].

This moderate effect is in contrast with the more pronounced protection reported for the 2009/10 season [7-11]. In addition, we detected a number of vaccine failures in persons with laboratory-confirmed influenza. Unlike the pandemic vaccine administered in 2009/10, the 2010/11 seasonal vaccine used in Navarre was not adjuvanted and this could explain a slightly lower immune response. The antigenic drift of the circulating virus could produce a certain degree of mismatch with the vaccine virus, although virological surveillance does not support this so far [14]. Factors such as advanced age or some immunodepression may be more common among people with major chronic conditions, which would explain a poor response to the vaccine. The reduced effect of the monovalent pandemic vaccine in this season can be explained by the loss of immune response more than a year after its administration.

The results presented here are preliminary and may have limited statistical power for some analyses. Therefore the final results for the season may be different. Cohort studies can be affected by biases if those who are vaccinated tend to have poorer health status or if, on the contrary, they tend to take better care of their health than the unvaccinated [15-16], but our analyses were controlled for the most frequently recognised confounders [17]. All the analyses were restricted to the population with major chronic conditions in whom vaccination was indicated. Calendar time was used as the underlying time variable in the Cox regression analysis to control for its possible confounding effect. The case–control analysis only included laboratory-confirmed cases and compared them with controls recruited in the same healthcare settings before patient and physician knew the laboratory result, a fact that reduced selection bias.

The analyses of the vaccine effectiveness against two outcomes, in the same place and period, provide complementary information. The effectiveness of 58% in preventing laboratory-confirmed influenza can be considered the best estimate of the actual protective effect of the trivalent 2010/11 seasonal vaccine. The effectiveness of 31% in preventing primary care-attended ILI describes the effect as seen in the clinical practice, where only a part of MA-ILI are confirmed for influenza virus (57% in the study period). That the results obtained using two designs for two different outcomes were consistent reinforces their validity.

Differences between unadjusted and adjusted estimates were greater in the cohort analysis than in the case–control comparison. The test-negative case–control analysis provides a better comparability since cases and controls were recruited in the healthcare system under similar circumstances. However, the comparability in the population-based cohort analysis requires a good control of confounding factors.

Conclusion

Our study shows that it is feasible to provide early estimates of influenza vaccine effectiveness during the season from cohort studies based on healthcare databases. These results support a moderate protective effect of the 2010/11 seasonal vaccine and a low residual effect of last season's monovalent pandemic vaccine against influenza disease in the high-risk population in the 2010/11 season. These results highlight the importance of annual immunisation against influenza of high-risk populations and complementing it with other preventive initiatives such as promotion of basic hygiene measures and avoiding contact with influenza cases.

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Surveillance trends of the 2009 influenza A(H1N1) pandemic in Europe

A Amato-Gauci (andrew.amato@ecdc.europa.eu)[1], P Zucs[1], R Snacken[1], B Ciancio[1], V Lopez[1], E Broberg[1], P Penttinen[1], A Nicoll[1], on behalf of the European Influenza Surveillance Network (EISN)[2]
1. European Centre for Disease Prevention and Control, Stockholm, Sweden
2. The members of the network are listed at the end of the article

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We describe the epidemiology and virology of the official length of the 2009 pandemic (68 weeks from April 2009 to August 2010) in the 27 European Union Member States plus Norway and Iceland. The main trends are derived from published literature as well as the analysis and interpretation of data provided to the European Centre for Disease Prevention and Control (ECDC) through the European Influenza Surveillance Network (EISN) and data collected by the ECDC itself. The 2009 influenza A(H1N1) pandemic started in Europe around week 16 of 2009 (although the World Health Organization (WHO) declared only in week 18). It progressed into an initial spring/summer wave of transmission that occurred in most countries, but was striking only in a few, notably the United Kingdom. During the summer, transmission briefly subsided but then escalated again in early autumn, just after the re-opening of the schools. This wave affected all countries, and was brief but intense in most, lasting about 14 weeks. It was accompanied by a similar but slightly delayed wave of hospitalisations and deaths. By the time the WHO declared the pandemic officially over in August 2010 (week 32), Europe had experienced transmission at low level for about 34 weeks.

Objectives

This review article provides a broad epidemiological overview of the entire official period of 68 weeks of the 2009 pandemic, from week 18 (end April) 2009 to week 32 (mid-August) 2010, in the 27 European Union (EU) Member States plus Norway and Iceland (in the following called EU+2). It is linked to a more extensive document developed with the help of national surveillance experts that provides further background on influenza epidemics and pandemics, notably their variability and unpredictability [1]. The review also identifies some initial lessons learnt, especially relating to surveillance needs in a pandemic, as discussed and agreed at the annual expert meeting of the European Influenza Surveillance Network (EISN) held in Sofia, Bulgaria, in June 2010 [2].

Data collection

The main surveillance trends and information presented here are derived from epidemiological analyses of the primary care and virological data (Table 1) reported to the European Centre for Disease Prevention and Control (ECDC)'s European Surveillance System (TESSy) by the European Influenza Surveillance Network (EISN; for more information on this network see: http://ecdc.europa.eu/en/activities/surveillance/EISN/Pages/home.aspx). Building on the existing reporting systems, new surveillance mechanisms were developed to meet additional needs for the pandemic, especially of capturing data on severe and fatal cases of influenza (Table 1). These were collected and reported in one of the Weekly Influenza Surveillance Overviews (WISO) published by ECDC during the pandemic [3,4].

Concurrently, epidemic intelligence [5] and targeted science watch methods (experts scan scientific journals and grey literature and summarise significant publications with public health relevance, significant developments or upcoming meetings) were employed to determine, as early as possible, the important parameters needed for risk assessment, adjusting projections and informing counter-measures in areas where the routine EU surveillance systems are less informative.

Early pandemic

Following its emergence in Mexico in March 2009 [6], the pandemic influenza A(H1N1)2009 virus appears to have started circulating in Europe around week 16 of 2009, initially in travellers returning from Mexico, or their direct contacts (Figures 1 and 2). Early on it was clear that this virus met the previously agreed criteria for a pandemic strain (see summary at: http://www.ecdc.europa.eu/en/healthtopics/H1N1/Documents/100503_health_topics_pandemic_definition_of_a_pandemic.pdf). In response to the threat, EU/EEA countries started to submit detailed case-based reports to the ECDC in May 2009, using an ad hoc database hosted on the secure Early Warning and Response (EWRS) platform. The earliest validated date

of onset of a European case was 19 April 2009 (week 16). When country representatives agreed in week 39 that central collection of case-based data was no longer justified, the database contained 11,275 individual records (11,207 of which were laboratory-confirmed) submitted by 28 countries. A detailed analysis of these first cases is available elsewhere [7].

The surveillance data, supplemented by the ECDC epidemic intelligence and targeted science watch activities, helped to quantify the main pandemic parameters resulting in a 'dynamic scientific risk assessment that was updated 10 times in 2009 as more information became available [8]. For example, the reproductive number R_0 for the infection was estimated with 95% confidence intervals between 1.1 and 1.4 [9] (95% confidence interval) [9], a serial interval between 2.2 and 2.3 days [10], a mean generation time between 2.5 and 3 days [9] and a mean incubation period of 1.5 to 2 days. These figures are consistent with those found for previously circulating influenza strains [9].

There was a paucity of reliable data early on but even so, organisations such as the ECDC and WHO agreed that this was not a severe pandemic. For example, the ECDC interim risk assessment issued on 12 June 2009 [8] concluded:

"The current ECDC threat assessment for Europe is that the new influenza A(H1N1)v virus will continue to spread. Though it seems that most of those infected in the US and in Europe experience a mild and self-limiting infection, this picture is still unclear as there has not been enough transmission to judge the effects, especially in those more at risk."

The pandemic waves spring/summer and autumn/winter

Following the detection of the initial cases imported from North America into Europe, there was a spring and summer wave of transmission in Europe which affected most countries. Figure 1 shows the weekly percentage of influenza-like illness (ILI) notifications over the total number of reports throughout the whole reporting period, accumulated for all reporting countries. However, the wave and burden on the health services was only striking in very few European countries, especially the United Kingdom (UK) [11,12] and to a lesser extent Spain [13].Transmission subsided as the summer progressed, in temporal association with the closure of schools [12,14]. However, transmission accelerated again following the re-opening of the schools, this time affecting all countries, as an early autumn/winter wave started around week 43 of 2009 (Figures 1 and 3) and progressed from west to east across the EU. The modal peak week for the 24 countries consistently reporting their sentinel ILI consultations in the season 2009/10 was week 48, 2009 (six countries), as opposed to week 4, 2009 (seven countries) for the previous season 2008/09. In most countries, the autumn/winter wave of disease was short and intense, lasting about 14 weeks and resembling the epidemic curve seen in the 1957 pandemic in Europe [15].

A similar wave of hospitalisations and deaths followed soon after (Figure 4), although these data on deaths and especially hospitalisation are less readily available because surveillance of severe disease attributable to influenza is not routine in most countries. For the whole pandemic period of 68 weeks (week 18, 2009 to week 35, 2010), the EISN experts reported 925,861 cases of ILI (25 reporting countries) and 7,202,014 cases of acute respiratory infections (ARI) (16 reporting countries) attending their clinics. This is just a small proportion of the true number of cases in the

Table 1

Data collected for the EU+2 Weekly Influenza Surveillance Overview

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 of tests done on non-sentinel respiratory specimens collected, describing virus type and subtype, the predominant strains, their antigenic and genetic characteristics and antiviral 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 and aggregated deaths reported by the countries[a]
Qualitative reporting[b]	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

EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.

[a] This was complemented by active monitoring of official national public health websites for announcements of deaths (see Figure 4).

[b] It was not necessary to activate this element.

Source: [3].

Figure 1

Percentage of weekly reported sentinel ILI caseload of the overall reports, cumulated for 25 EU+2 countries, week 40, 2008–week 34, 2010

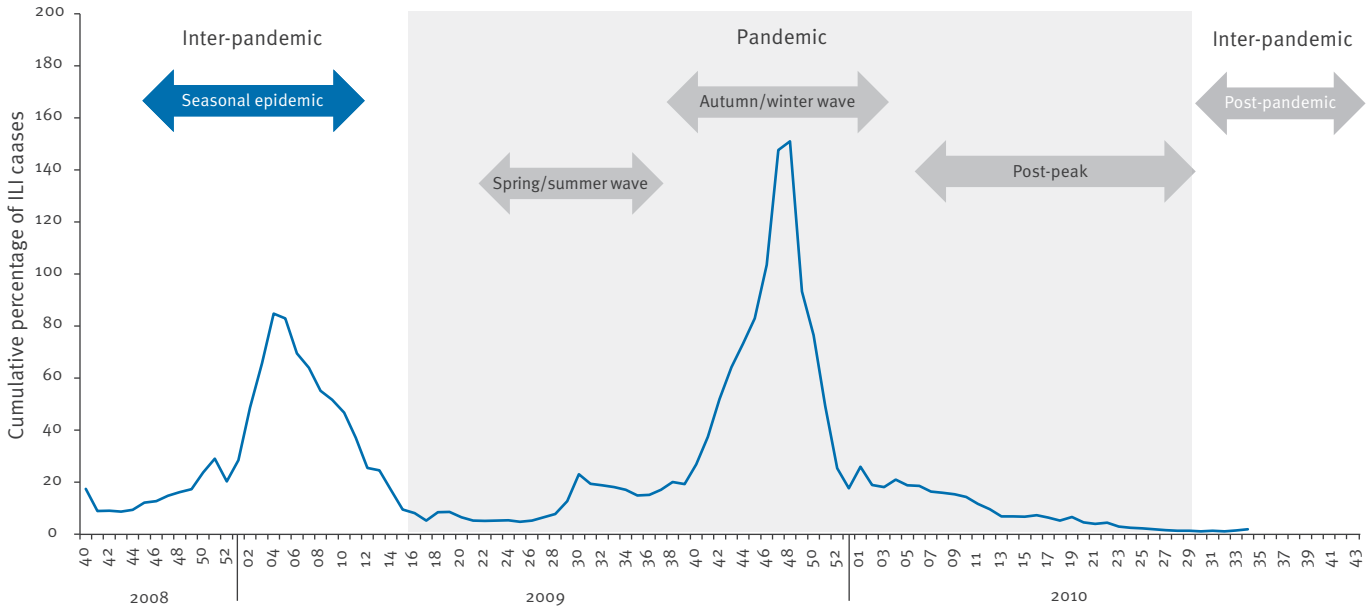
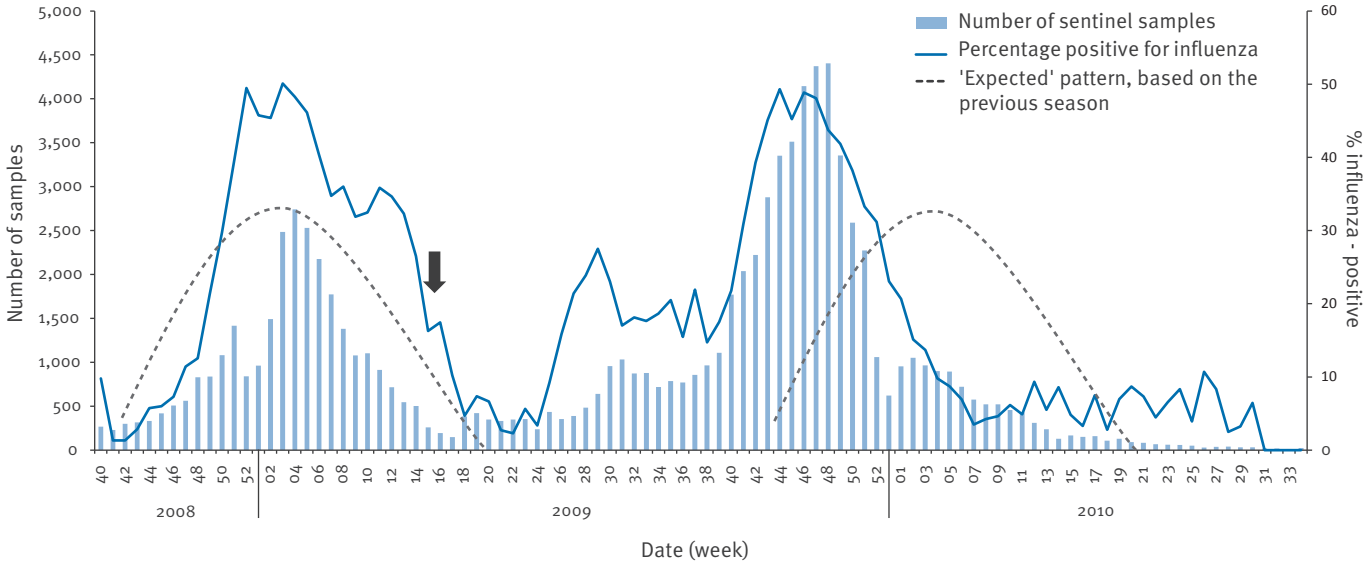


Figure 2

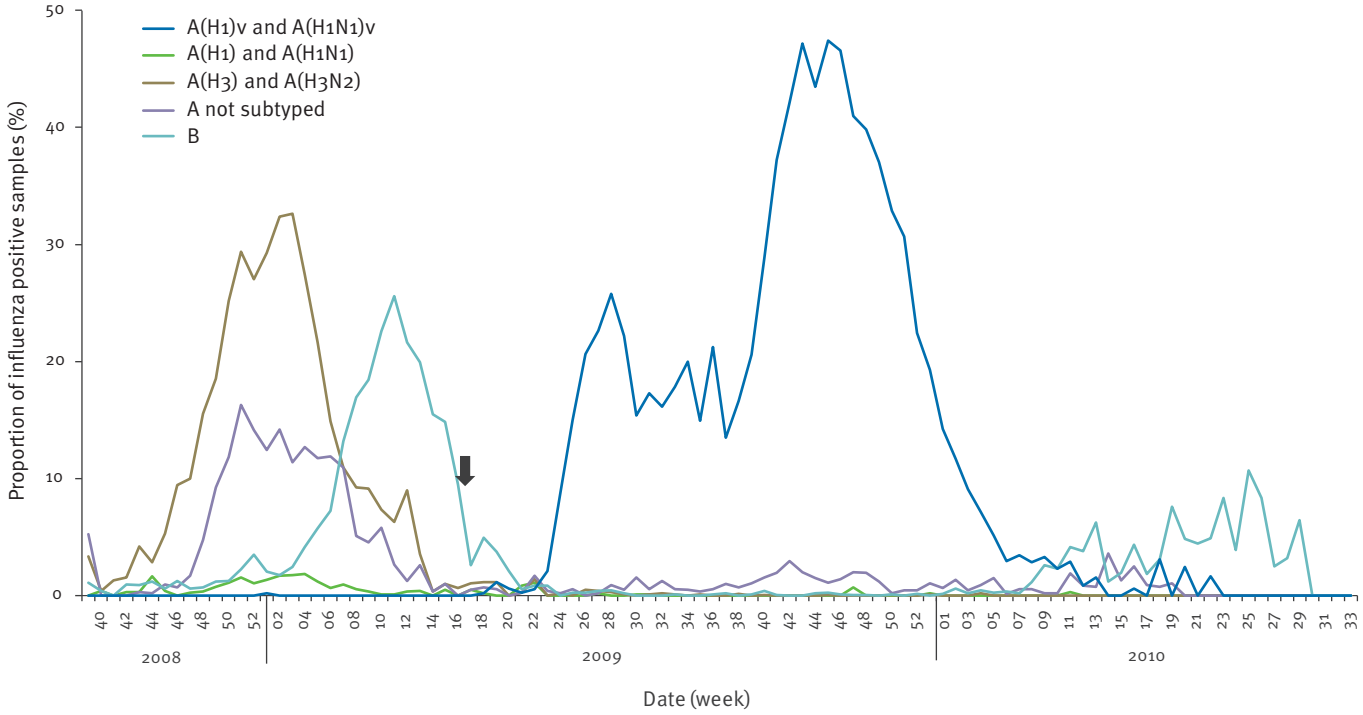
Distribution of the number of sentinel samples submitted and the percentage found positive for influenza, 28 EU+2 countries, seasons 2008/09–2009/10



EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.
The arrow denotes the probable start of the pandemic in Europe.
Source: European Influenza Surveillance Network (EISN) reports.
Data reported by 28 of 27 plus 2 countries.

Figure 3

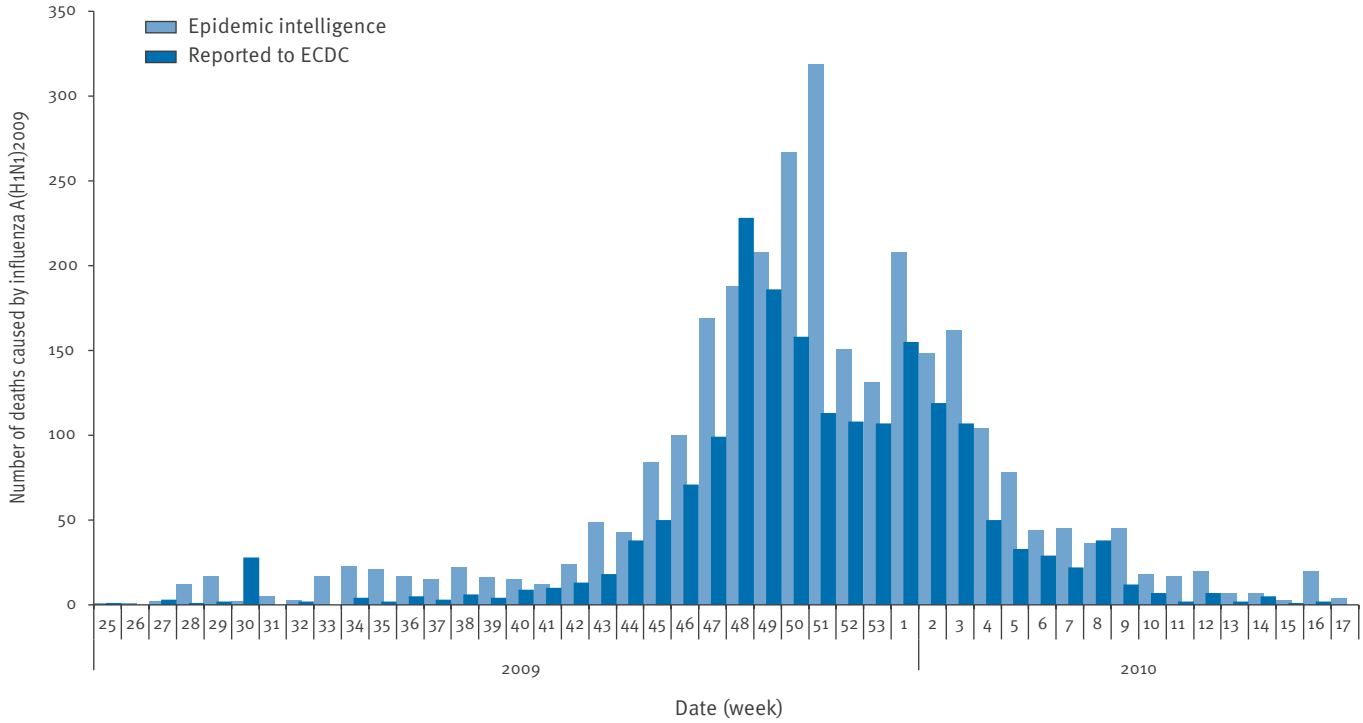
Distribution of virus types and subtypes detected from sentinel samples, seasons 2008/09 and 2009/10 in 28 EU+2 countries



EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.
The arrow denotes the probable start of the pandemic in Europe.
Source: European Influenza Surveillance Network (EISN) reports.

Figure 4

Officially announced and reported deaths due to pandemic influenza A(H1N1)2009 in the EU+2, by week of report, season 2009/10



ECDC: European Centre for Disease Prevention and Control; EU+2: the 27 European Union (EU) Member States plus Norway and Iceland.
Source: European Influenza Surveillance Network (EISN) reports and ECDC epidemic intelligence data collected from official national websites.

general population as the network data are collected from sentinel sites and not representative of the general population. Overall rates for the EU/EEA cannot be estimated due to the different denominators used in the different countries.

The sentinel ILI and ARI networks also provide data on a limited number of age groups, but not on sex. All countries showed a consistent age distribution with children under the age of 14 years affected most. The ratio of the four age groups (under 4 years, 5–14 years, 15–64 years and over 65 years) was: 8:5:2:1.

These figures represent only a small proportion of the true attack rate, i.e. those who felt unwell enough to attend a primary care practice that happened to be part of the sentinel reporting system for that country [16], and should only be used to compare with the figures and proportions of similar data collected in a normal influenza season. The proportion of those experiencing illness or infection differed considerably from what was seen outside the pandemic [17] and this is described in more detail elsewhere [1].

There was considerable geographic heterogeneity in the amount of transmission, within Europe and even within countries, especially in the spring/summer wave. While there was transmission in most countries, only Spain and the UK recorded a prevalence of infection high enough to produce substantial numbers of severely affected people [11-13]. Overall attack rates estimated by serology were higher than for seasonal influenza, although the pandemic virus affected fewer older persons (65 years and older), who had been exposed to a similar virus circulating in the 1950s and before [16,18]. There is clear evidence that there were many mild or asymptomatic cases in this pandemic, but whether they were more common than in the previously recorded pandemics is impossible to determine because it is only in this pandemic that there has been enough accurate seroepidemiology which combined with case reporting allowed such estimates to be made [7,12,17]. Attack rates were highest in young people, with country reports revealing that the highest rates of infection occurred in school-age children [16,18] and some hospital paediatric services and intensive care services were especially stressed [19]. There was also pressure on primary care services in some areas because attack rates exceeded what was normally seen with seasonal influenza. No countries reported any pressure on critical services outside the healthcare sector, which is consistent with the WHO description of the pandemic: *this pandemic, at least in its early days, will be of moderate severity* (statement to the press by WHO Director-General Dr Margaret Chan, 11 June 2009)

Virological surveillance

The pandemic influenza A(H1N1)2009 virus displaced the previously dominant seasonal influenza A virus strains in Europe, although late in both seasons 2008/09 and 2009/10, influenza B viruses were still prevalent enough to cause significant disease (Figures 2 and 3). From week 21, 2009 to week 16, 2010, 60,827 clinical samples were submitted by the sentinel practices reporting to the EISN, of which 25,304 (41.6%) tested positive for influenza virus, almost all for the 2009 pandemic virus.

All pandemic influenza A(H1N1)2009 viruses isolated from samples submitted by the EISN sentinel practices for testing, were found to be resistant to antiviral drugs in the adamantane class, but very few of these samples (2.5%) were found to be resistant to oseltamivir (Table 2). All oseltamivir-resistant strains were accounted for by the presence of the H275Y mutation. Most of these mutations were observed following treatment of immunocompromised patients, and in Europe, resistant virus was only rarely transmitted

Table 2

Antiviral resistance by influenza virus type and subtype in samples collected by primary care sentinel networks in the EU+2, week 40, 2008–week 18, 2010 (n=1,454)

Influenza virus type and subtype	Resistance to neuraminidase inhibitors								Resistance to M2 inhibitors			
	Oseltamivir				Zanamivir							
	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)	Isolates tested	Resistant n (%)
	Week 40, 2008–week 39, 2009		Week 40, 2009–week 18, 2010		Week 40, 2008–week 39, 2009		Week 40, 2009–week 18, 2010		Week 40, 2008–week 39, 2009		Week 40, 2009–week 18, 2010	
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	1,453	37 (2.5%)	415	0	1,447	0	56	56 (100)	205	205(100%)
B	117	0	0	0	113	0	0	0	NA	NA	NA	NA

EU+2: the 27 European Union (EU) Member States plus Norway and Iceland; NA: not applicable, as M2 inhibitors do not act against influenza B viruses.

Source: European Influenza Surveillance Network (EISN) and Influenza Community Network of Reference Laboratories (CNRL) data in the European Centre for Disease Prevention and Control (ECDC)/European Surveillance System (TESSy).

from one human to another unlike the seasonal influenza A(H1N1) virus with the same mutation, which is readily transmitted [20]. Although the viruses circulating during the pandemic were not identical, there is little evidence of significant drift or the emergence of dominant new variants to date [21]. A previously observed influenza A(H1N1)2009 variant with a D222G mutation has been associated with more severe disease, but it is still unclear whether this is due to a higher pathogenicity or a tropism for cells in the lower respiratory tract [21].

Mortality, severe disease and risk groups

In total, 2,900 pandemic deaths were announced by Member States in the first 12 months (Figure 4). This is probably only a proportion of the true burden of deaths due to the pandemic, but it remains unclear what that proportion is for Europe overall or for individual countries [22,23]. Pooling data from eight pilot countries, the EU-funded project European Monitoring of Excess Mortality for Public Health Action (EuroMOMO) detected excess all-cause mortality only in the 5-14 year-olds in the period between weeks 27 and 51 of 2009, compared with mortality in the previous three years. This estimate is probably conservative due to delays in reporting [24].

Before the autumn/winter wave of the pandemic, the EISN attempted to establish hospital-based sentinel surveillance of severe acute respiratory infection (SARI) cases, although this met with limited success [25]. During the autumn/winter wave, i.e. from week 36, 2009 to week 20, 2010, 11,904 SARI cases and 586 SARI-related fatalities were reported to ECDC by eleven EU countries (Austria, Belgium, Cyprus, Finland, France, Ireland, Malta, the Netherlands, Romania, Slovakia and the United Kingdom, France only reported pandemic influenza A(H1N1)2009 cases admitted to intensive care units) [1]. Information on those with severe disease can be ascertained partially from this data and also from focused studies in EU Member States [13,26].

Building on these findings, the EU Health Security Committee defined pregnant women, those over six months of age with chronic ill health and healthcare workers as the primary risk groups that should be offered immunisation against pandemic influenza [27,28]

Differences between the pandemic and seasonal influenza

The pandemic differed from the preceding influenza season in a number of ways (Table 3). Most notable was the difference in the age of those most severely affected. Previously, were concentrated persons aged 65 years and older accounted for 90% of deaths from seasonal influenza [29,30]. In the 2009 pandemic, nearly 80% of the deaths reported to ECDC occurred in persons under 65 years [25], probably because a sizable proportion of older adults were protected by prior exposure to a similar influenza virus that had been circulating before the mid-1950s [16,18]. However, not all those older than 64 years were immune, and those without immunity who were infected had the highest case fatality rate of all age groups [25,31]. While the majority of deaths occurred in persons with chronic medical conditions, especially respiratory and neurological conditions, between 20% and 30% of the deaths reported in studies occurred in previously healthy individuals [31]. A considerable proportion of deaths were caused by acute respiratory distress syndrome (ARDS, mortality rate in 612 ARDS patients: 24.5% [25]), an extremely rare condition that is difficult to treat and that requires high dependency support for several weeks [32,33] One of the reasons may have been that the new virus has shown a tropism for receptors found in the alveolar epithelium of the lungs [33].

Serological data

To date, there has been only limited data from serological surveys. These support the surveillance data indicating high infection rates, but they also suggest higher than expected levels of asymptomatic infection [16,39]. While the serological findings do not allow reliable predictions for the influenza season 2010/11, the experience of the temperate countries in the southern hemisphere during the European summer period of 2010 would probably provide some valuable clues.

Conclusions

The pandemic influenza A(H1N1) 2009 virus started circulating in Europe around week 16 of 2009 (although the declared phase 5 only in week 18). It progressed into an initial spring/summer wave of transmission which occurred in most countries, but was striking only in a few, notably the UK. As the summer advanced, transmission briefly subsided, but then escalated again in the early autumn, just after the re-opening of the schools, this time affecting all countries. This autumn/winter wave was seen to progress from west to east across the continent. In most countries, this second wave of infection was brief but intense, lasting about 14 weeks, and was accompanied by a similar but slightly delayed wave of hospitalisations and deaths. By the time the WHO declared the pandemic officially over in August 2010 (week 32, 2010), the EU+2 had experienced transmission at a very low level for about 34 weeks.

An excess of all-cause deaths in school-age children was observed. Even though this was an influenza virus never seen previously, prior exposure to an antigenically similar influenza virus circulating before the mid 1950s meant that many older people in Europe exhibited some immunity. Although many older people appeared to be protected, persons over the age of 65 years still had the highest case fatality rate of any age group.

The pandemic virus displaced the previously dominant seasonal influenza A viruses in Europe, although influenza B viruses continued to appear at a low level late in the seasons. Few pandemic viruses were resistant

to oseltamivir, and of these, very few seemed capable of human-to-human transmission. Although the pandemic viruses are not identical, there is little evidence of significant drift or the emergence of dominant new variants to date. One variant, influenza A(H1N1)2009-D222G has been associated with more severe disease, but a causative relationship has yet to be established.

Serological data suggest that there were a higher proportion of mild and asymptomatic infections than in the preceding influenza seasons. Nevertheless, transmission rates were higher than for seasonal infection and there were sufficient amounts of severe disease and notably cases of ARDS, which put a strain on intensive care services in many places. Young children (under five years of age) experienced the highest rates of disease, while country reports and serology indicate that the highest rates of infection (including asymptomatic) were in children at school age. These high rates of illness presented a particular burden for primary services, hospital paediatric services and especially intensive care in some areas.

Pandemic planning will now need to be revisited as the occurrence of this pandemic does not exclude the possibility of an influenza A(H5) or (H7) pandemic emerging in the future. The next generation of plans need to include more flexibility for reacting to different severity of disease and different combinations of epidemiological parameters. In this context it would be useful to reach

Table 3

Comparing influenza seasons 2000/01–2008/09 with 2009 pandemic influenza

	Seasonal influenza 2000/01– 2008/09	2009 pandemic influenza
Circulating influenza viruses	Two influenza A viruses: A(H1N1) and A(H3N2), and some influenza B viruses; the mix varies with the season	Almost exclusively the pandemic influenza A(H1N1)2009, a few influenza A(H3N2) viruses and increasing numbers of influenza B viruses towards the end of the season
When waves occurred	In season, in recent years most often starting after Christmas	Started out of season with a spring/summer wave, then an early autumn/winter wave in Europe
Levels of transmission	Variable from year to year, with local heterogeneity, but estimated to be 5–15% annually	Hard to estimate, local heterogeneity, estimated to be over 15% through serological studies in New Zealand [34] and in the United Kingdom [16]
Setting for transmission	Probably any setting where people come together	Schools considered especially important, along with household transmission
Experiencing severe disease	Those in clinical risk groups and older people	Young children, pregnant women and those in clinical risk groups; about 30% with severe disease were outside risk groups; many born before the mid-1950s were immune, but people in this age group who were not immune experienced severe disease outcomes [31]
Premature deaths	Around 90% considered to have occurred in people 65 years or older	In confirmed reported deaths, around 80% were under 65 years of age Increase in all-cause deaths in children detected across eight EU countries by EuroMOMO system[24]
Mortality and years of potential life lost	Few confirmed deaths reported each year in official statistics; estimates of up to 40,000 in a bad year using statistical methods	Substantial numbers of confirmed deaths announced by EU+2 Member States (n=2,900, Figure 4) but recognised to be an underestimate Only estimated in one EU Member State (the Netherlands, 35 disability-adjusted life years per 100,000 population) [35], but estimated in the United States with considerably higher levels [36]
Acute respiratory distress syndrome	Extremely rare	Uncommon, but recorded in many countries, even in young fit adults; partially explained by the tropism of the pandemic virus for epithelial receptors that predominate in the alveoli of the lung, while the previous seasonal viruses bind best to receptors found predominately in the upper airways [33]
Pathological findings	Viral pneumonia rare, but secondary bacterial infections more common in fatal cases	Fatal viral pneumonias relatively common with alveolar lining cells, including type I and type II pneumocytes the primarily infected cells; more than 25% of fatalities also involved bacterial infections [33,37]
Antiviral resistance	Common and transmissible oseltamivir resistance in influenza A(H1N1) emerged in season 2007/08 [38]	Observed most often following antiviral treatment of susceptible individuals; however, as of July 2010, only transmitted very rarely under certain circumstances [33]; resistant seasonal influenza A(H1N1) seemingly displaced by the new influenza, at least for now

ECDC: European Centre for Disease Prevention and Control; EU: European Union; EU+2: the 27 European Union (EU) Member States plus Norway and Iceland; EuroMOMO: project European Monitoring of Excess Mortality for Public Health Action; WHO: World Health Organization.

This table lists ten characteristics in which the new pandemic influenza differs from the 'old' seasonal influenza, especially as they appeared in more recent years (seasons 2000/01–2008/09).

Source: http://ecdc.europa.eu/en/activities/sciadvice/Lists/ECDC%20Reviews/ECDC_DispForm.aspx?List=512ff74f%2D77d4%2D4ad8%2Db6d6%2Dbf0f23083f30&ID=911&RootFolder=%2Fen%2Factivities%2Fsciadvice%2FLists%2FECDC%20Reviews

a European consensus on describing and assessing the severity of a pandemic, and matching the response with the different scales and characteristics. These plans must also provide for the consolidation and sustainability of the influenza surveillance systems that were introduced to meet the demands of the 2009 pandemic, in particular SARI, attributable mortality, and seroepidemiological surveillance. This surveillance work needs to be prioritised, given the right level of resources and allowed to develop and be tested during the interpandemic period so that the systems will be more resilient and effective in a future public health crisis.

At an early stage, it was appreciated that this pandemic was much less severe than what many European countries had feared and prepared for. This was highlighted in the first ECDC Risk Assessments (available at: http://ecdc.europa.eu/en/healthtopics/H1N1/risk_threat_assessment/Pages/risk_threat_assessment.aspx), 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 the health sector. In conclusion this pandemic was a mild one for Europe [40], testing the flexibility of existing preparedness plans in many countries. The greatest challenge during this pandemic was in the area of risk communication, as both the professionals and the general population expected something more severe [41].

The pandemic occurred at a time when diagnostic tests could be made available quickly, as well as preventive pharmaceutical countermeasures (antiviral drugs for a virus with little resistance to the neuraminidase inhibitors but almost complete resistance to the older adamantanes) and when appropriate vaccines were developed and made available faster than ever before. The occurrence of cases of ARDS when many intensive care units were already busy put particular pressure on the system without the ability to redeploy hospital staff internally, even though the rest of the hospitals were not that stressed [33]. The rapidly produced pandemic vaccines showed such a good immunological response that several formulations only required a single dose in adults [42]. They have also proved to be effective and relatively safe [42], although post-marketing surveillance still needs to be maintained to determine exactly how safe they are and to investigate initial signals of adverse events following immunisation (AEFIs) [43]. There were still delays in the production of vaccines, so that even countries with advance purchase agreements received too little vaccine too late to have any real impact at the population level. However, the high vaccine efficacy and targeting of risk groups may have saved lives of European citizens. Where vaccines were made available, they were greeted with varying degrees of enthusiasm among health professionals. That these vaccines were not widely accepted was partly due to the difficulty in transmitting the complex risk communication message. On the one hand the chance of severe disease following infection was very low unless the individual belonged to a risk group (young children, people with chronic ill health and pregnant women [33]). On the other hand, there was a small but real risk of severe disease and death from the pandemic in all healthy persons. The challenge of communicating this risk was considerable.

Limitations of the EU+2 data

The data used here were subject to limitations and the results should be interpreted with a degree of caution. The reported ILI or ARI surveillance data were not comparable between countries as there was variability in the data sources, size and representativeness of the networks. The ILI/ARI epidemic curves were also distorted because several countries, at different points in time, actively recommended that anyone with influenza-like symptoms should stay at home and not approach their primary care provider, (contrary to what the patients would do in a normal influenza season), thus excluding them being reported. In addition, there are indications from specialist studies that the usual patterns of seeking care were distorted during the pandemic and that this varied over time as the perception of risk changed [17].

The virological data are derived from samples sent for laboratory testing and confirmation. They represent only a selected subset of the cases, usually the more severely affected seeking medical help. The sentinel samples were representative of patients attending general practices, while the non-sentinel samples derive from a varying mix of general practitioners' diagnoses not included in the sentinel system and more seriously affected cases that were admitted to hospital. Therefore the non-sentinel data were a mixture of mild and severe cases, which can differ by country. One important aspect of laboratory- based surveillance that was missing at the European level was routine seroprevalence monitoring. Although a few countries carried out local studies that provided valuable information [16,18,44,45], this work was not carried out in a standardised and comparable manner early on in the pandemic. Also, the results were made available too late to be of use 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 pandemic, after the pandemic had already reached Europe. This is not the optimal 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 already stretched. There seem to be difficulties in capturing data on SARI cases in many European hospitals because it is not a diagnosis recognised by clinicians as it encompasses young children with bronchiolitis, older people with pneumonia and ARDS. Some countries found it easier to collect data on people hospitalised with an influenza diagnosis. Also, there was variability in what different sites reported as SARI as well as in providing reliable estimates of the denominators and the representativeness of the data, shedding doubt on the estimated rates.

Not only reported cases were underestimated, but also deaths due to the 2009 pandemic influenza, especially in the elderly where influenza is known to be frequently masked by other conditions as the underlying cause of death [46]. Presently, only ad hoc studies can attempt to estimate influenza-related mortality more accurately, and while such studies have been done in the United States [47], there have not been any in Europe

New characteristics of the 2009 influenza pandemic

Nevertheless, the EU/EEA surveillance data permit us to conclude on a number of new characteristics of this pandemic (Box), notably the reliance on clinicians to deliver the most powerful countermeasures. Much prominence was given to the doubts expressed by the professionals in some countries on the value of the countermeasures. Moreover, the role of the media in this pandemic was unprecedented and this was not always positive, for example when vaccine opponents and pandemic skeptics were given the same platform as expert opinions.

Lessons learnt for surveillance

The fact that the 2009 influenza A(H1N1) pandemic was less of a threat than what many countries had prepared for, tested the flexibility of existing plans. Nevertheless no country appears to have over-responded, while the systems developed by the European Commission, WHO and ECDC for discussing and sharing information and analyses proved resilient and useful. On balance, the EU+2 managed the response to the pandemic well [49], although this can be further improved. The EISN virological and primary care-based surveillance in particular worked well, and served to augment the data emerging from the ECDC epidemic intelligence and targeted science watch sources. Establishing surveillance in hospitals and sharing analyses from the first affected countries were less successful. It was fortunate that data and analyses were quickly available from North America and the southern hemisphere. Lessons to be learnt include:

- Routine 'severe end' surveillance of hospitalised cases and deaths due to severe respiratory infection should be established in Europe.
- In the future, the process for sharing early analyses from the first affected countries can work better, possibly by increasing the faith of expert colleagues in the confidentiality and security of certain communication systems and the discretion of other experts in the country not to pass on provisional data.
- Much work, including research and development, needs to take place to make seroepidemiology available in real time.

Box

New characteristics about the 2009 pandemic in Europe

- The first pandemic with instant communication so that early impressions (such as the experience in Mexico and the Ukraine) were transmitted ahead of any reasonable or thoughtful analysis;
- The first pandemic that took place within the context of a set of International Health Regulations [48] and global governance, although essentially untried;
- The first pandemic with early diagnostic tests which led to rapid diagnosis but also an early overly strong focus by the media and policymakers on the numbers of infected people;
- The first pandemic with antiviral drugs available which led to an expectation that the pandemic might be containable and the invention of a containment phase by some countries
- The first pandemic in which effective countermeasures (antiviral drugs and vaccines) could be provided by clinicians, which meant the confidence of those doctors and nurses had to be earned and retained;
- The first pandemic in a setting with effective intensive care and thus with a (false) expectation that everyone could be treated and cured;
- The first pandemic which received uncontrolled coverage in blogs that policy makers needed to monitor closely.

The members of the European Influenza Surveillance Network (EISN) are:

Gabriela El Belazi, Hubert Hrabcik, Peter Lachner, Reinhild Strauss, Robert Muchl, Theresia Popow – Kraupp, Monika Redlberger-Fritz, Françoise Wuillaume, Françoise Wuillaume, Viviane Van Casteren, Isabelle Thomas, Bernard Brochier, Mira Kojouharova, Rositsa Kotseva, Teodora Georgieva, Avraam Elia, Chryso Gregoriadou, Chrystalla Hadjianastassiou, Despo Pieridou Bagatzouni, Olga Kalakouta, Jan Kyncl, Martina Havlickova, Andreas Gilsdorf, Brunhilde Schweiger, Gabriele Poggensee, Gerard Krause, Silke Buda, Tim Eckmanns, Anne Mazick, Annette Hartvig Christiansen, Kåre Mølbak, Lars Nielsen, Steffen Glismann, Inna Sarv, Irina Dontsenko, Jelena Hololejenko, Natalja Njunkova, Natalia Kerbo, Olga Sadikova, Tiiu Aro, Amparo Larrauri, Gloria Hernandez – Pezzi, Pilar Perez – Brena, Rosa Cano – Portero, Markku Kuusi, Petri Ruutu, Thedi Ziegler, Sophie Vaux, Isabelle Bonmarin, Daniel Lévy-Bruhl, Bruno Lina, Martine Valette, Sylvie Van Der Werf, Vincent Enouf, Ian Fisher, John Watson, Joy Kean, Maria Zambon, Mike Catchpole, Peter Coyle, William F Carman, Stefanos Bonovas, Takis Panagiotopoulos, Sotirios Tsiodras, Ágnes Csohán, Istvan Jankovics, Katalin Kaszas, Márta Melles, Monika Rozsa, Zsuzsanna Molnár, Darina O'flanagan, Derval Igoe, Joan O'donnell, John Brazil, Margaret Fitzgerald, Peter Hanrahan, Sarah Jackson, Suzie Coughlan, Jeff Connell, Margaret Duffy, Joanne Moran, Professor William Hall, Arthur Löve, Gudrun Sigmundsdottir, Simona Puzelli, Isabella Donatelli, Maria Grazia Pompa, Stefania D'amato, Stefania Iannazzo, Annapina Palmieri, Sabine Erne, Algirdas Griskevicius, Nerija Kupreviciene, Rasa Liausediene, Danielle Hansen – Koenig, Joel Mossong, Mathias Opp, Claude P. Muller, Jacques Kremer, Patrick Hau, Pierre Weicherding, Antra Bormane, Irina Lucenko, Natalija Zamjatina, Raina Nikiforova, Charmaine Gauci, Christopher Barbara, Gianfranco Spiteri, Tanya Melillo, Marianne van der Sande, Adam Meijer, Frederika Dijkstra, Gé Donker, Guus Rimmelzwaan,, Simone Van Der Plas,Wim Van Der Hoek, Katerine Borgen, Susanne Dudman, Siri Helene Hauge, Olav Hungnes, Anette Kilander, Preben Aavitsland, Andrzej Zielinski, Lidia Brydak, Magdalena Romanowska, Malgorzata Sadkowska – Todys, Maria Sulik, Carlos Manuel Orta Gomes, Jose Marinho Falcao, Raquel Guiomar, Teresa Maria Alves Fernandes, Adriana Pistol, Emilia Lupulescu, Florin Popovici, Viorel Alexandrescu, Annika Linde, Asa Wiman, Helena Dahl, Malin Arneborn, Mia Brytting, Katarina Prosenc, Maja Socan, Katarina Prosenc, Maja Socan, Hana Blaskovicova, Margareta Slacikova, Mária Avdicová, Martina Molcanová, Šárka Kovácsová.

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Effectiveness of pandemic and seasonal influenza vaccine in preventing pandemic influenza A(H1N1)2009 infection in England and Scotland 2009-2010

P Hardelid (pia.hardelid@hpa.org.uk)[1], D M Fleming[2], J McMenamin[3], N Andrews[1], C Robertson[3,4], P SebastianPillai[1], J Ellis[1], W Carman[5], T Wreghitt[6], J M Watson[1], R G Pebody[1]

1. Health Protection Agency Centre for Infections, London, United Kingdom
2. Royal College of General Practitioners Research and Surveillance Centre, Birmingham, United Kingdom
3. Health Protection Scotland, Glasgow, United Kingdom
4. University of Strathclyde, Glasgow, United Kingdom
5. West of Scotland Specialist Virology Centre, Glasgow, United Kingdom
6. Health Protection Agency Regional Microbiology Network, Cambridge, United Kingdom

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Following the global spread of pandemic influenza A(H1N1)2009, several pandemic vaccines have been rapidly developed. The United Kingdom and many other countries in the northern hemisphere implemented seasonal and pandemic influenza vaccine programmes in October 2009. We present the results of a case–control study to estimate effectiveness of such vaccines in preventing confirmed pandemic influenza infection. Some 5,982 individuals with influenza-like illness seen in general practices between November 2009 and January 2010 were enrolled. Those testing positive on PCR for pandemic influenza were assigned as cases and those testing negative as controls. Vaccine effectiveness was estimated as the relative reduction in odds of confirmed infection between vaccinated and unvaccinated individuals. Fourteen or more days after immunisation with the pandemic vaccine, adjusted vaccine effectiveness (VE) was 72% (95% confidence interval (CI): 21% to 90%). If protection was assumed to start after seven or more days, the adjusted VE was 71% (95% CI: 37% to 87%). Pandemic influenza vaccine was highly effective in preventing confirmed infection with pandemic influenza A(H1N1)2009 from one week after vaccination. No evidence of effectiveness against pandemic influenza A(H1N1)2009 was found for the 2009/10 trivalent seasonal influenza vaccine (adjusted VE of -30% (95% CI: -89% to 11%)).

Introduction

Following the emergence and rapid global spread of pandemic influenza A(H1N1)2009 virus in April 2009 [1], several vaccines against this virus were quickly developed [2-6]. Clinical trials, including products with a new squalene adjuvant (MF59 or AS03) demonstrated that these novel pandemic vaccines were immunogenic in various target populations [2-6]. Published work on the possible effect of prior trivalent seasonal influenza vaccination on the subsequent risk of pandemic influenza infection has been conflicting: some have suggested a protective effect [7], others have found no association [8-10], and recent work from Canada has reported an increased risk of subsequent pandemic infection [11].

The United Kingdom (UK), as many other countries in the northern hemisphere, implemented its seasonal and pandemic influenza vaccine programmes in autumn 2009. Two pandemic vaccines were introduced in the UK: Pandemrix (GlaxoSmithKline), an inactivated low-dose influenza vaccine with one dose containing 3.75g haemagglutinin (HA) equivalent of the influenza A/California/7/2009 isolate combined with the AS03 adjuvant) and Celvapan (Baxter), a whole-virion, Vero cell-derived influenza vaccine with a dose of 7.5 µg of influenza A(H1N1) HA antigen of the A/California/07/2009 isolate. The pandemic vaccine programme was initially targeted at clinical risk groups older than six months, pregnant women and healthcare workers [12] and later extended to all healthy children six months to five years of age. Pandemrix was the main vaccine administered through the UK pandemic vaccine programme: by late February 2010, provisional uptake for the first dose of Pandemrix in England was 37.1% for clinical at-risk groups, 20.4% for healthy children six months to five years of age and 39.9% for healthcare workers [13].

The UK has an established surveillance system to monitor the effectiveness of the annual seasonal influenza vaccine programme. The system uses routine epidemiological data generated through swabbing of cases of influenza-like illness (ILI) presenting in primary care in England and Scotland [14]. Using this approach, this study sets out to provide estimates of the effectiveness of the pandemic and seasonal influenza vaccine

programmes in preventing infection with pandemic influenza A(H1N1)2009.

Methods

Study population and period

This study uses data from three influenza sentinel surveillance schemes in England and Scotland: the Royal College of General Practitioners' surveillance scheme (RCGP) covers 96 practices and ca. 900,000 patients throughout England (65 practices contribute to the swabbing programme), the Health Protection Agency (HPA) Regional Microbiology Network (RMN) surveillance scheme includes 45 contributing general practices and covers around 400,000 patients, and the Health Protection Scotland (HPS) scheme covers 101 general practices and 640,931 patients in Scotland (90 practices contribute to swabbing).

In all three schemes, clinicians are instructed to provide nose and throat swabs from a convenience sample of patients presenting with acute onset of respiratory illness, i.e.rapid development of appropriate symptoms usually with fever. No particular age group is specifically targeted and swabbing is undertaken regardless of prior influenza vaccination status of the patient.

This study covers samples collected in the period from 1 November 2009 (the pandemic influenza vaccination programme was rolled out across the UK on the 21 October) to 29 January 2010.

Cases were defined as individuals presenting with ILI in one of the participating practices in the defined study period who were swabbed and tested positive for pandemic influenza A(H1N1)2009 by RT-PCR. Controls were individuals presenting with ILI in the same period who were swabbed and tested negative. If they tested positive for other non-influenza respiratory viruses they were still included in the control group. Individuals who tested positive for other subtypes of influenza A or for influenza B were excluded from the vaccine effectiveness (VE) estimates.

A standard specimen request form provided demographic and clinical information on cases and controls including date of birth, gender, date of onset, date of specimen collection, influenza vaccination status and vaccination date. Information on type of vaccine and dose was also collected.

Laboratory methods

Samples were sent to the HPA Centre for Infections (RCGP scheme), local HPA Regional Microbiology Network laboratories (RMN scheme) or the West of Scotland Specialist Virology Centre (HPS scheme) for molecular testing. Laboratory confirmation was undertaken using RT-PCR assays for circulating influenza A viruses, influenza B viruses and other respiratory viruses including respiratory syncytial virus and adenovirus [15-17].

Statistical methods

The two exposures of interest were vaccination with 2009/10 seasonal trivalent influenza vaccine and vaccination with either Pandemrix or Celvapan. Respiratory samples with a delay greater than 29 days between illness onset and sample collection were excluded as viral load is likely to be substantially reduced so long after disease onset. Although any such reduction in sensitivity (provided specificity remains high) is unlikely to affect VE estimates [18], a sensitivity analysis was undertaken restricting the VE estimation to a maximum of seven days between illness onset and sample collection. Only two individuals (both controls) had received a second dose of pandemic vaccine at the time of this study; these were not categorised differently to those who had received one dose.

Individuals were considered vaccinated if their date of seasonal or pandemic vaccination was 14 days or more before the date of onset [2]. As there is some evidence that the immune response induced by pandemic vaccines is more rapid than for seasonal vaccines (E. Miller, HPA, personal communication), sensitivity analyses were carried out including individuals with a date of pandemic vaccination seven or more days before onset of symptoms.

For individuals whose date of onset was missing, the date of sample minus the median delay between illness onset and sample collection (three days) was assumed. As this assumption may affect the estimate of VE (if the exposure of interest is misclassified), we also investigated the effect of using the actual date of sample, or date of sample minus seven days for individuals with a missing date of onset. For the small number of samples (0.5%) for which the date of sample collection was missing, the date of receipt in the laboratory was used instead.

VE was estimated using logistic regression models with pandemic influenza A(H1N1)2009 PCR result as outcome and seasonal or pandemic vaccination status as the linear predictor. VE can then be estimated as 1-[odds ratio] [18]. Age (coded into five standard age groups, <5 years, 5-14 years, 15-44 years, 45-64 years and 65 years and above), sex, seasonal influenza vaccination status, country (England or Scotland), surveillance scheme (HPS, RCGP or RMN), date of sample collection (month) and the number of days delay between onset of symptoms and sample collection (coded into five categories: 0-1 day, 2-4 days, 5-7 days, 8-14 days and 15-29 days) were investigated as potential confounding variables.

Model selection for seasonal or pandemic VE estimation was performed by initially including age, date and vaccination status as covariates in the regression model. Other variables were added if they were significant and changed the vaccination odds ratios by 20% or more. Subgroup analyses by age group (<15 years and ≥ 15 years), for individuals who had received only

one dose of vaccine, and for samples collected within seven days of onset were carried out.

As there were a large number of individuals with missing pandemic vaccination status, including only complete case data could potentially have lead to bias if the missing information was not completely at random. Instead, these observations were coded as 'vaccination status unknown' and included in the logistic regression models. The effect of excluding these individuals or classifying them as unvaccinated was also investigated. Individuals coded as vaccinated with pandemic vaccine, but with an unknown date of vaccination, were initially excluded from the logistic regression models. A sensitivity analysis was then carried out by refitting the final model assuming that those with missing vaccination dates for seasonal vaccine had all been vaccinated before 17 October (implying they would all have had an immune response by 1 November), and that those with missing pandemic vaccination dates had all been vaccinated on 21 October. We also investigated the effect of using week rather than month of sample collection as an indicator of time period. All statistical analyses were carried out in R version 2.10.1[19].

Vaccination status information collected on the swab request forms was validated by linking swab records from the HPS and RCGP swabbing schemes to electronic records from a subset of the practice team information database from HPS and electronic database records from RCGP network practices, respectively [20,21]. Linkage was achieved using age, sex, date of swab collection and practice post code for RCGP and the community health index (CHI) number for the HPS scheme. This also allowed an investigation of the vaccination status of persons with missing vaccination information on the swab request form. Validation was not possible for swabs collected through the RMN scheme.

Ethics approval

In England, ethics approval was not required and informed consent was not sought. The work was carried out under National Health Service (NHS) Act 2006 (section 251) for England, which provides statutory support for disclosure of such data by the NHS, and their processing by the HPA, for purposes of communicable disease control. In Scotland, ethics approval was not required and informed consent was not sought. HPS remains a constituent part of the NHS and coordinates the investigation and management of all national outbreaks.

Results

This report comprises information on 5,985 individuals whose samples were collected through the three surveillance systems in the study period, and who had a known PCR result. Two persons were positive for influenza B and one other person was positive for influenza A(H3): these three individuals were not included at any stage of the analysis. Of the remaining 5982, 1,746 (29.2%) were positive for influenza A(H1N1), 630 individuals (10.5%) were positive for other respiratory viruses, and 3,606 individuals (60.3%) were negative for all viruses tested. Table 1 shows the distribution and completeness of the baseline characteristics of the study participants according to whether they were cases or controls.

For the 663 individuals (11.1%) for whom the date of onset was missing, the date of sample minus the median delay (three days) was used. The proportion with missing date of onset was not significantly higher among those positive for pandemic influenza A(H1N1)2009 than among those who were negative: 174 of 1,746 (10.0%) compared with 487 of 4,236 (11.5%), chi-square test p=0.09. The proportion of individuals with unknown pandemic vaccination status (Table 1) was significantly higher among cases than controls (chi-square test p<0.001). The proportion of individuals with unknown pandemic vaccination status decreased between November (1,982 of 3,572 with unknown vaccination status, 55.5%) and January (207 of 640, 32.3%).

Of the 186 individuals who had received pandemic vaccine, only two (1.1%) had received two doses of vaccine: the remainder had received one dose of pandemic vaccine. Of the 97 vaccinated individuals for whom vaccine brand was known, only one had received Celvapan (one dose) and the rest Pandemrix.

One hundred and thirty individuals had received both seasonal and pandemic vaccines. This amounted to 69.9% of the 186 pandemic vaccinees and 21.6% of the 601 individuals who had received seasonal vaccination

Pandemic vaccine effectiveness

Among individuals who had received the pandemic vaccine, four of 85 (4.7%) were positive for pandemic influenza A(H1N1)2009 14 days after vaccination, compared with 870 (28.4%) of 3,067 unvaccinated individuals who were positive. This difference was statistically significant (chi-square test p<0.0001), giving a crude pandemic VE estimate in preventing confirmed pandemic influenza A(H1N1)2009 infection of 88% (95% confidence interval (CI): 66% to 95%).

The four vaccine failures occurred in people aged between 15 and 64 years. Three of them had received Pandemrix, and for one vaccine brand was unknown. All had received one dose.

The VE of the pandemic vaccine, adjusted for age group and sampling date (month) was 72% (95% CI: 21% to 90%) (Table 2). These were the only two variables which altered the crude VE estimate by more than 20%. As the vaccine failures all occurred in adults, the unadjusted pandemic VE point estimate in children aged less than 15 years was 100% (binomial exact 95% CI: 74% to 100%), and in adults aged 15 years and over, the pandemic VE estimate was 67% (95% CI: 6% to 88%).

Adjusted seasonal influenza VE was -30% (95% CI: -89% to 11%). This estimate was adjusted for age group, sampling date (month) and pandemic vaccination status; these were the only variables which were significantly associated with a positive test result for pandemic influenza A(H1N1)2009 and altered the crude odds ratio for seasonal influenza vaccination status by more than 20%. If all individuals with an unknown date of seasonal influenza vaccination were assumed to be vaccinated on 17 October (and should therefore have developed protection by 1 November), the adjusted VE of the seasonal influenza vaccine was -22% (95% CI: -60% to 8%).

As a number of individuals included with a missing date of onset (*n*=616) were included in the final model, we examined the effect of setting the date of onset as equal to the date of sampling or date of sampling minus seven days if the date of onset was missing. The point estimates of the VE for either seasonal or pandemic vaccination remained the same. Several other sensitivity analyses were also carried out, with

Table 1

Personal and clinical characteristics of pandemic influenza A(H1N1) cases and controls, United Kingdom, 1 November 2009 – 29 January 2010 (N=5,982)

Variable	Number of cases (% of cases *N*=1,746)	Number of controls (% of controls *N*=4,236)
Received pandemic vaccine		
Vaccinated ≥14 days before onset	4 (0.2)	81 (1.9)
Vaccinated 7-13 days before onset	3 (0.2)	32 (0.8)
Vaccinated <7 days before onset	10 (0.6)	45 (1.1)
Vaccinated – date unknown	0 (0)	11 (0.3)
Unvaccinated[a]	877 (50.2)	2,225 (52.5)
Vaccination status unknown	852 (48.8)	1,842 (43.5)
Received seasonal vaccine		
Vaccinated ≥14 days before onset	52 (3.0)	234 (5.5)
Vaccinated<14days before onset	15 (0.9)	85 (2.0)
Vaccinated – date unknown	45 (2.6)	170 (4.0)
Unvaccinated[a]	1,476 (84.5)	3,313 (78.2)
Vaccination status unknown	158 (9.0)	434 (10.2)
Sex		
Female	934 (53.5)	2,486 (58.7)
Male	797 (45.6)	1,708 (40.3)
Unknown	15 (0.9)	42 (1.0)
Age group (years)		
<5	211 (12.1)	824 (19.5)
5-14	597 (34.2)	550 (13.0)
15-44	723 (41.4)	1,790 (42.3)
45-64	192 (11.0)	790 (18.6)
65+	21 (1.2)	265 (6.3)
Unknown	2 (0.1)	17 (0.4)
Date of sample		
November 2009	1,308 (74.9)	1,399 (33.0)
December 2009	371 (21.2)	2,264 (53.4)
1-29 January 2010	67 (3.8)	573 (13.5)
Interval (days between onset and sample collection)		
0-1	384 (22.0)	616 (14.5)
2-4	844 (48.3)	1,773 (41.9)
5-7	247 (14.1)	823 (19.4)
8-14	72 (4.1)	378 (8.9)
15-29	17 (1.0)	110 (2.6)
≥30	8 (0.5)	47 (1.1)
Unknown	174 (10.0)	489 (11.5)
Surveillance scheme		
RCGP	608 (34.8)	1,581 (37.3)
RMN	186 (10.7)	548 (12.9)
HPS	952 (54.5)	2,107 (49.7)

HPS: Health Protection Scotland RCGP: Royal College of General Practitioners' surveillance scheme; RMN: Health Protection Agency (HPA) Regional Microbiology Network.

[a] By date of onset.

varying assumptions about the vaccination status of individuals with missing vaccination status (Table 2).

The adjusted VE estimate remained robust to varying assumptions about the true vaccination status and date of vaccination of individuals for whom this information was missing, and restriction to various subgroups. If vaccine protection was assumed to be induced after seven or more days rather than 14 days, 120 individuals could be classified as vaccinated with pandemic vaccine, among whom seven (5.8%) were positive for pandemic influenza A(H1N1)2009. This gave an adjusted pandemic VE estimate of 71% (95% CI: 37% to 87%). There was only a minimal effect on VE when using week of sample collection rather than month (as a factor variable) in controlling for time period.

In order to validate data on pandemic vaccination status, RCGP and HPS swab data were linked to general practitioner (GP) records. Linkage was successful for a total of 1,468 individuals (of whom 910 were in the HPS scheme and 558 in the RCGP scheme). Of the 41 individuals recorded as vaccinated in the dataset from the swabbing programme, four (9.8%) did not have a record of vaccination in GP databases; however vaccination could have occurred in a hospital setting. Among the 606 individuals who were unvaccinated according to the swabbing dataset, only two (0.3%) were vaccinated according to the GP records and 604 were unvaccinated. Among the 821 individuals for whom there was no information on pandemic vaccination status in the swabbing dataset, only seven (0.9%) were vaccinated according to their GP records, the rest (99.1%) were unvaccinated. The proportion of vaccinated individuals in this group was significantly (chi-square test $p<0.001$) lower than among individuals with a known vaccination status, among whom 3.1% (95% CI: 2.7%, to 3.6%) were vaccinated (Table 1).

Discussion

This study has demonstrated high effectiveness of the newly developed monovalent pandemic influenza vaccine against confirmed pandemic influenza A(H1N1)2009 infection one week after vaccination – although the proportion of the study population that had received vaccination was low. No significant association, protective or otherwise, between trivalent seasonal influenza vaccination and confirmed pandemic influenza A(H1N1)2009 infection has been identified.

The case–control design employed in this study is an established method to estimate effectiveness of seasonal influenza vaccine in several countries [14, 22-26] and its robustness has been validated [21]. There are, however, potential limitations: Firstly, a convenience sample was used because random sampling of patients for a routine surveillance system based on GP-provided care is not feasible. It is unlikely, however, that the sampling would have caused substantial bias: although it is conceivable that a GP might selectively sample patients based on their vaccination status, their case or control status would not have been known at the time of sampling. Thus any selection bias would be randomly distributed. Selection bias could occur if severity of symptoms was related to influenza A(H1N1)2009-positive status, and GPs selectively sampled from persons with more severe symptoms whom they also know were vaccinated (although instructions are to sample the first few cases seen every week, regardless of vaccination status). This scenario would lead to an underestimation of VE. Secondly, as the vast majority of vaccinated individuals in this study for whom the vaccine brand was known had received Pandemrix, our results will not be applicable to Celvapan. Indeed, the study reflects the distribution of doses by vaccine brand delivered in the UK. Consequently, the estimated VE presented here is mainly applicable to Pandemrix. Thirdly, there were no data available on whether an individual had a chronic condition and therefore was in a target group for pandemic influenza vaccination. As

Table 2

Adjusted pandemic vaccine effectiveness under various assumptions and exclusion criteria, United Kingdom, 1 November 2009 – 29 January 2010

Assumption or exclusion criterion	Adjusted[a] pandemic vaccine effectiveness (95% confidence interval)	*n* in model
Individuals with missing vaccination dates excluded, individuals with missing vaccination status included as separate category	72% (21%–90%)	5,808
All individuals with missing vaccination status are assumed unvaccinated	71% (20%–90%)	5,808
All individuals with missing vaccination dates are assumed vaccinated on 21 October	74% (28%–91%)	5,819
Including only those individuals who received one dose of vaccine	71% (20%–90%)	5,806
Excluding individuals with missing pandemic vaccination status	73% (26%–90%)	3,147
Excluding individuals with an interval between onset and sampling of more than seven days	70% (15%–89%)	4,601
Pandemic vaccination protection begins after seven days	71% (37%–87%)	5,843
Using week rather than month as indicator of time period	73% (24%–90%)	5,808

[a] Adjusted for age group and sampling date (month).

the presence of a chronic condition may increase the severity of illness associated with influenza (compared to other respiratory infections) and thus the likelihood of seeking treatment in primary care, this may have lead to an underestimation of VE. A larger, more detailed study based on individual data from general practices would provide the possibility to adjust for such potential confounders. Fourthly, the impact of the influenza A(H1N1)2009 pandemic was greatest in children and young people, very few of whom had received the seasonal vaccine. For this reason, the effect of seasonal vaccination cannot be measured with precision. Finally, a number of samples lacked information on vaccination status. Several sensitivity analyses were carried out to examine the effect of various assumptions regarding vaccination status for those with missing vaccination status information. The pandemic VE estimates, however, appeared robust in these scenarios. Furthermore, validation of a sample of the RCGP and HPS swab data showed agreement of 99.1% between the information provided on the swab request form and the GP electronic record. The proportion of persons recorded as vaccinated by their GP was significantly lower among those with missing pandemic vaccination information on the swab request form compared to those where this information was available.

This study demonstrates that the pandemic influenza vaccine was highly effective in reducing confirmed pandemic influenza infection in persons consulting in primary care. In addition, it provides evidence of protection from as early as seven days after vaccination. This discovery corroborates findings of the high immunogenicity of pandemic vaccines in clinical trials: a UK study has reported that 79% of participants had seroconverted by 14 days after receiving a single dose of MF-59-adjuvanted vaccine [2]. More recent published work done after introduction of the pandemic vaccine into the German national programme has demonstrated it to be highly effective using the screening method [27]. However, although the investigators adjusted for the confounding effect of age, the screening method should be treated cautiously due to potential unrecognised confounding [28]. Our VE findings have been adjusted for various confounders. The results are similar to the estimated effectiveness of the traditional trivalent non-adjuvanted seasonal influenza vaccine during periods in which the vaccine is well matched with the circulating influenza strain [26,29], and the pandemic VE estimated here is considerably higher than in seasons of vaccine mismatch [23].

The peak of pandemic influenza activity during the second wave was in October 2009, at which stage the pandemic vaccine programme had only just started. Thus only a small proportion of the eligible population had been vaccinated at a time when pandemic virus was circulating widely. Consequently, although the observed pandemic VE was high in this study, because uptake was relatively low at this stage, any impact of the programme on disease at the population level would be more limited. This highlights the challenge of rapidly developing a new vaccine and implementing a new vaccine programme.

This study found no evidence that vaccination with 2009/10 trivalent seasonal influenza vaccine was associated with increased or decreased risk of subsequent pandemic influenza A(H1N1)2009 infection in the UK. This contrasts with conflicting published reports that seasonal influenza vaccine might either increase subsequent risk of pandemic influenza [11] or alternatively provide protection against pandemic influenza, particularly severe disease [7]. This study replicates findings from case–cohort studies in Australia and the United States, in which no protective effect was reported from the 2008/09 seasonal vaccine [8,9]. This observation suggests that cross protection from earlier seasonal vaccination cannot be assumed.

In conclusion, this study provides evidence that the pandemic influenza A(H1N1)2009 vaccine provided good protection against infection with pandemic influenza A(H1N1)2009 seven days or more after vaccination during the pandemic period. Further work is required to ascertain the effectiveness of the pandemic vaccine in children, in specific clinical risk groups and by individual vaccine brand.

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Conflicts of interest
All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that DMF has received funding to attend influenza related meetings and has received consultancy fees from influenza vaccine manufacturers who might have an interest in the submitted work in the previous there years. In addition, The Virus Reference Department of the Health Protection Agency receives funding from a variety of vaccine manufacturers who might have an interest in the submitted work. All other authors declare they have no conflicts of interest.

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Effectiveness of the 2009 seasonal influenza vaccine against pandemic influenza A(H1N1)2009 in healthcare workers in New Zealand, June-August 2009

S Jefferies[1,2], D Earl[2], N Berry[2], T Blackmore[2], S Rooker[2], N Raymond[2], A Pritchard[1], M Weatherall[2,3], R Beasley (Richard.Beasley@mrinz.ac.nz`)[1,2], K Perrin[1,2]

1. Medical Research Institute of New Zealand, Wellington, New Zealand
2. Capital and Coast District Health Board, Wellington, New Zealand
3. University of Otago Wellington, Wellington, New Zealand

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There is uncertainty whether the 2009 seasonal influenza vaccination influences the risk of infection with the 2009 pandemic influenza A(H1N1) virus. This issue was investigated in 548 healthcare workers from Capital and Coast District Health Board, Wellington, New Zealand, presenting with influenza-like illness during the influenza pandemic between June and August 2009. All workers completed an assessment sheet and had a nasopharyngeal swab tested by real-time RT-PCR. The risk of pandemic influenza A(H1N1) infection associated with the 2009 seasonal inactivated trivalent influenza vaccine was determined by logistic regression, with adjustment for potential confounding variables. In 96 workers pandemic influenza A(H1N1) RNA was detected and 452 tested negative. The multivariate analysis did not show any effect of vaccination on PCR-confirmed influenza A(H1N1)2009 infection (odds ratio 1.2, 95% confidence interval 0.7–1.9, p=0.48). We conclude that 2009 seasonal influenza vaccination had no protective effect against influenza A(H1N1)2009 infection amongst healthcare workers. To protect against further waves of the current pandemic influenza or future pandemics in which the influenza virus is antigenically distinct from contemporary seasonal influenza viruses, it would be necessary to vaccinate with a specific pandemic influenza vaccine, or a seasonal influenza vaccine that includes the pandemic influenza serotype.

Introduction

One of the important public health issues emanating from the global response to control the influenza pandemic was whether the seasonal trivalent inactivated influenza vaccination provided any protection. The novel reassortment of the influenza A(H1N1)2009 virus, combining swine, avian and human influenza genetic sequences, suggested that seasonal vaccination would confer little or no protection against this new virus [1-3]. This view was supported by a report from the United States that vaccination with seasonal influenza vaccines, regardless of whether they contained adjuvant, induced little or no cross-reactive antibody response to pandemic influenza A(H1N1) in any age group [4,5]. Consistent with these data, a case-cohort study from the United States [6], a case-control study from Australia [7], and a case series from Canada [8] have reported that the 2008/09 seasonal trivalent influenza vaccine provided no protective effect against pandemic influenza A(H1N1) infection.

In contrast, epidemiological studies from Mexico suggested that the seasonal trivalent inactivated influenza vaccine, administered as part of a national vaccination programme in 2009, provided partial protection against the 2009 pandemic influenza A(H1N1) [9,10]. In the case-control study [9], evidence was also provided that seasonal vaccination might protect against the most severe forms of the disease. It was proposed that these findings were consistent with an older report that showed that the 1967 seasonal influenza vaccine contributed towards preventing disease in the 1968/69 influenza pandemic in those who had not received the pandemic vaccine [11]. Furthermore, studies have reported variable levels of protection among infants, children and adults at times when seasonal influenza vaccine strains were not antigenically well matched to circulating endemic strains [12-17]. However, a case-control study based on Canada's sentinel vaccine effectiveness monitoring system reported that receipt of the 2008/09 seasonal influenza vaccine decreased the risk of seasonal influenza infection as expected, but was associated with an increased risk of pandemic influenza A(H1N1) infection [18]. In the same publication, two further Canadian case-control studies and one prospective cohort study were described in which seasonal influenza vaccination was associated with a 1.4 to 2.5-fold increased risk of medically attended illness due to pandemic influenza A(H1N1) [18]. Thus, epidemiological evidence exists to suggest that the 2009 seasonal influenza vaccination may increase, decrease

or have no effect on the risk of pandemic influenza A(H1N1) infection [19].

The provision of a comprehensive occupational health programme and the availability of occupational, virology and clinical databases of healthcare workers at Capital and Coast District Health Board (CCDHB) provided a unique opportunity to investigate this issue. In this prospective study, we report the potential effect of the 2009 seasonal influenza vaccine on the likelihood of acquisition of influenza A(H1N1)2009 in healthcare workers in New Zealand.

Methods

CCDHB has a comprehensive occupational health service which established an acute on-call programme for the investigation and treatment of workers who developed symptoms suggestive of influenza-like illness (ILI) during the 2009 influenza pandemic. The programme was activated in the second week of June 2009 within six weeks of the first confirmed case of pandemic influenza A(H1N1) infection in New Zealand [20]. In accordance with CCDHB policy, all staff who developed influenza-like symptoms, at work or elsewhere, were required to consult the occupational health service. The influenza-like symptoms included, but were not limited to, fever, runny nose, sore throat and cough. They completed a standardised influenza assessment sheet, provided a nasopharyngeal swab and were prescribed oseltamivir. The influenza assessment sheet collected information on variables such as age, sex, area of work, co-morbidity, pregnancy, the time between the onset of symptoms and nasopharyngeal swab, and whether the staff member self-reported having received the 2009 seasonal trivalent influenza vaccine. Travel from New Zealand in the four weeks prior to ILI was also recorded, although the virus had become largely endemic in the community by the time the data recording started.

The swabs were combined into one tube of viral and PCR transport medium and viral RNA was extracted using the High Pure Viral Nucleic Acid kit (Roche Diagnostics). Viral RNA specimens were analysed by realtime reverse transcription PCR (rRT-PCR) using the Capillary Lightcycler instrument version 1.2 (Roche Diagnostics) following protocols provided by the World Health Organization Collaborating Centre for the Surveillance, Epidemiology and Control of Influenza at the United States Centers for Disease Control and Prevention [21]. Swab specimens were tested using primers targeting the influenza A matrix gene, designed for universal detection of type A influenza viruses, and the influenza A haemagglutinin (H) gene (SwH1), specifically designed to detect pandemic influenza A(H1N1)2009. A sample was defined as positive for pandemic influenza A(H1N1) when both genes were detected. Specimens testing positive for the matrix gene but with no detectable levels of SwH1 were tested for seasonal human influenza A(H1) and A(H3) virus by rRT-PCR using primers and probes from version 2007 of the CDC protocol [21]. For the purposes of the analyses in this study, participants in whom pandemic influenza A(H1N1) RNA was detected (PI+ve) were compared with participants in whom no pandemic influenza A(H1N1)2009 or seasonal strains were detected (PI-ve).

The seasonal influenza vaccine used in New Zealand in 2009 was the inactivated trivalent vaccine Fluarix (GlaxoSmithKline), containing 15µg haemagglutinin each of the three strains A/Brisbane/59/2007, IVR-148 (H1N1), A/Uruguay/716/2007, NYMCX-175C (H3N2) and B/Brisbane/60/2008.

The CCDHB and Hutt Valley District Health Board (HVDHB) patient information systems of the participants were accessed to obtain information on ethnicity and deprivation decile. In New Zealand, deprivation decile is derived from nine variables descriptive of

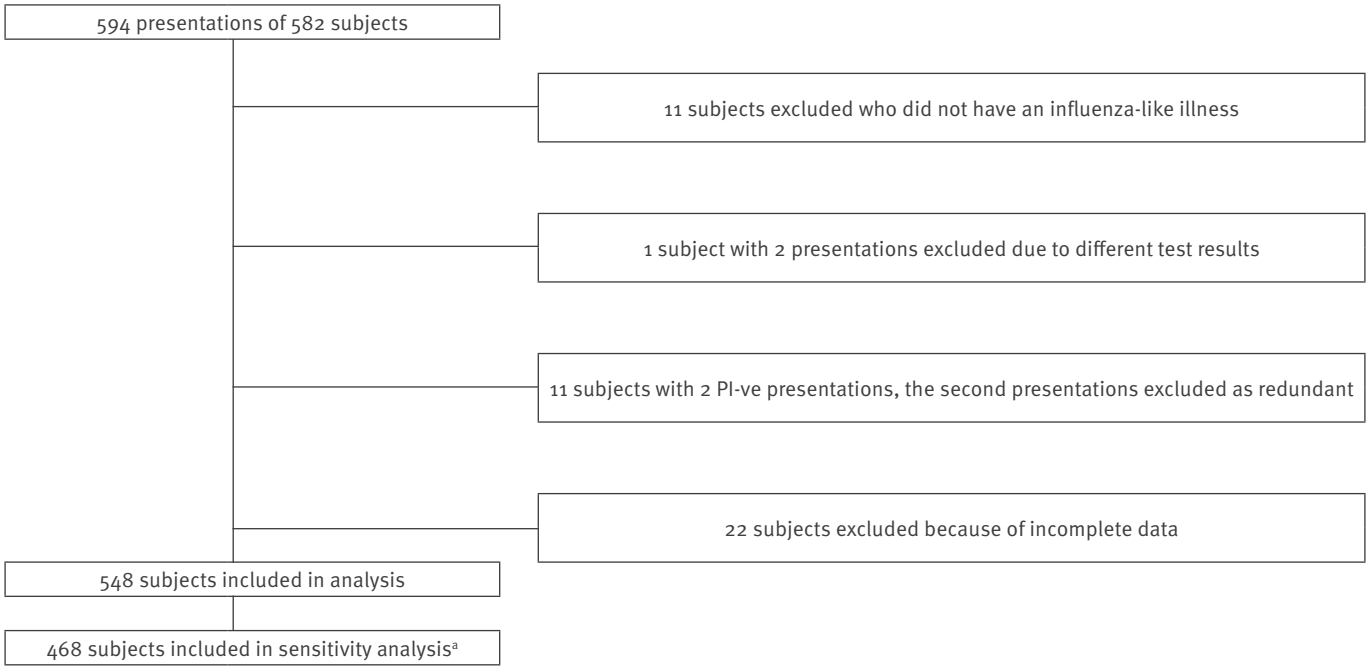
Table 1

Definition of comorbidities of study participants, New Zealand, 15 June–31 August 2009

Disorders included as comorbidity			Disorders not included as comorbidity
Respiratory	Cardiovascular	Other systemic	
Asthma	Arrhythmias	Addison's disease	Chronic backpain/spinal fusion
Bronchitis	Angina	Breast cancer on chemotherapy	Cyclic vomiting syndrome
Chronic obstructive pulmonary disease	Cardiomyopathy	Chronic renal failure	Depression
	Stroke	Diabetes mellitus	Eczema
	Hypertension	Hepatitis B/C	Epilepsy
	Pulmonary stenosis	Hypo/hyperthyroidism	Fibromyalgia
		Inflammatory bowel disease	Gout
		Renal transplant	Hypercholesterolaemia
		Rheumatoid arthritis	Irritable Bowel Syndrome
		Scleroderma	Marfan's Syndrome
		Systemic lupus erythematosus	Obstructive Sleep Apnoea
		Thalassaemia	Osteoarthritis
			Psoriasis
			Reflux gastritis

Figure

Inclusion criteria for study participants, New Zealand, 15 June–31 August 2009 (n=582)



PI+ve: pandemic influenza A(H1N1) RNA detected by rRT-PCR; PI-ve: pandemic influenza A(H1N1) RNA not detected by rRT-PCR.

[a] 80 subjects had no documentation of OHS administered seasonal influenza vaccine

Table 2

Characteristics of healthcare workers presenting with influenza-like illness, New Zealand, 15 June–31 August 2009 (n=548)

	Mean (standard deviation)		
Variable	PI+ve N=96	PI-ve N=452	All N=548
Age (years)	37.3 (10.8)	39.5 (11.3)	39.1 (11.3)
Deprivation decile	5.4 (2.9)	5.1 (2.9)	5.1 (2.9)
Days between symptom onset and swab	1.3 (1.1) N=92	1.5 (1.6) N=418	1.5 (1.5) N=510
	n/N (%)		
	PI+ve	PI-ve	All
Male sex	30/96 (31.3)	99/452 (21.9)	129/548 (23.5)
Ethnicity			
• Not stated	8/96 (8.3)	19/452 (4.2)	27/548 (4.9)
• Māori	8/96 (8.3)	31/452 (6.9)	39/548 (7.1)
• Pacific island	9/96 (9.4)	28/452 (6.2)	37/548 (6.8)
• Other	71/96 (74.0)	374/452 (82.7)	445/548 (81.2)
Patient contact	83/96 (86.5)	353/452 (78.1)	436/548 (79.6)
Travel[a]	2/96 (2.1)	15/452 (3.3)	17/548 (3.1)
Pregnancy (women only)	1/66 (1.5)	5/353 (1.4)	6/419 (1.4)
Comorbidities	31/96 (32.3)	114/452 (25.2)	145/548 (26.5)
Hospital admission	0/96 (0)	2/452 (0.4)	2/548 (0.4)
Emergency department attendance	6/96 (6.3)	9/452 (2.0)	15/548 (2.7)
Self-reported vaccination[b]	53/96 (55.2)	233/451 (51.7)	286/547 (52.3)
OHS-documented vaccination[c]	44/83 (53.0)	186/385 (48.3)	232/468 (49.6)

OHS: occupational health service; PI+ve: pandemic influenza A(H1N1) RNA detected by rRT-PCR; PI-ve: pandemic influenza A(H1N1) RNA not detected by rRT-PCR; realtime reverse transcription PCR.

[a] International travel within four weeks before influenza-like illness symptoms.

[b] One participant missing data.

[c] Documentation of 2009 seasonal influenza vaccination in occupational health service personal files. For 80 subjects a file was not available.

socio-economic status relative to the location of the home, such as income, home ownership and access to transport. It ranges from 1 (least deprived) to 10 (most deprived) [22]. We also used these databases to identify whether any of the participants were admitted to or attended the emergency department of Wellington, Kenepuru and Hutt hospitals for an ILI in the two days before and the two weeks after the swab was taken. These three government-funded hospitals represent the only hospitals in the greater Wellington region which provide acute medical services. Workers admitted to hospital with an ILI were considered to have experienced a severe influenza illness.

The CCDHB occupational health service keeps the records of the assessment and treatment of healthcare workers presenting with suspected pandemic influenza A(H1N1) (including the influenza assessment sheet, PCR results and prescribed treatment). The personal files of all healthcare workers employed at CCDHB were checked for documentation of the 2009 seasonal influenza vaccination. The sensitivity analysis of the effect of the 2009 seasonal influenza vaccination was based on these records. The demographic, clinical, occupational, vaccination and virological data was entered in a database where every subject was given a unique identifier. The dataset was coded and anonymised prior to analysis.

Statistical power

With 100 cases and 450 controls and assuming a 50% immunisation rate in the controls, the study had 80% power to detect an odds ratio of 0.52.

Statistical analysis

Logistic regression was used to determine the strength of association between PCR-confirmed pandemic influenza A(H1N1) infection and self-reported seasonal influenza vaccination, unadjusted and adjusted for potential confounding variables. The variables included age, sex, ethnicity (Maori, Pacific, other, not stated), deprivation decile, relevant overseas travel,

Table 3

Univariate associations between study participants' characteristics and confirmed pandemic influenza A(H1N1) infection, New Zealand, 15 June–31 August 2009 (n=548)

Variable	Odds ratio for association (95% confidence interval)	p value
Age (per decade older)	0.8 (0.7 to 1.0)	0.08
Deprivation decile (per level)	1.0 (0.96 to 1.1)	0.45
Male sex	1.6 (1.0 to 2.6)	0.05
Ethnicity		0.18 [a]
• Not stated	2.2 (0.9 to 5.3)	0.26 [a]
• Māori	1.4 (0.6 to 3.1)	0.76 [a]
• Pacific island	1.7 (0.8 to 3.7)	0.71 [a]
• Other	Reference level	
Patient contact	1.8 (1.0 to 3.4)	0.07
Travel[b]	0.6 (0.1 to 2.8)	0.53
Pregnancy (women only)	1.1 (0.1 to 9.3)	0.95
Comorbidities	1.4 (0.9 to 2.3)	0.15
Hospital admission	Not applicable	0.51
Emergency room attendance	3.3 (1.1 to 9.4)	0.02
Self-reported vaccination	1.2 (0.7 to 1.8)	0.53
OHS-documented vaccination[c]	1.2 (0.7 to 1.9)	0.49

OHS: occupational health service.

[a] Compared to 'Other'.

[b] International travel within four weeks before influenza-like illness symptoms.

[c] Documentation of 2009 seasonal influenza vaccination in occupational health service personal files. For 80 subjects a file was not available.

Table 4

Multivariate association between study participants' vaccination status and confirmed pandemic influenza A(H1N1) infection[a], New Zealand, 15 June–31 August 2009 (n=548)

Variable	Odds ratio for association (95% confidence interval)	p value
Self-reported vaccination	1.2 (0.7 to 1.9)	0.48
OHS-documented vaccination[b]	1.2 (0.7 to 1.9)	0.49

OHS: occupational health service.

[a] Adjusted for age, sex, ethnicity, deprivation decile, patient contact, relevant travel, pregnancy (all men coded as not-pregnant), comorbidities.

[b] Documentation of 2009 seasonal influenza vaccination in Occupational Health Service personal files. In 80 subjects no file was available.

comorbidity (yes/no) (Table 1), and pregnancy (yes/no, all men coded as not pregnant). SAS version 9.1 was used for the statistical calculations.

This analysis was restricted to subjects who presented with an ILI and had documentation of the influenza assessment sheet and PCR results. Subjects who presented on more than one occasion and had different PCR results from the different presentations were excluded. In subjects who presented on more than one occasion and pandemic influenza A(H1N1) was not detected on any presentation, the data from the first presentation was included.

Results

There were 582 healthcare workers who presented on 594 occasions to the CCDHB occupational health service between 15 June and 31 August 2009 (Figure). After application of the exclusion criteria, 548 workers who had presented with an ILI were included in the analysis.

The characteristics of these participants are shown in Table 2. The mean age of the participants was 39 years (range: 20 to 69 years) and 24% were male. People of Maori and Pacific origin made up 14% of the study group. The majority of participants (80%) had clinical patient contact as part of their work. Overall, 52% of the participants self-reported having received the 2009 seasonal influenza vaccination. In 27% of participants comorbidities were reported, of which the most common were asthma and hypertension. Among the 145 healthcare workers with documented comorbidities, 82 self-reported having received the 2009 seasonal vaccine, 62 self-reported not having received it, and for one the information was missing. The mean time from the onset of symptoms to nasopharyngeal swab was 1.5 days.

Influenza A was detected by PCR in 103 of the 548 included participants. In 96 of those pandemic influenza A(H1N1) was detected, in five seasonal human influenza A(H1), in one seasonal human influenza A(H3) and in one an untypable strain of influenza A. We therefore determined 96 (17.5%) participants with confirmed pandemic influenza A(H1N1) infection (PI+ve) and 452 (82.5%) in whom pandemic influenza A(H1N1) was not detected (PI-ve).

There was no difference in the proportion of workers with and without proven pandemic influenza A(H1N1) infection who reported having received the 2009 seasonal influenza vaccination, with 53 of 96 (55.2%) infected and 233 of 451 (51.7%) not infected at an odds ratio of 1.2 (95% confidence interval (CI): 0.7–1.8, p=0.53) (Table 2 and 3). The multivariate analysis, adjusted for age, sex, ethnicity, deprivation decile, patient contact, overseas travel, comorbidity and pregnancy, did not indicate any significant risk of pandemic influenza A(H1N1) being associated with the 2009 seasonal influenza vaccine (odds ratio: 1.2, 95% CI: 0.7–1.9, p=0.48) (Table 4).

Personal files of 468 of the participants were held by the occupational health service. In a sensitivity analysis based on the documentation from these files, we saw no significant effect of 2009 seasonal influenza vaccination on the risk of pandemic influenza A(H1N1) neither in the univariate analysis (odds ratio: 1.2, 95% CI: 0.7–1.9, p=0.49) (Table 3) nor multivariate analysis (odds ratio: 1.2, 95% CI: 0.7–1.9, p=0.49) (Table 4).

PI+ve participants were similar to PI-ve participants with regard to age, deprivation decile, pregnancy, comorbidities, relevant travel, and time between symptom onset and swab (Tables 2 and 3). There was no statistically significant difference in ethnicity between the swab-negative and swab-positive group, however this analysis was limited by the small numbers of people of Maori and Pacific origin, and the point estimates were consistent with an increased risk. Likewise, the point estimate for patient contact was consistent with an increased risk, but the difference was not statistically significant (odds ratio: 1.8, 95% CI: 1.0–3.4, p=0.07).

Fifteen people with an ILI visited an emergency department in the two days before and two weeks after presentation to the occupational health service. Participants who attended an emergency department were more likely to be PI+ve (odds ratio: 3.3, 95% CI: 1.1–9.4, p=0.02). Two people were admitted to hospital with an ILI, both of whom were PI-ve.

Discussion

In our prospective study the 2009 seasonal influenza vaccination had no protective effect against pandemic influenza A(H1N1) infection amongst healthcare workers in New Zealand. This suggests that to obtain protection against influenza A(H1N1)2009 in the current season 2010, it would be necessary to vaccinate with a specific pandemic influenza A(H1N1) vaccine, or to include the influenza A(H1N1)2009 antigenic group in the 2010 seasonal influenza vaccine.

A number of methodological issues are relevant to the interpretation of the study findings. Firstly, by recruiting healthcare workers, we were able to study a population with a high prevalence of seasonal influenza vaccination; about half of the workers included in the study had received the 2009 seasonal influenza vaccine. Secondly, by studying workers, all of whom were under 70 years-old, we were able to investigate a group that did not have prior widespread immunity to pandemic influenza, assuming that the age-specific rates of pre-existing protective antibodies in New Zealand are similar to those in the United Kingdom [23]. All subjects presenting to the occupational health service with an ILI provided nasopharyngeal swabs which were assessed by rRT-PCR. The mean time between onset of symptoms and nasopharyngeal swab was 1.5 days, with no significant difference between groups, suggesting that delay in viral sampling was unlikely to be a confounding factor [24].

Another issue is the accuracy of the seasonal vaccination records. For the primary analysis, information on vaccination status was provided by the workers when completing the influenza assessment sheet at the time of presentation to the occupational health service. As this information was provided without knowledge of the PCR results, and the seasonal influenza vaccinations had taken place in the three months before the study, we consider the findings unlikely to be influenced by recall bias. For the sensitivity analysis, seasonal influenza vaccination status was also determined from documentation in the participants' personal files held by the occupational health service. While this approach was limited by the fact that not all workers had personal files and some workers may have been vaccinated through community services, the comparable results provided internal validity to the study findings.

Pandemic influenza infection results in disease with a wide spectrum of severity, from asymptomatic to life-threatening illness [24-26]. All participants included in our analysis presented with a symptomatic ILI, which means that asymptomatic workers with influenza infection were not included in the study. Due to the low frequency of severe illness requiring hospital admission (none among the confirmed pandemic influenza A(H1N1) cases in our study) we were unable to determine whether seasonal influenza vaccination may protect against the most severe forms of the disease.

Thanks to the prospective collection of comprehensive data at the time of presentation and the availability of clinical databases, we were able to undertake multivariate analyses in which we adjusted for variables that could have influenced the association between 2009 seasonal influenza vaccination and infection with pandemic influenza A(H1N1)2009. These factors included age, sex, ethnicity, work-related patient contact, overseas travel, pregnancy and comorbidities. This approach lent strength to our statistical analysis.

Our findings add to recent data from studies that have identified no risk [6-8], a decreased risk [9,10], or an increased risk [18] of pandemic influenza A(H1N1) infection associated with seasonal influenza vaccination. An Australian study found no evidence in any age group of seasonal influenza vaccination providing significant protection against pandemic influenza A(H1N1) virus infection [7]. In that study the population had been vaccinated with an inactivated trivalent vaccine which contained the A/Brisbane/59/2007 antigenic group as the H1N1 component, the same subtype variant included in the trivalent vaccine in our study. The strength of their study was the validity of vaccination records, virological confirmation of influenza infection in subjects presenting with ILI and the age-stratified and age-adjusted analyses.

A case-control study from Mexico demonstrated that seasonal influenza vaccination had 73% effectiveness against pandemic influenza A(H1N1) [9]. This study was limited by the choice of controls, who had a higher rate of co-morbidity and for that reason may have been more likely to receive seasonal influenza vaccination, and by the fact that the vaccination status was retrospectively collected and there was no microbiological verification of the absence of influenza infection [27,28]. Similar limitations apply to a cohort study from the United States, which did not find any protective effect of seasonal influenza vaccination on pandemic influenza infection [6].

However, these potential limitations do not apply to a subsequent large surveillance study of pandemic influenza A(H1N1) virus infection in Mexico, which showed that the risk of infection was reduced by about one third in those who had been vaccinated for seasonal influenza [10]. Although it has been suggested that these study results could have been confounded by selection bias, if elderly people who are more likely to be vaccinated were less likely to be infected with pandemic influenza due to pre-existing immunity [29], this was not supported by subsequent stratified analysis [30]. Based on data from the first and second waves of the pandemic in Mexico up to 30 November 2009, the negative association between seasonal vaccination and risk of testing positive for pandemic influenza A(H1N1) was present across all age groups, including those younger than 60 years [30].

In contrast, three case-control studies and a prospective cohort study demonstrated a statistically significant 1.4 to 2.5-fold increased risk of medically attended illness due to pandemic influenza A(H1N1) [18]. The first of these studies, based on Canada's well established sentinel vaccine effectiveness monitoring system identified that seasonal influenza vaccination increased the risk of pandemic influenza infection to a similar extent as it reduced the risk of seasonal influenza infection (+68% versus -56%) [18]. A study of an outbreak of pandemic influenza A(H1N1) infection amongst United States military personnel also identified an increased risk of infection, although this association was limited to personnel on active duty and not their family members or retired staff [33].

The reasons for these contrasting results are uncertain. It is possible that they may be due to methodological differences between the studies, or to differences in the effect of the specific vaccines, in the immunisation programmes or in population immunity [18,34]. Regardless of the underlying reasons, these epidemiological studies suggest that seasonal influenza vaccination cannot be considered or recommended as an effective strategy for the prevention of pandemic influenza infection.

In conclusion, this study has shown that the 2009 seasonal influenza vaccination provided no protection against pandemic influenza A(H1N1) infection in healthcare workers in New Zealand. To obtain protection

against subsequent waves of the pandemic influenza A(H1N1)2009 by vaccination, it would therefore be necessary to either vaccinate with a specific pandemic influenza vaccine or a seasonal influenza vaccine which includes the influenza A(H1N1)2009 subtype. The findings also suggest that in future influenza pandemics in which the virus is antigenically and genetically distinct from contemporary human seasonal influenza viruses, development of a specific pandemic influenza vaccine is a high priority, as partial protection by the contemporary seasonal influenza vaccines cannot be assumed.

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Secondary attack rate of pandemic influenza A(H1N1)2009 in Western Australian households, 29 May–7 August 2009

D Carcione (dale.carcione@health.wa.gov.au)[1], C M Giele[1], L S Goggin[1], K SH Kwan[1], D W Smith[2], G K Dowse[1], D B Mak[1], P Effler[1]
1. Communicable Disease Control Directorate, Department of Health, Perth, Western Australia, Australia
2. PathWest Laboratory Medicine WA, Nedlands, Western Australia, Australia

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Understanding household transmission of the pandemic influenza A(H1N1)2009 virus, including risk factors for transmission, is important for refining public health strategies to reduce the burden of the disease. During the influenza season of 2009 we investigated transmission of the emerging virus in 595 households in which the index case was the first symptomatic case of influenza A(H1N1)2009. Secondary cases were defined as household contacts with influenza-like illness (ILI) or laboratory-confirmed influenza A(H1N1)2009, occurring at least one day after but within seven days following symptom onset in the index case. ILI developed in 231 of the 1,589 household contacts, a secondary attack rate of 14.5% (95% confidence interval (CI): 12.9–16.4). At least one secondary case occurred in 166 of the 595 households (a household transmission rate of 27.9%; 95% CI: 24.5–31.6). Of these, 127 (76.5%) households reported one secondary case and 39 (23.5%) households reported two or more secondary cases. Secondary attack rates were highest in children younger than five years (p=0.001), and young children were also more efficient transmitters (p=0.01). Individual risk was not associated with household size. Prophylactic antiviral therapy was associated with reduced transmission (p=0.03). The secondary attack rate of ILI in households with a confirmed pandemic influenza A(H1N1)2009 index case was comparable to that described previously for seasonal influenza.

Introduction

The world experienced the first influenza pandemic of the 21st century in 2009. Pandemic influenza A(H1N1)2009 (hereafter to be referred to as pandemic influenza) was identified initially in Mexico and the United States (US) [1,2] and spread rapidly to the southern hemisphere, becoming the dominant strain during the 2009 Australian winter [3]. In Western Australia (WA), pandemic influenza comprised over 90% of influenza notifications for which subtyping data were available. Pandemic influenza has since dominated the 2009/10 northern hemisphere winter and the 2010 southern hemisphere winter.

Understanding the transmission dynamics of pandemic influenza, including risk factors for transmission, is important in informing public health strategies to reduce the impact of the virus. Unfortunately, household transmission studies of the current [4-6], and previous influenza pandemics are scarce [7], and rely on studies of seasonal influenza [8-12]. Secondary attack rates reported for seasonal influenza range from 10% to nearly 40% and vary with age, circulating strain, family composition, and levels of community exposure [8-12].

In the period between the notification of the first case in WA in late May 2009 and early August 2009 (before distribution of pandemic influenza vaccine), we investigated household transmission of pandemic influenza in WA. The objectives were to estimate the secondary attack rate and to describe the characteristics of index cases and their household contacts that were associated with risk of transmission.

Methods

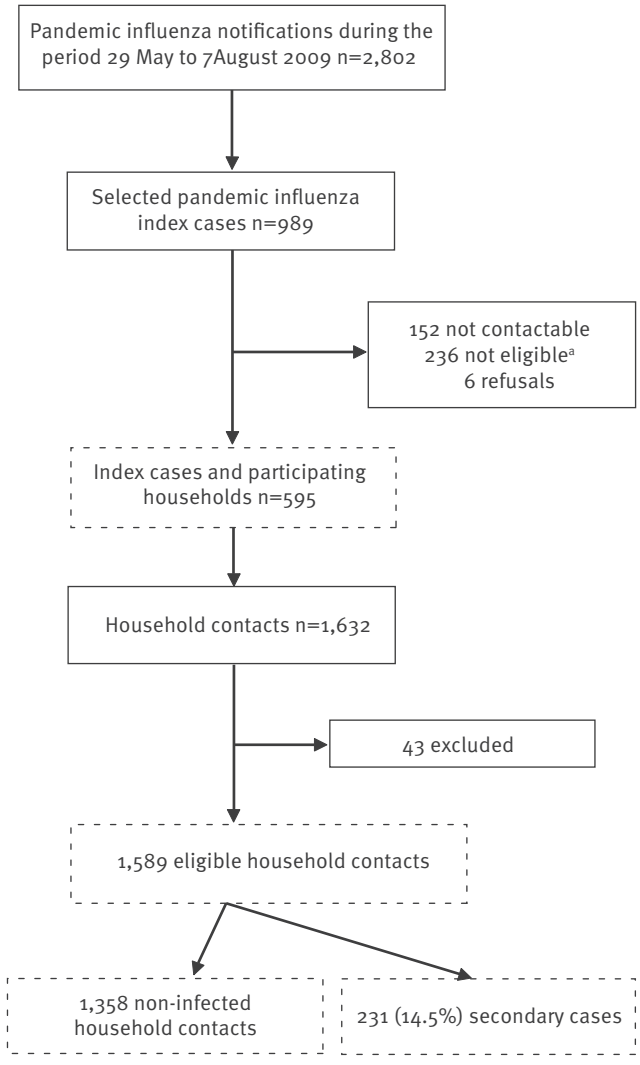
Pandemic influenza index cases and their household contacts were recruited during a ten-week period encompassing the peak of pandemic influenza activity, from 29 May 2009 (four days after notification of the first confirmed case in WA), to 7 August 2009 [13]. Influenza is a notifiable disease in Australia, and cases were identified from the WA Notifiable Infectious Diseases Database, which is maintained by the Communicable Disease Control Directorate (CDCD). This database captures all notifiable disease reports for the State of WA, which has a population of over 2.2 million people [14]. All laboratory testing for pandemic influenza was carried out by PathWest Laboratory Medicine WA, a World Health Organization-designated National Influenza Centre. As a minimum, all specimens were tested by PCR directed at specific targets in the influenza A matrix gene and the pandemic influenza

H1 haemagglutinin gene [15]. Over 90% of specimens were also tested for influenza B, and seasonal influenza A(H1) and A(H3) by PCR [15].

An index case was defined as anyone notified with pandemic influenza diagnosed by PCR during the study period and who otherwise met the eligibility criteria (see below). A household was defined as a group of two or more people living together in a domestic residence; residential institutions, such as boarding schools, hotels or prisons were excluded. A household contact was defined as any person who had resided in the same household as the index case for at least one night during the household exposure period (one day before to seven days after onset of illness in the index case). Index cases were excluded if they lived alone, did not spend time at the household after the onset of symptoms, had a co-infection with another influenza virus and/or were not the first symptomatic individual in the household. Household contacts who had the same symptom onset date as the index case, and were therefore possibly infected from the same source as the index case, were also excluded.

Figure 1

Flow diagram of the investigation, household transmission study of pandemic influenza A(H1N1)2009, Western Australia, 29 May–7 August 2009



[a] Non-eligible index cases include: 140 who were not the first case of influenza-like illness in the household, 62 who lived alone, 28 who did not live at a private residential address, four who had a co-infection with another influenza virus, and two who could not communicate in English.

Dotted boxes denote those included in the final analysis.

Influenza-like illness (ILI) was defined as fever ›38 ºC, or a reliable history of fever of unknown temperature, AND cough and/or sore throat. A *secondary case* was defined as a household contact who developed an ILI or laboratory-confirmed influenza within seven days of symptom onset in the index case (distinctions were not made between secondary and tertiary cases in the household). *Household transmission* was deemed to have occurred if at least one household contact became a secondary case. Household contacts who did not develop an ILI or test positive for pandemic influenza were classified as uninfected household contacts. The secondary attack rate was calculated as the number of secondary cases divided by the total number of eligible household contacts. The mean serial interval was calculated from the sum of the time between the onset of ILI symptoms in all index and secondary case pairs.

Public health nurses interviewed each selected index case twice by telephone: within 48 hours of notification to CDCD and the second time as close as possible to eight days after symptom onset. At the first interview, the reason for the investigation was explained and information was collected on: symptoms, use of antiviral medications, underlying medical conditions, vaccination for seasonal influenza and number of household contacts. The second interview collected information on household contacts, including: age, sex, number of days living in the household during the household exposure period, whether they shared the same room or bed as the index case, onset and symptoms of any illness during the exposure period, underlying medical conditions, use of antiviral prophylaxis, and vaccination for seasonal influenza. If an index case was unable to answer the questions or was under 18 years of age, an adult household member was interviewed as a proxy. A total of six attempts were made to contact the index case and/or household contacts, after which point they were deemed not contactable.

Information was sought on whether any household contacts had been notified with influenza in the exposure period by searching the notifications database for any confirmed influenza results matching the contact's name and date of birth with a specimen date within seven days of symptom onset. If no notification was recorded, PathWest Laboratory Medicine WA records were checked, to determine whether an influenza test had been performed and the result.

The secondary attack rate was analysed in relation to covariates measured at the index case and household contact levels using univariate chi-square test for proportions and t-tests for continuous variables.

Subjects were stratified by age into pre-school-aged children (≤4 years-old), school-aged children (5 to 18 years-old), 19 to 50 year-olds, and those aged over 50 years. Univariate odds ratios (OR) and 95% confidence intervals (CI) were determined, and if multiple variables were found to be significant, they were entered as input for a backward step-wise logistic regression analysis. To adjust for clustering by household, generalised estimating equations were used to obtain p values and confidence limits for ORs for all household contact analyses. All analyses were performed using PASW Version 17.0.2 (SPSS Inc., Chicago, IL). Information was collected as part of case follow-up for a notifiable disease of public health concern and did not require approval by a human research ethics committee.

Results

A total of 2,802 laboratory-confirmed pandemic influenza notifications were received during the ten-week study period. During the first six weeks, public health nurses attempted to contact each of the 468 pandemic influenza index cases notified in that period. Of those 468 notifications, 309 (66.0%) were contacted, assessed eligible, and agreed to participate in the study. From 14 July to 7 August 2009, due to the increasing volume of notifications, a daily random sample of 20 pandemic influenza notifications per day were selected [16]. Of 521 additional index cases chosen by this method, 286 (54.9%) were contactable and eligible for the study.

In total, 595 (60.2%) of the 989 selected pandemic influenza index cases were eligible and participated in the

Table 1

Characteristics of pandemic influenza A(H1N1)2009 index cases and their household contacts, Western Australia, 29 May–7 August 2009 (n=2,184)

Characteristic	Pandemic influenza index cases[a] N[b]=595	Household contacts N[b]=1,589
Age, mean (standard deviation)	25.7 (16.4)	30.1 (18.8)
Age range, years	0–79	0–103
Age group		
0–4 years	26 (4.4)	124 (7.8)
5–18 years	237 (39.8)	447 (28.1)
19–50 years	277 (46.6)	757 (47.6)
≥ 51 years	55 (9.2)	228 (14.3)
Sex		
Male	294 (49.4)	806 (50.7)
Female	301 (50.6)	783 (49.3)
Indigenous status		
Aboriginal	34 (5.7)	62 (3.9)
Underlying medical conditions		
Diabetes	35 (5.9)	35 (2.2)
Heart disease	19 (3.2)	33 (2.1)
Respiratory disease	116 (19.5)	126 (7.9)
Renal disease	2 (0.3)	5 (0.3)
Neurological disease	4 (0.7)	13 (0.8)
Haematological disorder	11 (1.8)	11 (0.7)
Metabolic disease (excluding diabetes)	9 (1.5)	2 (0.1)
Immune impairment	15 (2.5)	19 (1.2)
Morbid obesity	41 (6.9)	60 (3.8)
Current smoker	58 (9.7)	137 (8.6)
Pregnant (females only)	20 (3.4)	13 (1.7)
Any underlying condition[c]	232 (39.0)	270 (17.0)
Antivirals		
Yes	238 (40.0)	220 (13.8)
No[d]	331 (55.6)	1,327 (83.5)
Seasonal influenza vaccination in 2009		
Yes	125 (25.0)	304 (19.1)
No	394 (66.2)	1,162 (73.1)

[a] Number of people (percentage), unless otherwise indicated.
[b] Respondents may not add up to total because of missing information for some variables.
[c] Patient reported at least one of the underlying medical conditions listed.
[d] Refers to treatment use of antiviral drugs in index cases and preventative use of antiviral drugs in household contacts.

Table 2

Characteristics of the household contacts of influenza A(H1N1)2009 index cases and secondary attack rates associated with these characteristics, Western Australia, 29 May–7 August 2009 (n=1,589)

Characteristic of household contact	Number of household contacts n[a]=1,589	Secondary attack rate, %	Odds ratio (95% CI)	p value
Age				
0–4 years	124	22.6	3.40 (1.80 to 6.45)	
5–18 years	447	17.2	2.43 (1.41 to 4.17)	**0.001**[b]
19–50 years	757	13.7	1.86 (1.10 to 3.14)	
≥ 51 years	228	7.9	1.00	
Sex				
Male	806	14.6	1.04 (0.79 to 1.37)	0.80
Female	783	14.3	1.00	
Indigenous status				
Aboriginal	62	8.1	0.49 (0.20 to 1.24)	0.13
Non-Aboriginal	1,474	15.1	1.00	
Present for the entire index illness				
Yes	1497	14.9	2.49 (0.99 to 6.22)	0.05
No	76	6.6	1.00	
Shared the same room as the index				
Yes	337	16.6	1.24 (0.89 to 1.72)	0.20
No	1226	13.9	1.00	
Shared the same bed as the index				
Yes	289	17.6	1.35 (0.96 to 1.90)	0.09
No	1275	13.7	1.00	
Underlying medical conditions[c]				
Diabetes	35	8.6	0.54 (0.16 to 1.78)	0.31
Heart disease	33	15.2	1.04 (0.40 to 2.73)	0.93
Respiratory disease	126	22.2	1.76 (1.13 to 2.75)	**0.01**
Renal disease	5	20.0	1.46 (0.16 to 13.12)	0.74
Neurological disease	13	23.1	1.76 (0.48 to 6.44)	0.39
Haematological disorder	11	0.0	–	0.17
Metabolic disease (excluding diabetes)	2	0.0	–	0.56
Immune impairment	19	21.1	1.57 (0.52 to 4.78)	0.43
Morbid obesity	60	16.7	1.17 (0.59 to 2.35)	0.65
Current smoker	137	10.2	0.64 (0.36 to 1.14)	0.13
Pregnant (females only)	13	0.0	–	0.22
Any underlying condition[d]	270	18.5	1.40 (0.99 to 1.98)	0.06
Prophylactic antiviral therapy				
Yes	220	9.5	0.58 (0.36 to 0.94)	**0.03**
No	1,327	15.3	1.00	
Seasonal influenza vaccination in 2009				
Yes	304	15.1	1.01 (0.71 to 1.44)	0.95
No	1,162	15.0	1.00	
Household size				
2 persons	135	16.3	1·00	
3 persons	273	12.5	0·73 (0·41 to 1·31)	0.65[b]
4 persons	514	14.2	0·85 (0·51 to 1·43)	
≥5 persons	667	15.3	1·01 (0·59 to 1·73)	

[a] Respondents may not add up to total because of missing information for some variables.

[b] Chi-square test for trend.

[c] Odds ratio for individual underlying medical conditions is the odds of infection among contacts with that condition, versus the odds in those not reporting that condition.

[d] Patient reported at least one of the underlying medical conditions listed.

Variables in blue were statistically significant and were included in the multivariate logistic regression.

investigation (Figure 1). Participating index cases were very similar with respect to age (median age 25 years) and sex, to all remaining pandemic influenza cases who were notified in the study period and who were not interviewed or eligible to participate (n=2,207).

There were 1,632 household contacts in the 595 participating households. Forty-three contacts were excluded, 14 with insufficient information and 29 who became ill on the same day as the index case, leaving 1,589 household contacts for the final analysis (Figure 1). Characteristics of index cases and household contacts are shown in Table 1. Index cases were younger, and more likely to report underlying medical conditions and to have had seasonal influenza vaccine, than the household contacts.

Overall, 231 secondary cases occurred among the 1,589 household contacts, giving a secondary attack rate of 14.5% (95% CI: 12.9–16.4). The secondary attack rate in households without co-primary household contacts (n=570) was similar to that in all households including those with co-primary contacts (13.6% and 14.5%, respectively, p=0.47).

In order to estimate the proportion of ILI cases due to pandemic influenza, we identified all secondary cases who had swabs collected within 48 hours of onset of ILI symptoms, at which time the yield should be optimal [17]. Among these 29 cases, 27 were PCR-positive for pandemic influenza, suggesting ILI was highly predictive of pandemic influenza infection in these households.

One or more secondary cases occurred in 166 of the 595 households (27.9%; 95% CI: 24.5–31.6). Of the 166 households with secondary cases 127 (76.5%) reported one case, 20 (12.0%) reported two, 13 (7.8%) reported three, five (3.0%) reported four, and one (0.6%) reported five secondary cases.

Table 2 shows the characteristics of the household contacts and secondary attack rates associated with these characteristics. Secondary cases (mean age 25.2 years) were significantly (p<0.001) younger than uninfected household contacts (mean age 31.0 years). There was a clear inverse association between age and secondary attack rate (p=0.001), with the odds of illness 3.4 times higher in 0 to 4-year-old children compared to adults aged 51 years or older. Secondary attack rates were elevated in household contacts who were present for the entire household exposure period, although this just failed to reach statistical significance (OR=2.49, p=0.05). Among a range of underlying medical conditions, only respiratory disease (including asthma) was significantly more prevalent in secondary cases (OR=1.72, p=0.01) compared to uninfected contacts. Uninfected contacts were more likely to have taken antiviral prophylaxis (14.7%) compared to secondary cases (9.1%; p=0.03). Transmission was not associated with sex, indigenous status, smoking, sharing a room or bed with the index case, household size or 2009 seasonal influenza vaccination status of household contacts. In the multivariate logistic regression model, which included age (p<0.001), respiratory disease (p=0.031) and prophylactic antiviral therapy (p=0.031), all remained independent predictors for (or against, in the case of prophylactic antiviral therapy) becoming a secondary case.

As illustrated in Figure 2, there was an inverse association between secondary attack rates and age of both index cases and household contacts. Young index cases were more likely to transmit infection to their household contacts, and young household contacts were more likely to be infected.

Amongst the range of symptoms reported by index cases, the following resulted in significantly more transmission to secondary cases than others: cough (p=0.04), shortness of breath (p<0.001), fatigue (p<0.001), myalgia (p=0.009), rigors (p=0.003), diarrhoea (p=0.001) and vomiting (p<0.001). There was no difference in the secondary attack rate associated with index cases who had taken antiviral treatment (14.9%) compared to those who had not (14.1%, p=0.70). The mean interval from onset of illness to treatment of the index case was three days and the median interval was two days.

Figure 2

Secondary attack rate of influenza A(H1N1)2009 index cases and household contacts, by age group, Western Australia, 29 May–7 August 2009 (n=2,184)

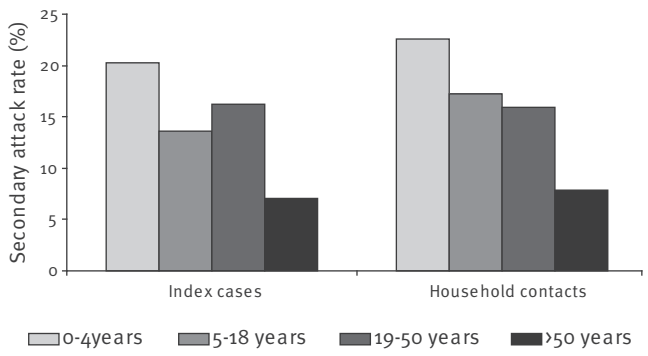
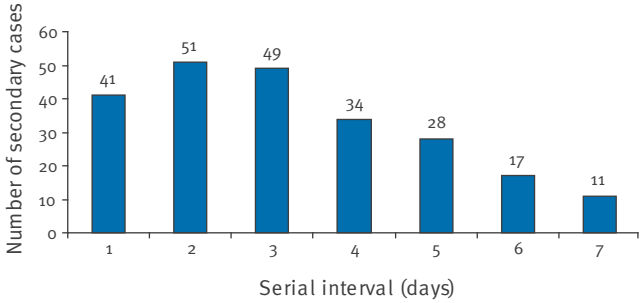


Figure 3

Distribution of days (serial interval) from onset of illness in the index case to onset of influenza-like illness in the secondary case(s), Western Australia, 29 May-7 August 2010 (n=231)



The median serial interval was 3.0 days (range: 1–7 days) and the mean serial interval was 3.2 days (Figure 3). Of the 28 secondary cases occurring six to seven days after the index case, 10 occurred in households with two or more secondary cases. The median and mean serial intervals were unchanged if households with more than one secondary case (i.e. possible tertiary cases) were excluded.

Discussion

This investigation found that the secondary attack rate of ILI among household contacts of a confirmed pandemic influenza index case in Western Australia was 14.5%, and that household transmission (to at least one secondary case) occurred in 27.9% of households.

Some studies on pandemic influenza and seasonal influenza A(H1N1) epidemics have estimated considerably higher secondary attack rates. A US modelling study based on case clusters early in the 2009 influenza pandemic, estimated the risk of ILI in household contacts of pandemic influenza index cases to be 27.3% [18]. Similarly, the secondary attack rate of laboratory-confirmed pandemic influenza cases in Kenya between June and July 2009, prior to the use of antiviral drugs, was 26.0% [19] and in a recently published Canadian study of 42 households reached as high as 45% [5]. In the 1978-1979 influenza A(H1N1) seasonal epidemic, the US had an estimated secondary attack rate of 30.6% [9]. There are no estimates of transmissibility within households for the 1918-1919 influenza A(H1N1) pandemic.

However, other studies report much lower rates, with one study in an English boarding school estimating a 5.4% to 11.9% secondary attack rate for ILI, depending on the school year [20]. Epidemiological field studies undertaken in several states of the US during the initial wave of 2009 pandemic influenza found secondary attack rates of ILI ranging from 8% to 12% in household contacts of those with ILI [21], and in more recently published US studies the household secondary attack rate associated with index cases of pandemic influenza 2009 was 13% for acute respiratory illness, and ranged from 9-10% for ILI [4,6]. The secondary attack rates from these studies of pandemic influenza are comparable to the one we observed in WA. The slightly higher secondary attack rates of ILI in WA may reflect the greater intensity of a winter pandemic season compared to the late spring season experienced in the initial northern hemisphere pandemic wave.

Transmission was highest in households with an index case of pre-school age. Although a recent US study found children with pandemic influenza to be no more infectious than adults [4], our findings are consistent with the many other studies that have shown increased transmission from children in both households and communities. This is presumably because children shed larger amounts of influenza virus and for longer periods of time than adults, are less conscious of hygiene and require more close contact [9,12,22-26]. In addition, children have been found to be the main source of influenza in households during interpandemic seasons [9,12].

Other characteristics of pandemic influenza index cases that were significantly associated with transmission in households included the symptoms cough, shortness of breath, fatigue, myalgia, rigors, diarrhoea, and vomiting. These symptoms were possibly markers of more serious illness which was associated with higher or more prolonged virus shedding, and/or required closer and more prolonged contact with their carers. The lack of a statistically significant effect of fever or other respiratory symptoms such as sore throat and runny nose on infectivity of pandemic influenza is similar to the findings in the above-mentioned US study in 2009 [4].

In our investigation household contacts of pre-school age had the highest secondary attack rate (22.6%), and adults aged 51 years and older the lowest (7.9%). This is similar to the secondary attack rates reported during the pandemic influenza season in the US in late spring 2009 [4,6]. Children, in particular those who attend day care or school, are considered to be at high risk of influenza infection, with attack rates ranging from 20% to 50% during seasonal interpandemic years [23-25, 27]. The low secondary attack rates in household contacts aged over 50 years is consistent with the relatively low incidence of pandemic influenza 2009 in older adults that has been attributed to cross-protection against the pandemic virus following exposure to influenza A(H1N1) viruses early in life [28,29].

Treatment of index cases with the antiviral drug oseltamivir did not reduce transmission in households, possibly because it was given late, as indicated by the mean interval of three days between onset of illness in the index case and treatment. Conversely, secondary attack rates among household contacts who had received a prophylactic course of oseltamivir was significantly lower than in those who had not (9.5% versus 15.3%), consistent with its reported efficacy for prevention of pandemic [30] and seasonal influenza household transmission [31,32]. A study in Japan in mid-2009 showed an even more dramatic difference in secondary attack rates among household contacts who did not receive prophylaxis compared to those who did (7.6% versus 0.8%), although this could be biased by the mass use of chemoprophylaxis in the community [30]. Our results provide support for the recommendation for early antiviral use as a preventive measure for close contacts during a pandemic, notwithstanding the need to consider that recommendation in the context of parameters such as the severity of illness attributable to the pandemic virus, the stage of the pandemic response, possible adverse effects, emergence of resistant strains, and the cost and feasibility of widespread use of antiviral prophylaxis.

Household contacts with an underlying respiratory disease were independently associated with becoming a secondary case. It is possible that people with underlying respiratory disease are no more likely to become infected, but are more likely to become symptomatic when infected with influenza and therefore to be identified as a secondary case.

Interestingly, household size was not associated with individual risk of secondary infection in household contacts. The same was observed in a French study [33]. By contrast, a recent US study found an inverse association between secondary attack rate and household size [4], highlighting the need for further investigation and the consideration of data from different geographical and cultural backgrounds when determining transmission dynamics.

Estimates of the mean serial interval for seasonal influenza from empirical data range from two to four days [11,34], and different estimates of the mean serial interval of the 2009 pandemic influenza, using both empirical and modelling data, were 2.5 to 2.7 days [35,36], 2.6 to 2.9 days [4], and 3.2 days [18]. Our empirical estimate of the serial interval of pandemic influenza in WA households, 3.2 days, matches these results closely.

Our investigation has a number of strengths and limitations. Whilst we did not include all confirmed pandemic influenza cases in WA, the sample size was large and representative of all laboratory-confirmed pandemic cases (although we were unable to control for biases stemming from who was tested and who was not) during the study period. Data were collected from nearly all participants within seven days of notification, increasing the likelihood of accurate recall of information. While a number of index cases were unable to answer the questions and an adult proxy answered questions on their behalf, this was unlikely to introduce any systematic bias, and if anything would be expected to weaken any real associations.

The fact that the household contacts who reported ILI were not all tested for influenza infection may have resulted in an overestimation of the number of secondary cases actually attributed to pandemic influenza. However, of the secondary cases who did undergo testing within 48 hours of symptom onset, the majority (27 of 29) were confirmed to have pandemic influenza infection. This estimate may be biased upwards by preferential testing of those with influenza, as they may have had more severe clinical illness than individuals whose ILI had other causes.

It is also possible that secondary cases occurred as a result of exposure outside the household. However, a study of the molecular epidemiology of seasonal influenza A virus transmission found that the majority of cases of influenza in a household were the result of transmission from the household index case and not from external community sources [37].

This was a unique opportunity to study transmission of pandemic influenza within households at a time when little information on the disease was available. This large-scale investigation has shown that secondary attack rates were similar to those seen with seasonal influenza, as was the estimated serial interval. While the secondary attack rate for children at pre-school age was within the lower range of published rates for interpandemic seasonal influenza, young children still had the highest attack rates of all age groups, and infected index children were more likely to transmit infection. The results also indicate household contacts with a respiratory disease are at an increased risk of becoming secondary cases. In a pandemic setting where antiviral medications are in short supply, it may be important to prioritise the provision of prophylaxis to the young and those with specific underlying medical conditions, such as respiratory disease, so as to optimise the likelihood of reducing the individual, family and community burden of disease.

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Pandemic influenza A(H1N1)2009: molecular characterisation and duration of viral shedding in intensive care patients in Bordeaux, south-west France, May 2009 to January 2010

L Malato[1,2], V Llavador[1,2], E Marmier[1], J Youssef[3], C Balick Weber[3], H Rozé[3], E Bessede[4], H J Fleury (herve.fleury@viro.u-bordeaux2.fr)[1]
1. Virology laboratory, University Hospital of Bordeaux, France
2. These authors contributed equally to this work
3. Intensive care units (Hospitals St André, Pellegrin and Haut Lévèque), University Hospital of Bordeaux, France
4. Bacteriology Laboratory, University Hospital of Bordeaux, France

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From May 2009 to January 2010, the Virology Laboratory at the University Hospital of Bordeaux received more than 4,000 nasopharyngeal samples from the Aquitaine region (south-west France) for the diagnosis of pandemic influenza A(H1N1)2009. Eighty-three infected patients deteriorated and were admitted to intensive care units. Our study focused on 24 of these patients. Positivity for influenza A(H1N1)2009 was monitored by realtime PCR and duration of viral shedding was determined. The first available sample of each patient was analysed for bacterial, fungal and viral co-infection. We observed six bacterial (or bacterial/fungal) co-infections and one viral co-infection with respiratory syncytial virus. The samples were analysed for the presence of the neuraminidase H275Y (N1 numbering) mutation, which confers resistance to oseltamivir, by realtime PCR of the neuraminidase gene. No H275Y mutation was observed in any of the viral strains screened in this study. In parallel, a fragment of the haemagglutinin gene encoding amino acid residues 173 to 362 was sequenced to detect mutations that had been reported to increase the severity of the disease. Two patients were infected by strains bearing the D222G (H3 numbering) mutation. The viral shedding of A(H1N1)2009 in this study ranged from four to 28 days with a median of 11 days.

Introduction

During the influenza A(H1N1)2009 pandemic, the virology laboratory at the University Hospital of Bordeaux received from May 2009 to January 2010 more than 4,000 samples collected from the Aquitaine region (south-west France), an area with three million inhabitants. Some 1002 (24.9%) samples were confirmed as positive for pandemic influenza A(H1N1)2009 by real-time PCR. During this period, the three intensive care units (ICUs) of the University Hospital of Bordeaux received 83 patients with severe clinical conditions including acute respiratory distress syndrome (ARDS). Six of them required extracorporeal membrane oxygenation (ECMO) support. We could study those six and an additional 18 influenza-positive ICU patients in detail to address the following points: to establish the presence of microbial co-infection on admission, to obtain molecular data on the oseltamivir resistance-associated H275Y mutation [1] in the neuraminidase gene, to screen for already identified mutations in the haemagglutinin (HA) gene that may have an influence on the virulence of the virus [2-5], and to evaluate the duration of viral shedding.

Methods

Patients with confirmed influenza A(H1N1)2009 were selected retrospectively for this study after their admission to the ICU for influenza complications, for example respiratory failure or exacerbation of an underlying chronic condition requiring surveillance or assistance. The patients in this study were admitted to the ICU between May 2009 and January 2010.

The detection of influenza A(H1N1)2009 viral RNA was carried out in nasal swabs, bronchoalveolar lavage fluids or respiratory secretions. Pandemic influenza A(H1N1)2009 was diagnosed using the Roche detection kit for influenza A (RealTime ready Influenza A(H1N1) detection set) and operated on a Roche LightCycler 480.

We screened each patient at admission for viral, bacterial and fungal co-infections. Viral respiratory co-infections were investigated using a multiplex PCR assay (Seegene Seeplex RV5-ACE screening) which allows the detection of influenza A, influenza B, respiratory syncytial virus (RSV) A/B, adenovirus A/B/C/D/E, parainfluenzavirus 1/2/3, bocavirus 1, metapneumovirus, human rhinovirus and coronavirus OC43/229E/NL63/HKU1. Bacterial and fungal co-infections were diagnosed after culture and/or serology.

The H275Y (N1 numbering) mutation conferring resistance to oseltamivir was investigated on admission on the first specimen by a fluorescence resonance energy transfer (FRET)-based assay designed in the virology laboratory in Bordeaux as previously described [6].

For sequencing of the HA gene, influenza A RNA was reverse-transcribed using the Titan One Tube RT-PCR kit (Roche) with primers HA1S (ATGAAGGCAATACTAGTAGTTATGCTATATAC) and HA1AS (TTAAATACATATTCTACACTGTAGAGACCC). cDNA was then subjected to a nested PCR to amplify a fragment encoding for amino acid residues 173-362 with primers HA3S (CCAAAGCTCAGCAAATCCTAC) and HA3AS (ATCTCGTCAATGGCATTCTGT). The sequences were aligned to the reference strain A/California/06/2009 using Clustalw and Jalview softwares.

Duration of viral shedding was determined as the period between the onset of symptoms and the last positive PCR for influenza A(H1N1)2009 with exception of some cases for whom onset of symptoms could not be determined (the first positive PCR being used as Do of viral shedding). As there was no standard protocol for the follow-up of influenza patients, sampling could have stopped while the patients were still positive for influenza A(H1N1)2009. Using such a method we may have underestimated the duration of the shedding but were not dependent on a negative PCR to evaluate the shedding.

Results

We studied 24 patients admitted to the ICU for severe influenza A(H1N1)2009 between May 2009 and January 2010. All the data collected are summarised in Table 1. The patients had a median age of 51.5 years ranging from 2 to 85 years and the female:male sex ratio was 0.45. Eight patients were immunocompromised (one with lung carcinoma with metastasis, one with co-infection with human immunodeficiency virus (HIV) and hepatitis C virus (HCV), two with leukaemia, two with lymphoma and two patients under follow-up for transplantation), seven had chronic cardiovascular and/or pulmonary diseases, four were obese (BMI>30), and nine had no comorbidity. During the study four patients died.

We were able to collect data concerning antiviral treatment for 20 of the 24 patients. The 20 patients had received the neuraminidase inhibitor oseltamivir. The median time of oseltamivir treatment initiation in the 17 patients for whom this information was available, was five days after the onset of symptoms (range: 1-12 days).

Screening on admission for microbial co-infections revealed only one viral co-infection with respiratory syncytial virus (RSV) and six bacterial or fungal co-infections: *Staphylococcus aureus, Haemophilus influenzae, Streptococcus agalactiae, Branhamella catarrhalis, Enterobacter cloacae, Mycoplasma pneumoniae* and *Candida albicans* (Table 1)

We were able to follow up positivity for influenza A(H1N1)2009 viral RNA in 18 patients for whom we had several specimens. The median duration of viral shedding was 11 days (4-28 days, Table 2). Immunodepression was associated with prolonged viral shedding, with six of the eight immunocompromised patients PCR-positive 14 or more days after onset of symptoms (Table 1); the two other patients who also shed virus for longer than 14 days were obese. Immunocompetent and immunocompromised patients shed virus for a median duration 10 days and 16 days, respectively.

The H275Y mutation was not detected in any of our patients, nor was any other mutation at position 275 of the neuraminidase gene.

We amplified 26 HA sequences from 21 patients (two patients were investigated with several successive samples). The different substitutions of our isolates compared to the reference strain are shown in the Figure. Three samples from two different patients exhibited the D222G substitution. The first (Patient 1 in Table 1) was a patient with morbid obesity (body mass index>40) presenting a severe ARDS requiring ECMO support for nine days and mechanical ventilation for a further 20 days. The HA sequence of virus isolated from their bronchoalveolar lavage fluid showed a mixed population at codon 222: D222EG. As shown in Table 1, she exhibited prolonged viral shedding of 28 days (already published [7]) but recovered and was discharged after one month. The second case (Patient 8 in Table 1) had a lymphoma and chronic obstructive pulmonary disease. Viral shedding lasted for a minimum of 14 days (from the first to the last positive sample), and the patient died after 19 days of hospitalisation. Four influenza A-positive samples from this patient were subjected to HA sequencing. The first sample, a nasal swab, did not contain the D222G substitution, nor did the second one which was a respiratory secretion. Interestingly, the D222G was identified in the third and fourth specimens obtained from secretions 12 and 14 days after the first sample. A mixed population (D222DG) was noted in the fourth specimen. In addition to the D222G mutation, isolates from all four samples contained a V321F substitution in HA that did not match any HA sequences published as of May 2010.

Other substitutions are listed in Table 3 and include S203T (13/26 sequences), and less frequently D222E (4/26), Y230H (1/26), M257I (1/26), Q293H (1/26), I295V (2/26), K305R (1/26), V321I (2/26) and V321F (5/26).

Discussion

In Aquitaine, 13–25% of the population were infected with influenza A(H1N1)2009 during the pandemic [8].. Between May 2009 and January 2010, 83 patients suffered from a complicated influenza and were admitted

Table 1

Clinical and microbiological features of influenza A(H1N1)2009 patients requiring intensive care, Bordeaux, May 2009- January 2010 (n=24)

Patient	Age group (years)	Sex	ECMO	Outcome	Immunodepression	Respiratory symptom	Cardiac symptom	Obesity[a]	Viral co-infection	Bacterial or fungal co-infection	Median time of NAI treatment initiation (days)	Viral shedding days)	D222G in HA
1	15-44	F	Yes					Yes			5	28	Yes
2	45-64	M	Yes		Hairy cell leukaemia			Yes			7	27	
3	45-64	F	Yes	Deceased	Cardiac transplantation						1	19	
4	45-64	M	Yes		Chronic lymphocytic leukaemia						ND	17	
5	15-44	M			HIV/HCV					*Haemophilus influenzae/ Candida albicans*	8	16	
6	45-64	F	Yes					Yes			6	14	
7	45-64	M		Deceased	Lung cancer	Asthma					9	14	
8	45-64	M		Deceased	Lymphoma	COPD					5	14	Yes
9	45-64	M									12	12	
10	15-44	M								*Streptococcus agalactiae*	4	10	
11	45-64	M				Respiratory failure					ND	10	
12	45-64	M		Deceased						*Staphylococcus aureus*	8	10	
13	45-64	F	Yes			Asthma		Yes			8	9	
14	45-64	F				COPD					9	7	
15	45-64	M			Lymphoma						ND	7	
16	0-15	F								*Enterobacter cloacae/Mycoplasma pneumoniae*	3	4	
17	45-64	F					Cardiopathy				ND	4	
18	15-44	M									4	4	
19	45-64	F							RSV	*Candida albicans*	2	ND	
20	15-44	F									ND	ND	
21	65+	F									ND	ND	
22	65+	F				Chronic bronchitis					ND	ND	
23	0-15	M								*Branhamella catarrhalis*	1	ND	
24	15-44	M			Lung transplantation						1	ND	

COPD: Chronic obstructive pulmonary disease; ECMO: extracorporeal membrane oxygenation; F: female; HA: haemagglutinin; HCV: hepatitis C virus; HIV: human immunodeficiency virus; M: male; NAI: neuraminidase inhibitor; ND: not determined; RSV: respiratory syncytial virus.

[a] Obesity was defined as a body mass index>30.

to an ICU. Influenza A(H1N1)2009 has been widely reported to affect subjects younger than those usually affected by seasonal influenza, i.e. people over than 65 years of age or with underlying chronic conditions [9,10]. This is in accordance with the 24 severely ill patients in our study who had a median age of 51 years. While one third of them (9/24) did not have an identified risk factor for influenza, the remaining two thirds were either immunocompromised or presented with underlying respiratory and/or cardiac disease or were obese.

While ARDS was also observed in previous seasonal influenzas, it was more frequent with the pandemic influenza A(H1N1)2009 virus strain. ARDS was responsible for 36–96% of admissions to ICUs during the pandemic [11-14] and might account for the increased need for ECMO support [15]. Among the 83 critically ill patients in Aquitaine, ARDS was involved in 57 [8]. Seven of the 83 received ECMO support for a median duration of 16 days, and six of those were included in the present study. Patients under ECMO in this study were either immunocompromised and/or obese. This is in line with other studies that identified obesity as a comorbidity for influenza A(H1N1)2009, as already noted in previous studies [13,16,17].

Our patients were screened on admission to the ICU for microbial co-infections that could increase the severity of the influenza. Viral co-infection was scarce: one case of influenza/RSV co-infection was seen in a patient in their 60s with no risk factors. In addition, we found six bacterial/fungal co-infections, the majority of which were not acquired in the hospital. While one of them, Patient 12, died of fatal septicaemia caused by a *S. aureus* infection, there was no suspicion that the bacterial co-infection had an effect on the severity of influenza in the five remaining patients. A recent study reported that the role of bacterial co-infection in the need for ICU admission is not clear, but that the virus is the cause of critical illness in the vast majority of cases [18].

The median duration of viral shedding was 11 days in our study, which is longer than the five to seven days noted in uncomplicated A(H1N1)2009 cases [19-21]. Eight of the nine patients shedding virus particles for longer than the median had an identified risk factor, among others immunodepression and/or obesity that are considered as a poor prognostic factor. However, the ninth patient had no comorbidity. It is widely accepted that the period of shedding of influenza virus is longer in immunocompromised patients [19,20]. Interestingly, viral shedding was longer in patient 1 (with a 28-day peak) whose immunological status was normal but who was obese. Furthermore, patients with ECMO or with a fatal outcome had longer viral shedding values than others.

The patients included in this study had been treated with the neuraminidase inhibitor oseltamivir. The

Table 2
Viral shedding in intensive care patients determined by detection of A(H1N1)2009 RNA by realtime PCR, Bordeaux, May 2009–January 2010 (n=18)

Patient	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Day 13	Day 14	Day 15	Day 16	Day 17	Day 18	Day 19	Day 20	Day 21	Day 22	Day 23	Day 24	Day 25	Day 26	Day 27	Day 28
1					+	+		+		+	+	+	+	+		+			+						+	+	+		
2								+					+											+			+		
3	+			+		+				+					+			+	+										
4													+				+												
5								+								+													
6								+						+															
7								+						+															
8	+		+			+	+			+		+		+															
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10	+					+				+																			
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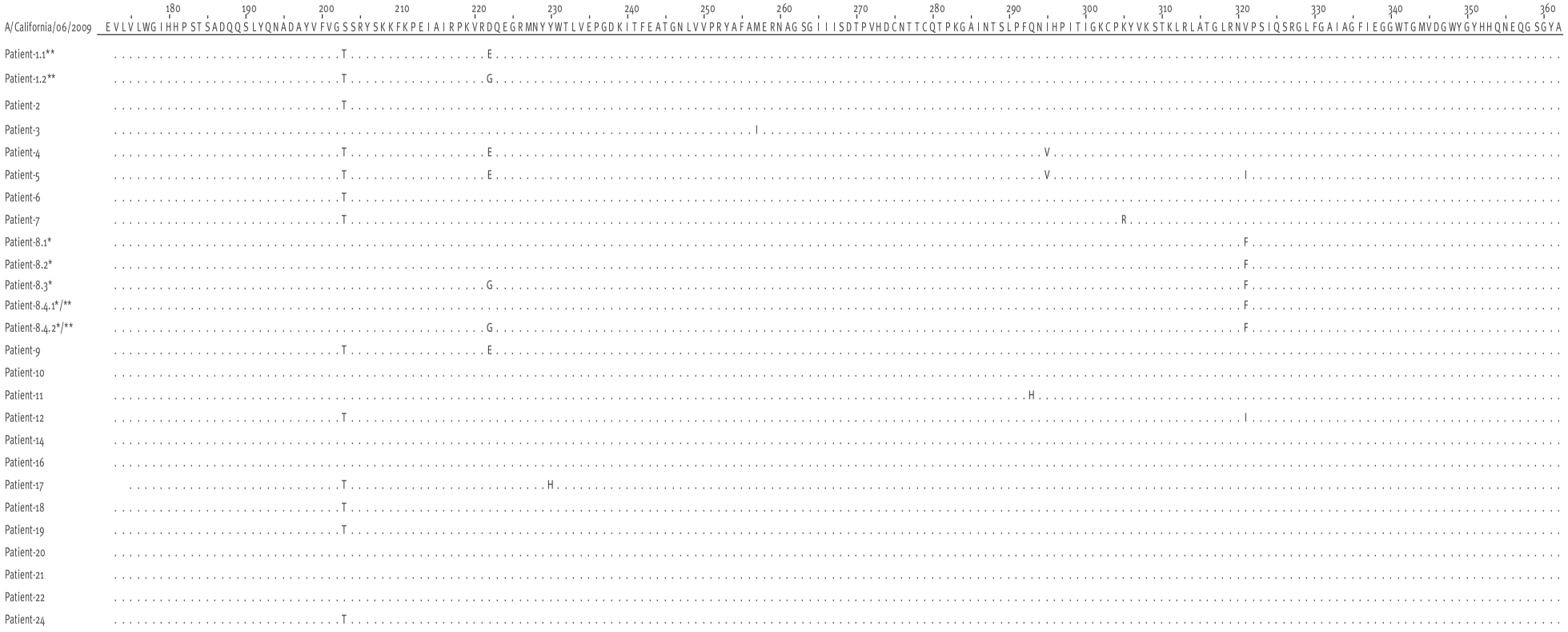
14							+																						
15	+						+																						
16	+			+																									
17	+			+																									
18				+																									

Dayo: Day of onset of symptoms (or first positive PCR when onset of symptoms could not be determined).

Figure

Alignment of influenza A(H1N1)2009 haemagglutinin amino acids 173-362 from intensive care patients with reference strain A/California/06/2009, Bordeaux, May 2009- January 2010 (n=21 patients)



* Four specimens were available for Patient 8.

** Sequences exhibiting a mixed population of substitutions were considered and processed as two different readings.

Only substitutions are shown. Seven residues were polymorphic.

median delay before initiation of treatment was five days, which exceeds the recommended time for the administration of oseltamivir at the latest 48 hours after the onset of symptoms [22]. Late treatment due to delayed admission to the ICU and comorbidities could account for prolonged viral shedding because of a slower viral clearance [23]; it has been shown that treatment initiated one to three days after infection significantly shortens viral shedding duration [24]. However, Patient 3 was shedding virus particles for 19 days despite rapid administration of oseltamivir.

As among the currently licensed drugs only neuraminidase inhibitors remain useful to treat influenza A(H1N1)2009, it is of particular importance to monitor the resistance/sensitivity of viral isolates to oseltamivir. Unfortunately worrying levels of oseltamivir-resistant isolates of the seasonal influenza A(H1N1) have emerged in Europe [25,26]. In these viruses, the most frequent mutation conferring resistance to oseltamivir is the H275Y substitution [27] in the neuraminidase gene, which does not cause cross-resistance to zanamivir.

Among the 26 isolates analysed, we have not observed any H275Y substitution. These data are in accordance with the literature showing that the prevalence of resistant A(H1N1)2009 viruses is at present very low. As of August 2010, 304 cases of oseltamivir resistance in this strain have been reported worldwide [28], all of which were due to the H275Y mutation in NA.

The HA protein is one of the determinants of virulence and host specificity through it's interaction with the sialic acid receptor on the cell surface. While avian influenza viruses preferentially bind to alpha2,3–linked sialic acid, human viruses prefer the alpha2,6 linkage [29]. It has been shown that two positions in HA are involved in determining sialic acid binding preference, namely amino acid residues 187 and 222 (190 and 225 in H3 numbering) [30]. A D222G mutation causes a shift to preferential binding to alpha2,3 receptors. This mutation has recently been described in influenza A(H1N1)2009 isolates from patients with severe disease or fatal outcome in several countries [2,4,5,31,32], but has also been detected in association with a mild disease [33].

Two D222G substitutions were observed in our study. Both patients experienced a severe clinical course of disease. One required ECMO and the estimated viral shedding lasted 28 days [7], while the other died after 19 days and was at the time probably still positive for influenza A(H1N1)2009, although no autopsy was performed. In the deceased patient, this mutation was not present on admission but appeared 12 days after the first positive sample, therefore suggesting a selection event. We propose that the long duration of viral shedding allowed the virus to evolve and acquire this substitution. Whether or not this mutation accounted for the severity of the disease in this patient remains to be investigated.

Interestingly, the 1918 Spanish influenza isolate NY18 carried the combination D190/G225 and had double specificity for both alpha2,3– and alpha2,6–linked sialic acid [30]. It has been shown in ferrets that this viral isolate fails to transmit efficiently but remains virulent [30,34]. Alpha2,3 sialic acid receptors are found in the lower respiratory tract in humans [35]. Like the avian influenza A(H5N1) virus, strains with mutations that affect receptor binding might be less efficiently transmitted but could have an increased pathogenicity [4].

In addition to the D222G substitution, we observed four D222E substitutions in this study (Table 3, Figure). Although these patients had prolonged viral shedding, we could not clearly establish a link with the severity of the disease as they all, except Patient 9, presented comorbidities. Studies have shown that the proportion of D222E is similar in mild and severe cases [32].

In parallel, we found Q293H and I295V mutations whose pejorative role has been mooted but remains to be confirmed [3].

Table 3

Frequency of haemagglutinin substitutions identified in influenza A(H1N1)2009 isolates from intensive care patients, Bordeaux, May 2009- January 2010 (n=21 patients)

Mutations in HA	Frequency (among the 26 sequences)	Number of patients exhibiting this mutation
S203T	50%	12
D222G	8%	2
D222E	15%	4
Y230H	4%	1
M257I	4%	1
Q293H	4%	1
I295V	8%	2
K305R	4%	1
V321I	8%	2
V321F	19%	1

HA: haemagglutinin.

Conclusion

In 24 patients hospitalised in the ICU for pandemic influenza A(H1N1)2009 infection, the requirement for ECMO was mainly associated with comorbidities (immunodepression/pulmonary disease/obesity) and long viral shedding despite oseltamivir treatment.

All strains were found susceptible to oseltamivir. The D222G substitution was observed in only two patients and we hypothesise that this mutation is selected for in the lower respiratory tract but is not transmitted. Microbial co-infections were detected, but with one exception it was not clear whether they contributed to the severity of the disease. We think that the influenza virus alone was responsible for the severe disease and the evolution toward ARDS.

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Impact of the 2009 influenza A(H1N1) pandemic on public health workers in the Netherlands

L Vinck[1], L Isken (leslie.isken@rivm.nl)[1], M Hooiveld[2], M C Trompenaars[3], J IJzermans[2], A Timen[1]
1. Preparedness and Response Unit, Centre for Infectious Disease Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands
2. Netherlands Institute for Health Services Research, Utrecht, the Netherlands
3. Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands

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A cross-sectional study was undertaken to analyse the impact of the 2009 influenza A(H1N1) pandemic on frontline public health workers in the Netherlands and to consider its implications for future pandemics. A structured, self-administered questionnaire was made available online (26 March to 26 May 2010) for frontline public health workers employed by the communicable disease departments of the public health services in the Netherlands (n=302). A total of 166 questionnaires (55%) were completed. The majority of respondents reported an increased workload, perceived as too busy (117 respondents, 70.5%) or extreme (13 respondents, 7.8%). Most respondents were not anxious about becoming infected (only seven were regularly concerned). The overall compliance with the control measures was good. The case definition was strictly applied by 110 of the 166 respondents (66%); 56 of 141 (39.7%) consistently consulted the Preparedness and Response Unit within a centralised assessment system, while 68 of 141 (48.2%) consulted the unit only at the beginning of the pandemic. Of 145 respondents with available data, 128 (88.3%) always used personal protective equipment. Reported adherence to the advice to discuss the various isolation measures with patients and their contacts was between 71% and 98.7%. Our study shows that the surveyed frontline public health workers considered the workload to be high during the first 3.5 months of the pandemic and their level of anxiety about becoming infected was reported to be low. During the pandemic, these workers were able to accommodate what they considered to be an excessive workload, even though initially their assignments were unfamiliar to them.

Introduction

On 25 April 2009, the World Health Organization (WHO) declared the outbreak of influenza A(H1N1)2009 to be a public health emergency of international concern [1]. On 11 June 2009, WHO raised the pandemic alert level to phase 6, thereby acknowledging a worldwide pandemic [2]. In the Netherlands, influenza A(H1N1) 2009 virus infection became mandatorily notifiable on 29 April 2009, as a group A disease. This group consists of diseases that pose a very serious threat to public health and thus require national control decisions and coordination. Physicians and staff in laboratories that suspect or confirm a group A disease in a patient need to notify the regional public health service, which then reports anonymised patient data to the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (RIVM). Within the Centre for Infectious Disease Control, the Preparedness and Response Unit is responsible for coordinating disease control and implementing national control policies. During the pandemic, the unit worked closely with the local public health services.

From 30 April to 15 August 2009, infection with influenza A(H1N1)2009 virus was reported in 1,473 cases nationwide [3]. The policy for carrying out active case finding was defined on 29 April 2009. Patients were classified according to the national case definition, which is based on the European Union case definition [4]. The epidemiological criteria within the case definition changed frequently as the affected areas with sustained human-to-human transmission changed.

The assessment and management of each case (including the need for sampling, classification according to the case definition, assessment of the risk of infection in close contacts, provision of antiviral drug prophylaxis, monitoring of home isolation procedures for cases and their contacts and informing them about the isolation measures and the need for them) was done by frontline public health workers from the public health services together with an expert from the Preparedness and Response Unit (until 29 June 2009), within a centralised assessment system. Initially, samples were taken from all patients with suspected influenza A(H1N1)2009 virus infection and their contacts and antiviral drugs were given if the diagnosis was confirmed. From 15 June 2009, antiviral drugs were also administered to probable cases (i.e. without confirmation of the diagnosis). Personal protective equipment (FFP2 masks, gloves, gown and goggles) was provided for health professionals who took the samples. After

10 July 2009, FFP1 masks and gloves were considered sufficient, as there was increasing evidence that these would prevent droplet transmission. After 22 July 2009, general practitioners were responsible for assessing and managing individual cases and when clusters of cases appeared, they contacted public health service professionals.

As the number of cases increased rapidly during the summer and the clinical picture proved to be relatively mild [5], the notification procedure was adjusted on 15 August 2009. From then, only hospitalised patients or deaths due to influenza A(H1N1)2009 were notified to the public health service. This approach was consistent with the WHO pandemic plans stating that where there is widespread community transmission, containment strategies requiring control measures for each individual case should be replaced by mitigation strategies [6]. In the Netherlands, between 24 April 2009 and 24 June 2010, a total of 2,196 patients with influenza A(H1N1)2009 virus infection were hospitalised and 63 died. Of the deceased patients, 53 had an underlying disease [7].

It is known that communicable disease outbreaks can have a substantial impact on healthcare workers [8], as a result of increased workload, uncertainty about the pathogenicity of the causative agent and anxiety about becoming infected [9,10]. However, there is limited knowledge on the impact of a pandemic on healthcare workers, as the most recent pandemic was the 1968 influenza pandemic [11]. During the 2009 influenza pandemic, public health workers were requested to function as the first-line filter in assessing, sampling and treating cases, meaning that they had to perform new tasks that required additional skills – tasks that interfered with their usual daily routine. Our goal was therefore to assess the consequences of the 2009 influenza A(H1N1) pandemic on frontline public health workers (public health physicians, public health nurses and health department managers) employed by a public health service in the Netherlands in order to contribute to a knowledge base for optimising response strategies in future infectious disease outbreaks.

Methods

Study population

In the Netherlands, there are 28 public health services employing 302 frontline public health workers (119 public health physicians, 166 public health nurses and 17 health department managers). The smallest public health service has a catchment area of 216,403 inhabitants, the largest has 1,245,516.

Questionnaire development and administration

A structured, self-administered questionnaire was developed on the basis of a literature study (using MEDLINE) and 11 in-depth interviews with frontline public health workers (the search strategy and results of the literature study and interviews are available from the authors on request). The questionnaire was tested in a pilot study – to assess its feasibility and completeness – involving two public health workers, two policy advisors from the Preparedness and Response Unit and seven regional public health consultants. After revision, based on the results of the pilot study, the final questionnaire was made available online to the 302 frontline public health workers from 26 March to 26 May 2010. A hyperlink was sent to them by the Preparedness and Response Unit, along with a request to complete the questionnaire.

The questionnaire addressed the first months of the pandemic (29 April to 15 August 2009). Several topics were covered: 12 questions addressed the characteristics of the respondents (profession, sex, age, whether there were children in household, years of work experience, previous experience of working in an infectious disease outbreak, amount of days worked per week, amount of overtime worked, whether they had had direct contact with a confirmed case, whether they had had an infection with influenza A(H1N1)2009 virus, whether they assumed that they had been infected with influenza A(H1N1)2009 virus during work and whether any family members had been infected); other questions were related to perceived workload (n=10), anxiety about becoming infected (n=4) and compliance with the control measures (n=7). The 10 questions for measuring workload were a validated set of questions [12] that are often used to measure workload in medium or small businesses.

At the start of the questionnaire, a detailed timeline was displayed, showing all control measures taken, to facilitate the respondents' recall.

Variables

We composed overall scales for two variables: perceived workload (Cronbach's alpha of 0.886) and anxiety of becoming infected (Cronbach's alpha of 0.799). The validated set of questions on workload used a four-point Likert scale (1 = never; 2 = sometimes; 3 = regularly; 4 = always) and consisted of questions such as 'were you working under time pressure?' and 'did you have to work extra hard to finish your work?' The questions were combined to create the variable perceived workload, which reflected the retrospectively reported perceived workload. Workload was categorised as a relaxed (10–14 points), normal (15–20 points), too busy (21–30 points) and extreme (31–40 points).

For the second variable (anxiety of becoming infected), responses to statements concerning home isolation measures were dichotomised: neutral responses (neither agreed nor disagreed) were excluded from the analysis.

To increase our understanding of the differences between the public health services, three other variables were created. The variable 'degree of urbanisation' was created based on data from Statistics Netherlands (CBS) [13]. The variable 'catchment area'

was based on data received from the Dutch association of public health services (GGD Nederland) (categories: regions with 200,000–500,000 inhabitants, those with 500,001–900,000 and those with 900,001–1,200,000). The variable 'objective workload' was based on the number of cases for which the respondents had consulted the Preparedness and Response Unit within the centralised assessment system of each public health service (categories: 0–40 cases, 41–80 cases and 81–120 cases).

Data analysis

Data were analysed using SPSS v. 18.0. Descriptive statistics (frequencies) were generated. Means were calculated for the answers given on the Likert scale. Differences in means were assessed by Student's t-tests. Differences in proportions were assessed by chi-square test. A p value of ≤0.05 was considered statistically significant. Cronbach's alpha was used to assess whether various questions could be combined: the cut-off value was 0.6. Statements with responses ranging from 'totally disagree' to 'totally agree' were recoded 1 to 5 and four-point scales were recoded 1 to 4. Parametric and non-parametric tests and analysis of covariance (ANCOVA) for regression analysis were used when appropriate. Non-responder analysis was performed for sex and profession.

Results

Of the 302 public health workers contacted, 166 completed the questionnaire (response rate: 55%). Responses were received from all 28 public health services. The proportion of responders among the public health physicians was higher than the proportion of responders among the public health nurses (p=0.023). The general features of the respondents are listed in Table 1.

Non-responder analysis showed that the male–female ratio was not significantly different between responders and non-responders (p=0.221).

Workload

Of the 166 respondents, 117 (70.5%) reported that they were too busy, 13 (7.8%) had an extreme workload, while 36 (21.7%) had a normal or a relaxed workload, during the first months of the pandemic (29 April 2009 to 15 August 2009) (Figure).

A higher perceived workload was associated with a higher degree of urbanisation of the public health service (ANCOVA F-value (1, 162)=9,223, p=0,003) and with regularly working overtime (F(2, 162)=4,687, p=0.010). There were no differences in perceived workload between respondents who worked full-time (4–5 days per week) and those who worked part-time (1–3 days per week).

Anxiety about becoming infected

The level of anxiety about becoming infected during the pandemic was relatively low among the respondents: 100 (60.2%) had no fear of infection at all, 59 (35.5%) were sometimes worried about infection and seven (4.2%) were regularly afraid of becoming infected. Having children (p=0.030) and having doubts about the effectiveness of personal protective measures taken (p=0.044) increased the level of anxiety regarding infection.

Compliance with control measures

We measured how consistently the respondents had applied the criteria for the case definition that was issued to identify suspected patients from whom sampled had to be taken. We also measured the amount of consultation with the centralised assessment system for the final classification of patients, the extent of use of personal protective equipment during sampling and home visits and whether the workers informed patients and contacts about the isolation measures.

Case definition

Of the 166 respondents, 110 (66.3%) reported that they had always strictly followed the case definition, while 50 (30.1%) had only occasionally followed the case definition (Table 2). The main reasons for not following the case definition were that there was already sustained transmission of the influenza A(H1N1)2009 virus in many other countries not included in the case definition (56.6%), that patients or general practitioners applied pressure on the respondents (15%) or because the respondents felt that the criteria defining a contact were too strict (9.6%). Respondents who were public health physicians followed the case definition less strictly than those who were public health nurses (p=0.000) and compliance was lower in male respondents compared with female respondents (p=0.002).

Centralised assessment

Of 141 respondents, 56 (39.7%) reported that until 29 June 2009 they always consulted the Preparedness and Response Unit for centralised assessment, 68 (48.2%) consulted the unit only at the beginning of the pandemic, while 17 sometimes (n=14, 9.9%) or never (n=3, 2.1%) consulted the unit (Table 2). Reasons for non-compliance were that they found it unnecessary (38.3%), time consuming (22.7%) or that the assessments were sometimes contradictory or divergent from the advice specified in the case definition (9.9%). Female respondents consulted the unit less often than male respondents (p=0.008). The compliance of respondents who regularly worked overtime was reduced compared with those who did not (p=0.024).

Personal protective equipment

Personal protective equipment was always used by 128 of 145 respondents (88.3%), regularly by 15 (10.3%) and only sometimes by two (1.4%) (Table 2). The extent of use of personal protective equipment was higher in female respondents (p=0.037) and in those who had been working at a public health service for one to 10 years (p=0.034).

Table 1

General characteristics of questionnaire respondents during 29 April to 15 August 2009, Netherlands (n=166)[a]

Characteristic	Percentage of respondents[b]	Number of respondents
Sex		
Female	66	110
Male	34	56
Profession		
Public health physician	46	77
Public health nurse	51	85
Health department manager	2	4
Age (years)		
<25	4	7
26–35	26	44
36–45	26	44
46–55	32	54
56–65	10	17
Children in household (n=165)		
Yes	50	83
No	50	82
Number of years of work experience		
<1	7	12
1–5	38	63
6–10	30	49
>11	25	42
Previous work experience in an infectious disease outbreak		
Yes	49	81
No	51	85
Number of working days per week		
1	8	14
2	11	19
3	29	48
4	28	47
5	23	38
Working overtime		
Regularly	62	103
Sometimes	34	57
Never	4	6
Having had direct contact with a confirmed case		
Yes	76	127
No	23	39
Had had an influenza A(H1N1)2009 virus infection		
Yes, laboratory confirmed	1	2
Considered as likely	19	32
No	79	132
Infected with influenza A(H1N1)2009 virus during work (n=34)		
Yes	3	1
Considered as likely	27	9
No	62	21
Did not know	8	3
Family member with laboratory-confirmed influenza A(H1N1)2009 virus infection (n=136)		
Yes	7	9
No	70	95
Did not know	23	32

[a] Unless otherwise indicated.

[b] The percentages in some categories do not total 100% due to rounding.

Informing patients and contacts about isolation measures

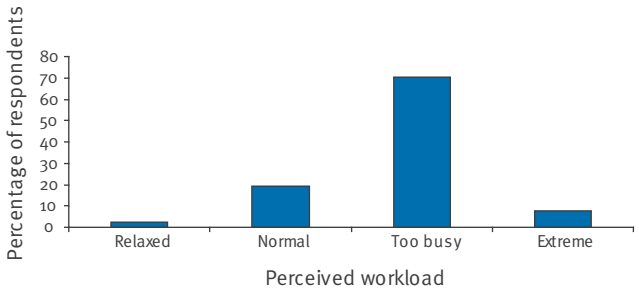
Of 121 respondents, 86 (71.1%) had always told patients that they should wear a mask indoors. Of 156 respondents, 154 (98.7%) had always informed patients about the need for social distancing and 142 of 149 respondents (95.3%) reported that they had informed patients that they were not supposed to leave their home while they were still ill. Further, 145 of 149 respondents (97.3%) had always provided patients with a leaflet containing a summary of the information about isolation measures (Table 2).

Working overtime was associated with increased compliance with informing patients that they were not supposed to leave their home while ill (p=0.048) and providing patients with the information leaflet (p=0.002). The confidence of respondents regarding the effectiveness of the home isolation measures was positively associated with informing patients about wearing a mask indoors (p=0.006) and about social distancing (p=0.004) and informing them that they were not supposed to leave their home while ill (p=0.044).

The perceived workload, anxiety of becoming infected and compliance with control measures were not influenced by the number of inhabitants within the catchment area of the public health service or by the number of cases for which consultation within the centralised assessment system of each public health service with the Preparedness and Response Unit was carried out (objective workload).

Figure

Perceived workload of questionnaire respondents during 29 April to 15 August 2009, Netherlands (n=166)



Discussion and conclusions

This study is one of the first systematic evaluations of the impact of the 2009 influenza A(H1N1) pandemic on public health services. The low level of anxiety of public health workers about becoming infected with the influenza A(H1N1)2009 virus is in stark contrast to that reported during outbreaks of other infectious diseases, such as severe acute respiratory syndrome (SARS) [9,14-18] and the degree of anxiety experienced by the public during the first months of the 2009 influenza A(H1N1) pandemic in the Netherlands [19]. The low level of anxiety in our study may be explained by the fact that the course of illness in the pandemic was mild [5]. This knowledge, which became increasingly clear during the pandemic, might have influenced the health workers' perception of their own health risks and thus might have diminished any anxiety and stress. It has been reported in studies mainly involving experience with SARS that several factors were associated with

Table 2

Compliance of questionnaire respondents with control measures during 29 April to 15 August 2009, Netherlands (n=166)[a]

Compliance with control measures	Percentage of respondents[b]	Number of respondents
Applying case definition (n=166)		
Strictly followed	66	110
Sometimes followed	30	50
Did not know	4	6
Centralised assessment (n=141)		
Always	40	56
Only at the beginning of the pandemic	48	68
Sometimes	10	14
Never	2	3
Use of personal protective equipment (n=145)		
Always	88	128
Regularly	10	15
Sometimes	1	2
Informing patients and contacts about isolation measures[c]		
Wearing a mask indoors (n=121)	71	86
Social distancing (n=156)	99	154
Not leaving home (n=149)	95	142
Additional information (n=149)	97	145

[a] Unless otherwise indicated.

[b] The percentages in some categories do not total 100% due to rounding.

[c] Multiple responses possible.

anxiety, fear or psychological distress, such as direct contact with patients [14,20] and years of working experience [10]. However, in our study population, only having children in the household and having doubts about the effectiveness of the personal protective equipment had an effect on anxiety levels. Such associations have also been reported elsewhere [14,20]. However, we found no association between the length of work experience and the level of anxiety regarding infection.

Our study shows that during the first months of the pandemic, compliance with control measures was good. Confidence in the appropriateness of personal protective measures to reduce transmission can lower the level of anxiety, as was observed by Nickel *et al*. during the SARS outbreak [20]. We believe that confidence in the appropriateness of the personal protective measures further strengthened compliance of the respondents in our study, as Cabana *et al*. reported that having trust in recommended control measures makes a professional more likely to comply with control measures or to emphasise the importance of the measures to patients [21]. In our study, the majority of the surveyed health professionals used personal protective equipment for house visits, even though only a minority was concerned about getting infected. Interestingly, respondents who were less compliant had been working at a public health service for either less than one year or more than 10 years. Therefore, efforts to increase compliance should be focused primarily on these groups.

Previous studies have shown that, during the SARS outbreak, 53–66% of the healthcare workers had an increased workload [9,10,22]. Similarly, in our study, the workload was reported to be very high to extremely high. However, we are not able to compare the workload during the pandemic with that in the period before it, as workload has not been systematically assessed for these groups of professionals outside outbreak periods. The increased workload was partially due to carrying out tasks that normally do not belong to the regular work of public health services, such as systematic sampling of patients, and prescribing and distributing antiviral drugs, which are rather the domain of general practitioners and pharmacists. Given that the pandemic demanded prolonged exertion from most frontline public health workers, including tasks that required new skills, it is likely that the maximum response capacity of public health services was reached. Such a high workload could probably not have been maintained for a longer period of time and workload can therefore become an issue in future outbreaks of diseases with high severity and involving a high number of cases. Therefore, the importance of thorough preparedness plans needs to be emphasised. These plans should consider ways to increase numbers of staff at short notice.

In our study, although the level of anxiety about infection among the respondents was low during the pandemic, our results showed that confidence in the appropriateness of personal protective measures to reduce transmission can lower the level of anxiety. Thus preparedness plans should include strategies that increase the confidence of public health workers in infection control measures. Adequate and timely information on such measures has been reported to be a major factor affecting health professionals' confidence in them [23]. In the light of these findings, we support the view that information about the choice and rationale for infection control measures, together with the expected efficacy, should be made available to health professionals at the very beginning of a crisis or outbreak, to increase their confidence in the measures and thus reduce concerns about possible infection. Furthermore, new insights from research or daily practice should prompt timely adjustments of the measures to increase credibility and stimulate adherence.

We believe that our findings are applicable to other European countries with a similar structure of communicable disease control. A pandemic may be seen as the ultimate test for public health response capacity. Our study shows the importance of thorough preparedness for crisis situations due to infectious disease outbreaks and its implications extend beyond the 2009 influenza A(H1N1) pandemic. To the best of our knowledge, the impact of the 2009 pandemic on healthcare workers has not been previously investigated. However, an initial response of healthcare institutions regarding experiences, barriers and perceived future needs was studied by Lautenbach *et al*., who concluded that revision of preparedness plans seems to be necessary, including items related to workload and education [24]. We also consider preparedness and planning for an optimal response and surge capacity an important subject of concern for the future, given the likelihood that severe outbreaks and communicable disease threats will occur again [25-29] and will be a serious burden on the public health system.

One limitation of our study is that data were collected nine months after the beginning of the 2009 pandemic and therefore could be subject to recall bias. A detailed timeline was displayed on the questionnaire, to aid the respondents' memory, but recall bias could lead, for example, to underestimation of the level of anxiety about becoming infected during the first months of the pandemic. Nevertheless, our results show that the pandemic had a substantial impact on the surveyed public health workers and that this was still felt nine months later.

A second aspect that should be considered is that in our study, the proportion of responders among the public health physicians was higher than the proportion of responders among the public health nurses. This is not surprising, considering the fact that in the Netherlands public health physicians carry final responsibility for

the management of public health issues and are more likely to consult the Preparedness and Response Unit than public health nurses would. Or it may be that the questionnaire was of greater interest to public health physicians than to public health nurses, as it dealt with issues regarding strategies used during outbreaks. Therefore, our results may be more applicable to public health physicians than to public health nurses.

In conclusion, during the pandemic, the frontline public health workers surveyed in the Netherlands showed they were able to accommodate a substantially increased workload, even though initially their assignments were unfamiliar.

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A multiplex one-step real-time RT-PCR assay for influenza surveillance

I Huber[1,2], H Campe (Hartmut.Campe@lgl.bayern.de)[1,2], D Sebah[1], C Hartberger[1], R Konrad[1], M Bayer[1], U Busch[1], A Sing[1]
1. Bavarian Health and Food Safety Authority (LGL), Oberschleißheim, Germany
2. These authors contributed equally to this work

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For surveillance purposes real-time PCR assays for influenza viruses had to be adapted to the pandemic influenza A(H1N1)2009 strain. We combined published primers and probes for influenza A, influenza B and an internal amplification control with a detection system for influenza A(H1N1)2009 to set up a rapid, reliable, simple and cost-effective high-throughput multiplex one-step real-time RT-PCR. The workflow also includes automated sample preparation for high-throughput screening. The lower limit of detection of the multiplex assay was 3.5x10² RNA copies per PCR reaction. The diagnostic sensitivity of the multiplex assay was 87.7%, but increased to 99.4% for influenza-positive samples yielding C_t values of less than 34 cycles in the respective diagnostic assay. High specificity was confirmed by sequencing and correct detection of 15 reference samples from two quality assurance studies. The multiplex PCR was introduced for surveillance of samples from a network of general practitioners and paediatricians in Bavaria, Germany during the influenza pandemic of 2009. Comparison with surveillance data from reported cases proved the reliability of the multiplex assay for influenza surveillance programmes.

Introduction

In April 2009, a novel influenza A(H1N1) virus emerged [1] that could not be detected by routine diagnostic assays for subtyping seasonal influenza A(H1N1) viruses. Therefore, accurate and reliable diagnostic tests for the new influenza A strain had to be established to screen patients with influenza-like illness (ILI) for the 2009 pandemic influenza virus [2-9]. At the onset of the pandemic, public health control measures, namely the isolation of patients and suspected cases to limit the spread of the virus, were guided by the results of these tests [10].

In October 2009, mass vaccination programmes with different pandemic influenza vaccines were implemented globally. In Germany, about 6 million people were vaccinated from the end of October to the end of December 2009. At that stage of the pandemic the World Health Organization (WHO), the European Centre for Disease Prevention and Control (ECDC) and the Robert Koch Institute in Germany (RKI) recommended strengthening the influenza surveillance. This surveillance should persist throughout the whole year and include the new influenza strain as well as seasonal influenza strains, because co-circulation was reported and also expected in the future. At that time, no multiplex real-time RT-PCR assay was available for the simultaneous detection of seasonal influenza A, influenza B and pandemic influenza A(H1N1)2009 viruses. Published diagnostic assays focused more on subtyping of influenza viruses using microarrays and sequencing [11-14]. However, these tests are not suitable for high-throughput routine diagnostic screening.

For large scale surveillance of ILI patients cost effective and time-saving methods for the detection of influenza viruses are needed. The multiplex real-time RT-PCR assay described here provides a diagnostic tool for the fast, simultaneous and reliable diagnosis of influenza A and B viruses with validated and well established real-time PCR protocols with minor modifications, and includes an officially recommended real-time PCR protocol for simultaneous subtyping of the pandemic influenza A(H1N1)2009 virus.

Methods

Specimen collection

For specificity and sensitivity testing as well as for the evaluation of the multiplex assay different panels of clinical samples and reference material were used in this study:
The specificity of the PCR protocol for subtyping pandemic influenza A(H1N1)2009 virus was assessed by sequencing 50 PCR products from clinical samples collected in the beginning of the pandemic in May 2009.

We tested the specificity of the multiplex assay with the following samples: influenza A/Bavaria/63/2009 (a pandemic influenza (H1N1)2009 virus) in six consecutive dilutions, influenza A/Brisbane/59/2007 (H1N1) in four dilutions, influenza A/Brisbane/10/2007 (H3N2), influenza A/chicken/Germany/R3294/2007 (H5N1) in two dilutions, influenza A/whooper swan/Germany/R65-2/2006 (H5N1) and influenza B/Brisbane/60/2008.

The samples were provided for two external quality assurance studies (organised by INSTAND e.V., Germany in 2009/10. In addition, the oseltamivir-resistant strain influenza A/Berlin/58/2008 (H1N1) was provided by the national reference centre for influenza at the RKI in Berlin.

The analytical sensitivity (limit of detection) of the multiplex real-time RT-PCR assay was determined using plaque-quantified influenza A/Hamburg/05/2009 (H1N1) virus with a concentration of $3.5x10^5$ PFU/ml [15]. A 10-fold dilution series of extracted RNA was generated from $3.5x10^5$ to 3.5 plaque-forming units per ml (PFU/ml) and analysed in triplicate in the FAM-channel (matrix gene) as well as the ROX channel (HA gene) of the multiplex PCR assay. To compare the sensitivity of the multiplex and each single assay, RNA was prepared from egg cultures of an early case of pandemic influenza A(H1N1)2009 in Bavaria, detected on 29 April 2009 and confirmed by the national reference centre for influenza at the RKI, as well as from cell cultures of reference material: influenza A/Bayern/89/2007 (H1N1), influenza A/Sydney/5/1997 (H3N2) and influenza B/Brisbane/60/2008. RNA was analysed in 10-fold dilution series in nuclease-free water containing background calf thymus DNA (Type I fibres, Sigma-Aldrich) in a concentration of 100 ng/µl. RNA dilutions were prepared from 100 ng to 1 pg per PCR reaction.

For evaluation of the multiplex one-step real-time RT-PCR assay and to determine diagnostic sensitivity, we used clinical samples obtained from ILI patients during the influenza season 2008/09 and the 2009 influenza pandemic in Bavaria. ILI was defined by sudden onset with fever (>38.5°C), cough, sore throat and myalgia and/or headache. We had previously tested the samples with diagnostic real-time RT-PCR assays for seasonal influenza A and B [16,17] and for influenza A(H1N1)2009 [2,9]. The panel consisted of 317 samples: 90 influenza-negative samples, 47 samples positive for seasonal influenza A(H3N2) and A(H1N1), 50 samples positive for influenza B viruses as well as 130 samples positive for influenza A(H1N1)2009 virus. Original specimens included nasopharyngeal and throat swabs in viral transport medium. After screening for influenza, the remaining RNA was stored at -80°C until testing with the multiplex assay.

Nucleic acid extraction

Viral nucleic acid was extracted using the QIAamp Virus Bio Robot 9604 kit (Qiagen) adapted to the robot Hamilton Microlab Star (Hamilton) for large numbers of samples or the Viral RNA mini kit (Qiagen) for small numbers of samples. From our routine diagnostic analyses we know that the extraction method has no influence on the results.

Internal amplification control

Commercially available heterologous *in vitro*-transcribed RNA (INTYPE IC-RNA Labordiagnostik, Leipzig, Germany) was used as PCR inhibition control. This *in vitro* transcript has proven its robustness in previous multiplex real-time RT-PCR assays [18]. The stock solution ($8x10^5$ copies/µl) of the *in vitro*-transcribed RNA was stored at -80°C, and the working dilutions of $1x10^5$ copies/µl were stored at -20°C.

Multiplex real-time RT-PCR assay

Different published primers and probes of real-time RT-PCR assays specific for influenza A, influenza B and pandemic influenza A(H1N1)2009 viruses were tested to determine whether they could be used together in a multiplex assay. We show here only those primer and probe sets that performed well when combined in preliminary tests.

In order to minimise the risk of PCR product contamination, we introduced one-step RT-PCR protocols using

Table 1

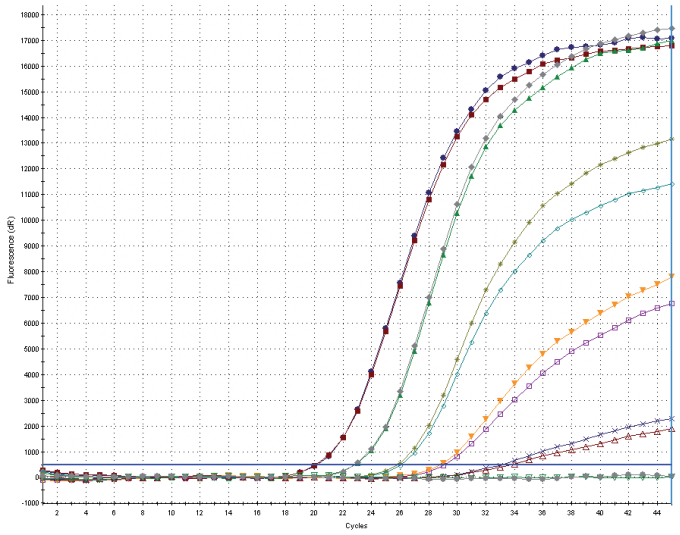
Primers and probes used in the multiplex one-step real-time RT-PCR assay for the detection of different influenza virus strains

	Primers and probes	Sequence (5'→3')	Working concentration	Reference
Influenza A	InfA M+25	AGATGAGTCTTCTAACCGAGGTCG	400 nM	15
	InfA M-124	TGCAAAAACATCTTCAAGTCTCTG	400 nM	
	InfA M-124-mod	TGCAAAGACACTTTCCAGTCTCTG	400 nM	
	InfA M + 64-FAM	6FAM-TCAGGCCCCCTCAAAGCCGA-BBQ	200 nM	
Influenza A(H1N1)2009	Flu Sw H1 F236	TGGGAAATCCAGAGTGTGAATCACT	400 nM	9
	Flu Sw H1R318	CGTTCCATTGTCTGAACTAGRTGTT	400 nM	
	Flu Sw H1 TM298-TEX	TEX-CCACAATGTAGGACCATGAGCTTGCTGT-BBQ	200 nM	
Influenza B	InfB BP-13	GAGCACAATTGCCTACCTGC	400 nM	16
	InfB BMP102	CCACCGAACCAACAGTGTAAT	400 nM	
	InfB BMP-72-CY5	CY5-AGATGGAGAGGCAGCGAACTAGC-BBQ	200 nM	
Internal amplification control	IAC EGFP-12-F	TCGAGGGCGACACCCTG	400 nM	18
	IAC EGFP-10-R	CTTGTACAGCTCGTCCATGC	400 nM	
	IAC EGFP-HEX	HEX-AGCACCCAGTCCGCCCTGAGCA-BBQ	200 nM	

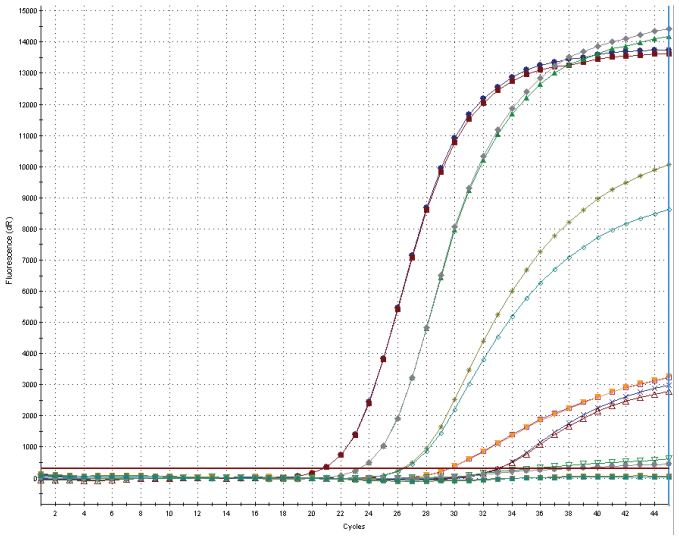
Figure 1

Typical RT-PCR amplification curves for influenza viruses

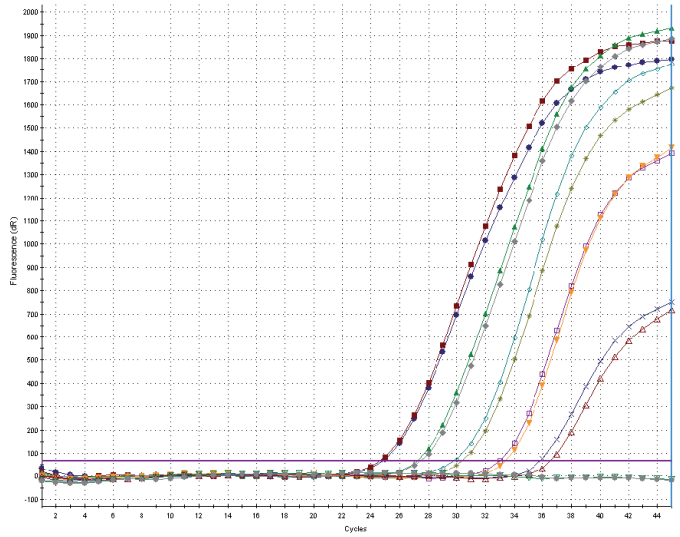
A: Seasonal influenza A virus detected in the FAM channel



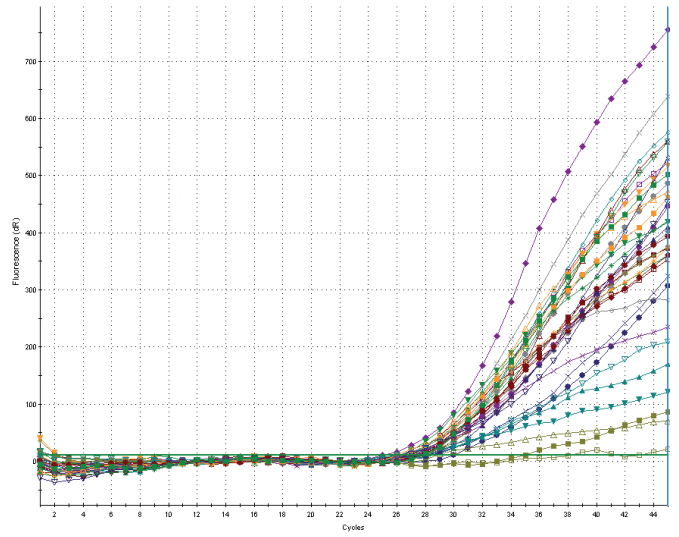
B: Pandemic influenza A(H1N1)2009 virus detected in the TEX channel



C: Influenza B virus detected in the CY5 channel



D: HEX channel showing the internal amplification control



All viruses in dilution series of 10 ng RNA to 1 pg RNA.

Table 2

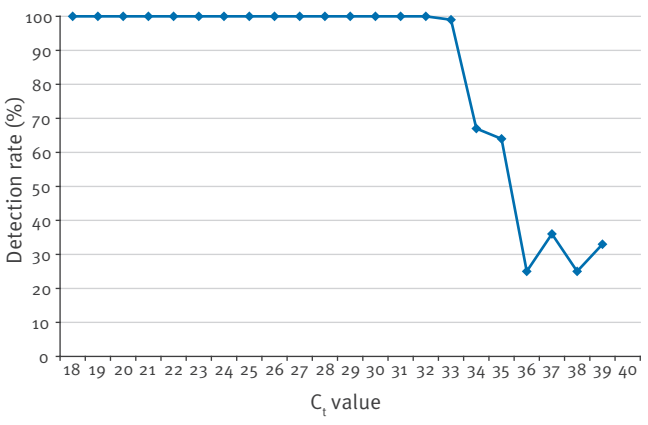
PCR efficiencies of the single assays compared to the multiplex assay

	E single	E multiplex
Influenza A	112.9%	112.9%
Influenza A(H1N1)2009	103.1%	105.5%
Influenza B	92.0%	120.0%

E: PCR efficiency

Figure 2

Detection rate of the multiplex PCR for influenza viruses in samples with different C_t values in the respective diagnostic assay



the commercially available QuantiTect Virus +ROX Vial kit (Qiagen) including QuantiTect Virus No Rox (NR) Mastermix and QuantiTect virus RT. For specific detection of influenza A, influenza A(H1N1)2009, influenza B and the internal amplification control (IAC), we used primers and probes of published or officially recommended real-time PCR systems (Table 1): a previously published real-time RT-PCR assay [16] for influenza A viruses targeting the matrix gene, with an optimised reverse primer (InfA M-124-mod) for reliable detection of pandemic influenza A(H1N1)2009 (recommended by the national reference centre for influenza at the RKI); an officially recommended real-time PCR system with primers and a TaqMan probe for the specific detection of influenza A(H1N1)2009 [9] targeting the HA gene, and a real-time RT-PCR assay for the detection of influenza B [17] targeting the matrix gene, with a slightly modified reverse primer that has been routinely applied for years for routine diagnosis in our laboratory. The detection system for the internal amplification control has been described previously for multiplex real-time PCR assays [18].

All primers and probes were synthesised by TIB Molbiol. For the three influenza single target real-time RT-PCR assays a 25 µl PCR reaction was prepared containing: 400 nM of each forward and reverse primer (see Table 1), 100 nM of TaqMan probe, 1x QuantiTect virus reverse transcription mix, 1x QuantiTect virus NR mastermix, 4U RNase inhibitor (Invitrogen) and 5 µl RNA extract.

For optimisation of the multiplex assay all primer concentrations were titrated from 100 to 500 nM and all probe concentrations from 100 to 300 nM. Fluorescence filter sets for 6-carboxyfluorescein (FAM), hexachloro-6-carboxy-fluorescein (HEX/VIC), Texas Red (TEX/ROX) and a cyanine dye (CY5) were used simultaneously. The influenza A- and B-specific probes were labelled with FAM and CY5, respectively. The probe specific for pandemic influenza A(H1N1)2009 was labelled with TEX. The IAC probe was labelled with HEX. All four TaqMan probes were labelled with Black Berry Quencher (BBQ) as quencher dye. For the multiplex real-time PCR assay optimised probe concentrations were applied (see Table 1).

For single and multiplex real time PCR thermal cycling was performed on MX3000P and MX3005P real-time PCR instruments (Agilent Technologies) under the following conditions: 20 min at 50°C; 10 min at 95°C; 45 cycles of 15 s at 95°C and 45 s at 60°C.

Efficiency of the multiplex assay

PCR efficiencies were determined for influenza A, influenza B and pandemic influenza A(H1N1)2009 in each single assay as well as the individual channels of the multiplex assay. PCR efficiency was calculated according to the PCR amplification formula $E = 10^{(1/slope)}-1x100\%$, E being the PCR efficiency.

Results

Optimisation of the multiplex assay

Primer titration from 100 to 500 nM as well as probe titration from 100 to 300 nM indicated an optimal primer concentration of 400 nM and an optimal probe concentration of 200 nM for all four assays in the multiplex real-time RT-PCR (see Table 1). Higher or lower concentrations did not alter the sensitivity of the multiplex assay significantly (results not shown).

The optimised multiplex real-time RT-PCR assay in a 25 µl PCR reaction volume was composed as follows: 400 nM of all primers and 200 nM of each of the four TaqMan probes, 1x QuantiTect virus RT mix, 1x QuantiTect virus NR mastermix, 4U RNase inhibitor, 0.25 µl IAC RNA ($2.5x10^4$ copies) and 5 µl RNA extract. Thermal cycling was performed on MX3000P and MX3005P under the same conditions as the individual single assays. The optimised multiplex real-time RT-PCR assay is shown in Figure 1 for 10-fold dilution series of viral RNA from 10 ng to 1 pg RNA.

Specificity of the multiplex assay

The specificity of the diagnostic assays for influenza A and influenza B has previously been tested and confirmed [16,17]. Therefore it was not further tested during multiplex optimisation. We checked the specificity of the PCR for pandemic influenza A(H1N1)2009 virus that was unpublished at the time [9] by sequencing the 80 bp amplicons (HA gene) of positive pandemic influenza A(H1N1)2009 samples. All fifty sequenced PCR products were 100% identical to published sequences of pandemic influenza A(H1N1)2009 proving the high specificity of the assay. The specificity of the multiplex assay was confirmed in two official external quality assurance studies (INSTAND e.V., Germany) comprising 15 samples of six different influenza strains, which were tested in duplicate. No cross-reactivity was observed in any of the 15 samples, and all specific targets showed strong positive signals. Furthermore the oseltamivir-resistant strain influenza A/Berlin/58/2008 (H1N1) was tested and correctly identified by the multiplex real-time RT-PCR assay.

Analytical sensitivity of the multiplex assay

With plaque-quantified influenza A/Hamburg/05/2009 (H1N1) we found a linear dynamic range from 10^5 to 10^2 genome equivalents. The detection limit was below $3.5x10^2$ PFU/ml for the matrix gene as well as the HA gene. Testing of each RNA concentration of the influenza A (Sydney/5/1997 (H3N2) and B (Brisbane/60/2008) reference material in triplicates yielded a sensitivity of 10 pg per PCR reaction for each detection system in the single assays as well as in the multiplex assay and detected RNA extracted from influenza-infected cell cultures (seasonal influenza A(H3N2) and B) and from egg cultures (influenza A(H1N1)2009) with equal sensitivity.

Table 3

Sensitivity, specificity, positive predictive value and negative predictive value of the multiplex assay

	All single assays					C_t<34 in the single assays					C_t>34 in the single assays				
	Samples	Sensitivity	Specificity	PPV	NPV	Samples	Sensitivity	Specificity	PPV	NPV	Samples	Sensitivity	Specificity	PPV	NPV
Seasonal influenza A	47	78.7	100	100	90.0	31	100	100	100	100	16	37.5	100	100	90.0
Seasonal influenza B	50	76.0	100	100	88.2	28	96.4	100	100	98.9	22	50	100	100	89.1
Pandemic influenza A(H1N1)2009	130	95.4	98.9	99.2	93.7	116	100	98.9	99.1	100	14	57.1	98.9	88.9	93.7
Overall	227	87.7	99.6	99.5	90.6	175	99.4	98.9	99.4	98.9	52	48.1	98.9	96.2	76.7

NPV: negative predictive value; PPV: positive predictive value.
Numbers are also shown for samples with Ct-values below and above 34.

Efficiency of the multiplex assay

The real-time PCR runs of the sensitivity tests for influenza A (Sydney/5/1997 (H3N2), influenza A/Hamburg/05/2009 (H1N1) and influenza B (Brisbane/60/2008) were applied for the determination of the PCR efficiencies in the multiplex real-time PCR compared to the individual single real time PCR assays. The PCR efficiencies of the single real-time PCR assays in comparison to the individual channels of the multiplex PCR assay are shown in Table 2. The PCR efficiency of each individual assay was determined as between 92% to 120% for the individual assays. The PCR efficiencies of the respective single assay were comparable to the PCR efficiency in the multiplex assay. The influenza B assay had a PCR efficiency of 92% in the single assay while in the multiplex assay the PCR efficiency was 120%, which was considered as acceptable for a screening assay.

Evaluation of the multiplex assay with samples of ILI patients

A total of 317 stored RNA samples from the respiratory tract of ILI patients that had previously been tested with diagnostic real-time RT-PCR assays, were retrospectively tested with the multiplex assay. The overall diagnostic sensitivity of the multiplex assay was 87.7%, specificity was 99.6% and positive (PPV) and negative predictive values (NPV) 99.5% and 90.6%, respectively, compared to the respective diagnostic assay. Ninety samples had been negative in all diagnostic assays. Of those 90, 89 were also negative when we tested them in the multiplex assay, but one sample yielded a positive result for pandemic influenza A(H1N1)2009 in the multiplex assay (C_t value 35).

Of 175 influenza-positive samples with C_t values under 34 in the respective diagnostic assay, 174 were confirmed by the multiplex assay, with positive signals for seasonal influenza A (31/31), influenza B (27/28) and pandemic influenza A(H1N1)2009 (116/116) viruses. The influenza B-positive sample that was missed in the multiplex PCR had had a C_t value of 34 in the diagnostic PCR. In samples that had C_t values above 34 in the respective diagnostic assay, the reliability of detection with the multiplex assay was lower: 25 of 52 influenza samples overall, with 6 of 16 seasonal influenza A, 11 of 22 influenza B, and 8 of 14 influenza A(H1N1)2009 (Figure 2 and Table 3). The sensitivity of detection of influenza A(H1N1)2009 was slightly lower with the primers targeting the matrix gene (116/130; 89.2%) than with primers targeting the HA gene (124/130; 95.4%) especially in samples that had been only weakly positive in the respective diagnostic PCR (C_t values>34). The IAC was positive in all influenza-negative samples, indicating that failure to detect influenza virus was not due to inhibition.

Based on the detection rates of this evaluation we calculated that the multiplex assay would have correctly identified at least 1,238 of the 1,322 (93.6%) influenza A(H1N1)2009-positive samples (Figure 3), which

were analysed at the Bavarian Health and Food Safety Authority between 27 April and 9 November 2009 using the diagnostic assays. The C_t values were between 20 and 32 for 1,025 of these samples.

The multiplex assay was introduced as the sole screening test into laboratory influenza surveillance in Bavaria on 10 November 2009. Until 16 April 2010, 310 of 1,228 nasopharyngeal and throat swabs of ILI patients tested positive for influenza A(H1N1)2009 using this assay. The results reflected the epidemic curve of reported cases of influenza A(H1N1)2009 in November 2009 in Bavaria.

The IAC was negative in five throat swabs which all tested negative for influenza viruses. After 10-fold dilution of the sample, the IAC was positive in all five samples. The negative results of three of these samples were confirmed negative when retested in dilution in the multiplex assay, while two were positive for pandemic influenza A(H1N1)2009.

Discussion

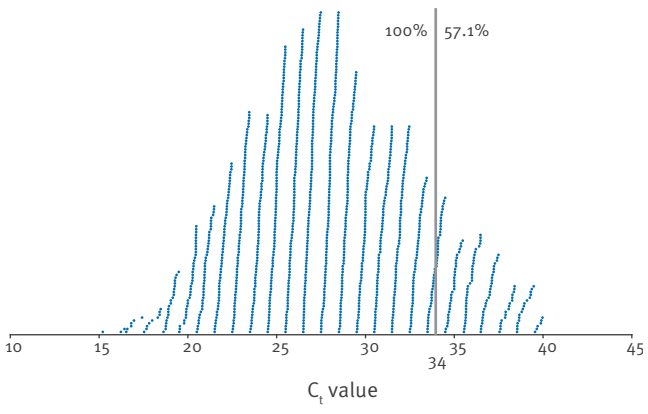
We report on a multiplex one-step real-time RT-PCR assay for the simultaneous detection of seasonal influenza A and B as well as influenza A(H1N1)2009 viruses. The assay was optimised for multiplex real-time PCR from published, validated and well established PCR protocols with minor modifications. The multiplex assay proved to be as specific as the respective diagnostic PCR assay. Only one sample tested negative in the diagnostic assays but positive for influenza A(H1N1)2009 in the multiplex assay in two replicates. We ran out of patient material and could not retest the sample with the diagnostic assay. As we detected only a low positive signal, neither a false positive result of the multiplex assay due to contamination, nor a false negative result of the diagnostic assay could be ruled out. A PCR inhibition control was successfully integrated into the assay for accurate interpretation of negative results. Interestingly, two samples positive for pandemic influenza A(H1N1)2009 would have been missed without the IAC. Dilution of the RNA before PCR successfully abolished the inhibitory effect. As we used the *in vitro*-transcribed RNA as an amplification control we could not control for inhibitory effects due to the extraction protocol.

We consider our multiplex assay that has shown its functionality in a high number of patient samples a useful tool for general public health laboratories. In contrast to the evaluation of other published assays [5,7,19], we have tested our multiplex assay on a very large number of clinical samples, including a high number of positive samples. In our analysis of patient samples, the diagnostic sensitivity of the multiplex PCR was slightly lower than that of the respective diagnostic assays, even if RNA dilution series of reference material showed equal sensitivity when determining the detection limit of the multiplex assay in comparison to the single assays. This might be explained by degradation due to storage of weakly positive patient RNA samples for up to one year, whereas dilution series were performed with freshly isolated RNA from reference material for the single as well as the multiplex assays. The overall sensitivity was 87.7%, but was 99.4% for samples with moderate and high viral loads (C_t value>34). In a situation with population-wide screening in which patients with acute ILI yielding high viral loads are tested, we consider the slightly lower sensitivity acceptable. The assay has been validated for routine diagnosis of influenza and is used for large scale surveillance of influenza activity. While the pandemic subtype was reliably recognised during the 2009 pandemic, specificity and sensitivity of the multiplex assay was also shown for seasonal, avian and an oseltamivir-resistant virus. The assay is used to monitor influenza viruses throughout the whole year. By introducing the multiplex assay we were able to lower costs by saving reagents and working time. Furthermore we reduced sample turnaround time in comparison to the diagnostic PCR assays.

Diagnostic tools for surveillance are applied for the general identification of influenza viruses. Although mutation of the pandemic influenza A(H1N1)2009 virus was rare in the 2009 pandemic [20], we also addressed this possibility by including conserved regions (matrix genes) as PCR target. Our multiplex assay is capable to both identify the circulating pandemic strain (HA gene) and screen for other influenza A and B viruses (matrix genes). These should be further subtyped to confirm other seasonal influenza A subtypes or to detect changes in the circulating strain.

Figure 3

C_t values of samples positive for pandemic influenza A(H1N1)2009 in the diagnostic PCR, Bavaria, 27 April–9 November 2009 (n=1,322)



Each dot represents one sample. The performance of the multiplex assay was retrospectively calculated for the first wave of the 2009 influenza pandemic. The resulting detection rates of the multiplex assay for influenza A(H1N1)2009 in the validation study for samples below (100%) and above (57.1%) a C_t value of 34 are shown. The multiplex assay would have detected at least 93.6% of the positive samples.

Chen *et al.* [21] also published a multiplex real-time RT-PCR assay for the simultaneous detection and subtyping of influenza viruses including the pandemic influenza AH1N1(2009), that has been evaluated on a high number of patient samples. Compared with our one-step real-time RT-PCR assay, this assay is based on a two-step real-time RT-PCR.

The 2009 pandemic is a reminder for public health laboratories to monitor influenza activity not only during the season of influenza circulation, but during the whole year. Our assay proved to be a convenient, rapid, reliable and cost effective way to meet this requirement.

Acknowledgements

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The impact of the 2009 influenza A(H1N1) pandemic on attitudes of healthcare workers toward seasonal influenza vaccination 2010/11

C Brandt[1], H F Rabenau[2], S Bornmann[3], R Gottschalk[4], S Wicker (sabine.wicker@kgu.de)[5]
1. Institute of Medical Microbiology and Infection Control, Hospital of the Johann Wolfgang Goethe-University, Frankfurt, Germany
2. Institute of Medical Virology, Hospital of the Johann Wolfgang Goethe-University, Frankfurt, Germany
3. Institute of Occupational, Social and Environmental Medicine, Friedrich-Schiller-University, Jena, Germany
4. Health Protection Authority, City of Frankfurt am Main, Frankfurt, Germany
5. Occupational Health Service, Hospital of the Johann Wolfgang Goethe-University, Frankfurt, Germany

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The emergence of the influenza A(H1N1)2009 virus provided a major challenge to health services around the world. However, vaccination rates for the public and for healthcare workers (HCWs) have remained low. We performed a study to review the reasons put forward by HCWs to refuse immunisation with the pandemic vaccine in 2009/10 and characterise attitudes in the influenza season 2010/11 due to the emergence of influenza A(H1N1)2009. A survey among HCWs and medical students in the clinical phase of their studies was conducted, using an anonymous questionnaire, at a German university hospital during an influenza vaccination campaign. 1,366 of 3,900 HCWs (35.0%) were vaccinated in the 2010/11 influenza season. Of the vaccinated HCWs, 1,323 (96.9%) completed the questionnaire in addition to 322 vaccinated medical students. Of the 1,645 vaccinees who completed the questionnaire, 712 had not been vaccinated against the influenza A(H1N1)2009 virus in the 2009/10 season. The main reason put forward was the objection to the AS03 adjuvants (239/712, 33.6%). Of the HCWs and students surveyed, 270 of 1,645 (16.4%) stated that the pandemic had influenced their attitude towards vaccination in general. Many German HCWs remained unconvinced of the safety of the pandemic (adjuvanted) influenza vaccine. For this reason, effective risk communication should focus on educating the public and HCWs about influenza vaccine safety and the benefits of vaccination.

Introduction

Healthcare workers (HCWs) are at risk of occupational exposure to influenza and when infected, may transmit the disease to vulnerable patients [1-3]. The most important prevention strategy is immunisation [4]. However, despite official recommendations, e.g. from the World Health Organization (WHO), the European Union [5] and the Robert Koch Institute (RKI) in Germany, and the availability of a safe effective and well-tolerated vaccine, acceptance of seasonal influenza vaccine among HCWs is problematic and leads to low coverage, as detailed in many studies from all over of the world [6-10].

High influenza vaccination rates among HCWs can reduce the spread of influenza in healthcare facilities and help maintain a sustainable and effective healthcare workforce. Rumours and fears such as 'the vaccine does not work' or 'the vaccine causes flu' about a vaccine for which substantial health-related and economic benefits have been demonstrated also for healthy adults, should not hinder vaccination of HCWs because this ultimately compromises patient safety and public health [11,12].

During the influenza A(H1N1) pandemic in 2009/10 many HCWs worldwide expressed concerns about the safety of the monovalent pandemic vaccine and refused to receive it because it was a 'new' vaccine, 'untested', and 'rushed to the market' [13]. For most, the infection with influenza A(H1N1)2009 virus turned out to be less severe than first feared, however, severe disease and deaths occurred not only in the traditional risk groups for influenza but also in healthy young people and pregnant women [14]. However, if the virus had been more pathogenic and virulent, the impact of the pandemic could have been devastating [13].

A population of vaccinated, working and informed HCWs is crucial for an effective response to the burden of influenza and the mitigation of the associated morbidity and mortality [15]. Although we do not know which influenza virus subtype will cause possible future pandemics, a number of lessons can be learned from the influenza A(H1N1)2009 pandemic in 2009/10. Healthcare organisations and policy makers need to

rethink current practices and ought to wonder whether voluntary influenza immunisation programmes for HCWs, which do not lead to satisfactory vaccination rates, are adequate to protect patient safety with regards to both seasonal and pandemic influenza [11,16].

The influenza H1N1/09 pandemic was discussed with HCWs of the university hospital Frankfurt for the first time in July 2009, when the first cases became hospitalised. In order to prevent transmission, HCWs caring for patients with respiratory symptoms were obliged to wear a surgical mask. Moreover, HCWs were instructed to wear a FFP2 mask during direct contact with a patient with laboratory confirmed 2009 pandemic influenza A(H1N1) when they had not been vaccinated against the relevant virus. The pandemic vaccine became available from 26 October, 2009. The uptake of the pandemic vaccination at the university hospital Frankfurt was 36.3% in the 2009/10 season.

We conducted a cross-sectional study to characterise the reasons why HCWs vaccinated against influenza in 2010/11 had refused the pandemic vaccine in 2009/10 at a time when it was unclear how the pandemic would unfold. Further, we evaluated their attitudes towards the pandemic. In this paper, we describe why the results support the need for well-defined risk communication.

Study population and questionnaire

The Frankfurt University Hospital is a 1,169-bed hospital with approximately 3,900 employees including 726 physicians, 1,300 nurses and 850 medical technicians. It has approximately 42,000 in-patient admissions and about 200,000 out-patients per year. At the Frankfurt Medical School, which is organisationally within the Frankfurt University Hospital, there are approximately 3,300 medical and dental students, including 1,200 medical students who are in the clinical phase of their studies. A comprehensive influenza vaccination campaign, which included publicity (posters, leaflets), education (information sessions), and vaccination started in the influenza season 2003/04. Influenza vaccination as well as advice to HCWs is offered by the occupational health service of the university hospital. In the past seven years we achieved an improvement in seasonal influenza vaccination uptake from 3.2% in 2002/03 to 40.5% in 2009/10.

To address why higher vaccination uptakes were not met during the pandemic 2009/10, we developed a questionnaire for 2010/11, after reviewing published studies on reasons why HCWs accept or refuse influenza vaccination and after conducting a preliminary survey one week before the vaccination campaign with 20 HCWs. The final questionnaire comprised seven closed questions divided into three areas: demographic data (age, sex, profession group, field of work), acceptance of the pandemic influenza A(H1N1)2009 vaccination in 2009/10, and attitudes in response to the pandemic. HCWs and medical students who came to get the seasonal influenza vaccine between October 2010 and February 2011 were asked to complete this anonymous self-administered questionnaire and to return it in a locked box.

Ethical considerations

Participants were informed that all the information gathered would be anonymous and kept confidential. Participation was voluntary, completion of the questionnaire implied consent for study participation. Participants cannot be identified from the material presented.

Statistical analysis

The statistical analysis of the frequency distributions was done using a two-tailed Pearson's chi-square test. The threshold p-value for statistical significance was set to $p<0.05$. The questionnaire was not based on a priori hypotheses; nevertheless, an α-adjustment was made with 14 and five four-field tables, using the Bonferroni post-test which considered selective (local) p-values of

Table 1

Demographic characteristics of participants, healthcare workers and medical students at Frankfurt University Hospital, October 2010–February 2011 (n=1,645)

Age (years)	n	%
Up to 30	648	39.4
31–40	434	26.4
41–50	337	20.5
51–60	191	11.6
Over 60	35	2.1
Sex		
Male	663	40.3
Female	982	59.7
Job description		
Physicians	505	30.7
Medical students	322	19.6
Nurses	394	23.9
Medical technicians	104	6.3
Administrative personnel	164	10.0
Maintenance, catering, workshop, transport	77	4.7
Others	79	4.8
Field of work		
Anaesthesia	144	8.8
Ophthalmology	24	1.5
Surgery	118	7.2
Dermatology	48	2.9
Gynaecology	53	3.2
Ear, nose and throat	20	1.2
Internal Medicine	338	20.5
Psychiatry	53	3.2
Paediatrics	145	8.8
Radiology	74	4.5
Neurology	86	5.2
Other department or not specified	542	32.9

p≤0.0036 (Table 2) and p≤0.01 (Table 3) as statistically significant at the global overall significance level of α=0.05. The significance calculations were made using the program BiAS for Windows 9.04 (Epsilon Verlag, Hochheim Darmstadt 2009). Furthermore, 95% confidence intervals (CI) were calculated.

Results

From October 2010 to February 2011, 1,366 of 3,900 (35.0%) HCWs of the University Hospital Frankfurt were vaccinated with the seasonal trivalent influenza vaccine. In total, 1,323 vaccinated HCWs (response rate 96.9%) and 322 of 1,200 (26.8%) medical students in the clinical phase of their studies at the Frankfurt Medical School completed the anonymous questionnaire and were vaccinated against influenza. All 1,645 questionnaires could be analysed. Overall 982 of 1,645 (59.7%) participants were female, and 663 of 1,645 (40.3%) were male, in accordance with the sex distribution of employees and student body at the university. Demographic characteristics of the study population are shown in Table 1.

Table 2

Healthcare workers reasons for refusing the AS03 adjuvanted pandemic influenza vaccine in the 2009/10 influenza season, Frankfurt University Hospital, October 2010–February 2011 (n=1,645)

Reason	Total persons (n=712) number percentage (95% CI)	Physicians (n=100) number percentage (95% CI)	Nurses (n=202) number percentage (95% CI)	Physicians vs nurses p value	Students (n=192) number percentage (95% CI)	Others (n=218) number percentage (95% CI)
No personal risk of contracting influenza	238 33.4% (30.0–37.0)	27 27.0% (18.6–36.8)	47 23.3% (17.7–29.7)	0.478	89 46.4% (39.1–53.7)	75 34.4% (28.1–41.1)
No severity of influenza illness	96 13.5% (11.1–16.2)	12 12.0% (6.4–20.0)	21 10.4% (6.6–15.5)	0.674	33 17.2% (12.1–23.3)	30 13.8% (9.5–19.1)
Vaccine does not work	86 12.1% (9.3–14.7)	11 11.0% (5.6–18.8)	22 10.9% (7.0–16.0)	0.977	31 16.1% (11.2–22.1)	22 10.1% (6.4–14.9)
Fear of side effects	187 26.3% (23.0–29.7)	25 25.0% (16.9–34.7)	66 32.7% (26.3–39.6)	0.171	43 22.4% (16.7–29.0)	53 24.3% (18.8–30.6)
Fear of adjuvants	239 33.6% (30.1–37.2)	35 35.0% (25.7–45.2)	83 41.1% (34.2–48.2)	0.307	47 24.5% (18.6–31.2)	74 33.9% (27.7–40.6)
Fear of needles	11 1.5% (0.8–2.7)	1 1.0% (0.0–5.4)	6 3.0% (1.1–6.4)	0.284	0 0% (0.0–1.5)	4 1.8% (0.5–4.6)
Vaccine causes flu	28 3.9% (2.6–5.6)	3 3.0% (0.1–8.5)	15 7.4% (4.2–12.0)	0.126	3 1.5% (0.3–4.5)	7 3.2% (1.3–6.5)
No time – too busy	52 7.3% (5.5–9.5)	12 12.0% (6.4–20.0)	7 3.5% (1.4–7.0)	0.004	19 9.9% (6.1–15.0)	14 6.4% (3.6–10.5)
Forgotten	36 5.1% (3.6–6.9)	6 6.0% (2.2–12.6)	8 4.0% (1.7–7.7)	0.428	12 6.3% (3.3–10.7)	10 4.6% (2.2–8.3)
Missed vaccination days at the hospital	31 4.4% (3.0–6.1)	7 7.0% (2.9–13.9)	7 3.5% (1.4–7.0)	0.169	10 5.2% (2.5–9.4)	7 3.2% (1.3–6.5)
Media hype alienated me	104 14.6% (12.1–17.4)	7 7.0% (2.9–13.9)	32 15.8% (11.1–21.6)	0.031	21 10.9% (6.9–16.2)	44 20.2% (15.1–26.1)
Insufficient information about vaccine	38 5.3% (3.8–7.3)	5 5.0% (1.6–11.3)	10 5.0% (2.4–8.9)	0.985	14 7.3% (4.0–11.9)	9 4.1% (1.9–7.7)
GP advised against pandemic vaccine	46 6.5% (4.8–8.5)	2 2.0% (0.2–7.0)	13 6.4% (3.5–10.8)	0.095	10 5.2% (2.5–9.4)	21 9.6% (6.1–14.3)
Got no appointment with GP	3 0.4% (0.1–1.2)	0 0% (0.0–2.9)	1 0.5% (0.0–2.7)	0.481	2 1.0% (0.1–3.7)	0 0% (0.0–1.4)

CI: confidence interval; GP: general practitioner.

Multiple answers were possible and 1,195 answers were provided. Overall 43.3% (712 of 1,645) of the participants of the study were not vaccinated with the pandemic vaccine.

When asked how much time the participants provided care to immunocompromised patients (i.e. haematology, oncology, intensive-care units), 576 (35%) of the respondents stated daily, 411 (25%) occasionally, and 658 (40%) never.

Of all respondents, 933 (56.7%) stated that they had been vaccinated with the AS03-adjuvanted pandemic vaccine in the 2009/10 influenza season. The 712 (43.3%) respondents who had not received this vaccine were asked to provide the reasons for this. The main reason for not getting vaccinated was the objection to the AS03 adjuvants (239/712, 33.6%), closely followed by the belief that they personally were unlikely to catch influenza (238/712, 33.4%) (Table 2). Regarding these two frequently mentioned reasons there was no significant difference between physicians and nurses (p=0.352) (Table 2) or between women and men (p=0.426). No significant differences (p<0.05) in answers to all 14 questions stated in Table 2 could be seen between HCWs who were in daily contact with immunocompromised patients (165/712, 23.2%) and HCWs with occasional or no contact with such patients. However, men (45/246, 18.3%) stated more often than women (51/466, 10.9%) that they did not get vaccinated with the pandemic vaccine because they did not perceive the influenza A(H1N1)2009 virus infection as a severe disease (p=0.006). On the other hand more women (137/466, 29.4%) than men (50/246, 20.3%) noted that they had refused the pandemic vaccine because they had feared side effects (p=0.009).

Of the 1,645 HCWs surveyed, 270 (16.4%) cited that the 2009 influenza A(H1N1) pandemic influenced their attitudes towards vaccination in general (Table 3). Nurses (59/87, 67.8%) stated more often than physicians (36/73, 49.3%) that due to the pandemic it became clear that influenza is a severe disease (p=0.018), and also more nurses (21/87, 24.1%) than physicians (8/73, 11.0%) noted that they were concerned owing to the media hype (p=0.031). Otherwise, physicians stated more often than nurses (43.8% versus 25.3%) that they had had a positive experience with reference to the influenza vaccination (p=0.013) (Table 3).

Discussion

Increasing the public's acceptance of the influenza vaccination might be more challenging than addressing the scientific challenges involved in producing a safe and effective influenza vaccine [14]. Because a large number of people refuse to be vaccinated, it is important to understand the attitudes of the public and HCWs towards influenza vaccination [14]. It is therefore not enough to provide a safe vaccine, one also needs to convince the public to accept it. We attempted to understand the reasons of HCWs for not accepting the pandemic influenza A(H1N1)2009 vaccine as well as the impact of the pandemic on attitudes toward influenza infection.

The study showed that many German HCWs were unconvinced of the safety of the pandemic influenza vaccine. Fear of adjuvants was the most common reason cited for refusal of the adjuvanted pandemic vaccine. Since the 18th century, fear and mistrust have arisen every time a new vaccine has been introduced [17]. For this reason, communication is an issue which requires constant improvement. The media plays an

Table 3

Changes in attitudes following the emergence of pandemic influenza A(H1N1)2009, healthcare workers at Frankfurt University Hospital, October 2010–February 2011 (n=270)

	Total persons (n=270) number percentage (95% CI)	Physicians (n=73) number percentage (95% CI)	Nurses (n=87) number percentage (95% CI)	Physicians vs nurses p value	Students (n=40) number percentage (95% CI)	Others (n=70) number percentage (95% CI)
Pandemic created awareness for immunisations and caused me to check my vaccination card	51 18.9% (14.4–24.1)	20 27.4% (17.6–39.1)	9 10.3% (4.8–18.7)	0.010	17 42.5% (27.4–59.1)	5 7.1% (23.6–15.9)
Due to the pandemic it became clear that influenza is a severe disease	148 54.8% (48.7–60.9)	36 49.3% (37.4–61.3)	59 67.8% (56.9–77.4)	0.018	17 42.5% (27.4–59.1)	36 51.4% (39.2–63.6)
I had a positive experience with the influenza vaccination, therefore I am going to get vaccinated every year	84 31.1% (25.6–37.0)	32 43.8% (32.2–55.9)	22 25.3% (16.6–35.7)	0.013	8 20.0% (9.1–35.6)	22 31.4% (20.9–43.6)
Media hype alienated me and lowered my confidence in vaccination policies	50 18.5% (14.1–23.7)	8 11.0% (4.8–20.5)	21 24.1% (15.6–34.5)	0.031	1 2.5% (0.1–13.2)	20 28.6% (18.4–40.6)
Having heard a lot about adjuvanted vaccines and side effects, I became sceptical towards vaccinations	61 22.6% (17.7–28.1)	13 17.8% (9.8–28.5)	19 21.8% (13.7–32.0)	0.526	7 17.5% (7.3–32.8)	22 31.4% (20.9–43.6)

CI: confidence interval.

Multiple answers were possible; 394 answers about risk perception were provided. Overall 16.4% (270 of 1,645) of the participants stated that the influenza A(H1N1)2009 pandemic influenced their attitudes towards vaccination in general.

important role in translating scientific information and in shaping the public's understanding of health issues and risk perception of infectious diseases [18]. Greater efforts in educating the public and HCWs about influenza vaccine safety and the benefits of vaccination are needed for an effective public health response [13].

To appreciate the results of our study, some potential limitations need to be addressed: Firstly, results from a single German academic institution may not be applicable to other institutions. Secondly, given that we only questioned HCWs who received the 2010/11 seasonal influenza vaccination, it is possible that HCWs who were not willing to get vaccinated may have had other reasons to decline the adjuvanted pandemic influenza vaccine. Thirdly, the social desirability bias, i.e. selecting a choice of answers considered as being socially most favourable may have lead to bias in our survey. Fourthly, it would have been interesting to compare the reasons to accept the seasonal influenza vaccination with the reasons for accepting or declining pandemic influenza immunisation. Unfortunately, we did not survey this in the present study.

For infectious diseases that potentially have a large impact on public health, risk communication is a particular challenge. Providing the public and HCWs with relevant information about an outbreak could decrease levels of concern by reducing levels of uncertainty about the nature, prevention or treatment of the infectious disease [19]. It is important to identify the most appropriate type of information which can be understood and trusted.

Problems along the way include the unacceptably low influenza vaccination rates amongst HCWs for more than three decades despite official vaccination recommendations [11,20], and the perception of the H1N1/2009 pandemic on behalf of the public that boarders ignorance and hysteria [21,22]. It has to be communicated better that HCWs who do not get vaccinated are taking two risks: firstly, the risk of themselves contracting influenza, a potentially long and serious illness, and secondly, the risk of transmitting influenza to their patients. Patients have a right to expect that HCWs and the institutions in which they work will take all necessary and reasonable precautions to keep them safe and minimise harm. The healthcare system will have to define a strategy to reach a sufficient influenza vaccination coverage among HCWs [11,16].

In conclusion, many German HCWs were unconvinced of the safety of the adjuvanted influenza vaccine. Greater efforts to educate HCWs about influenza vaccine safety and the need to increase influenza vaccination rates to ensure patient safety are of the utmost importance.

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Conflict of interest

The views in this article are the personal views of the authors and do not necessarily represent the views of the professional organizations or institutions within which we are members.
Sabine Wicker is a member of the German Standing Committee on Vaccination (STIKO) at the Robert Koch Institute (RKI). She has been a member of an advisory board on nasal influenza vaccines for AstraZeneca Germany. She has received honoraria for non-product-related talks on influenza vaccination from GlaxoSmithKline, Sanofi Pasteur, and Novartis.

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Virological analysis of fatal influenza cases in the United Kingdom during the early wave of influenza in winter 2010/11

J Ellis (joanna.ellis@hpa.org.uk)[1], M Galiano[1], R Pebody[1], A Lackenby[1], CI Thompson[1], A Bermingham[1], E McLean[1], H Zhao[1], S Bolotin[1], O Dar[1], J M Watson[1], M Zambon[1]
1. Health Protection Agency, Centre for Infections, London, United Kingdom

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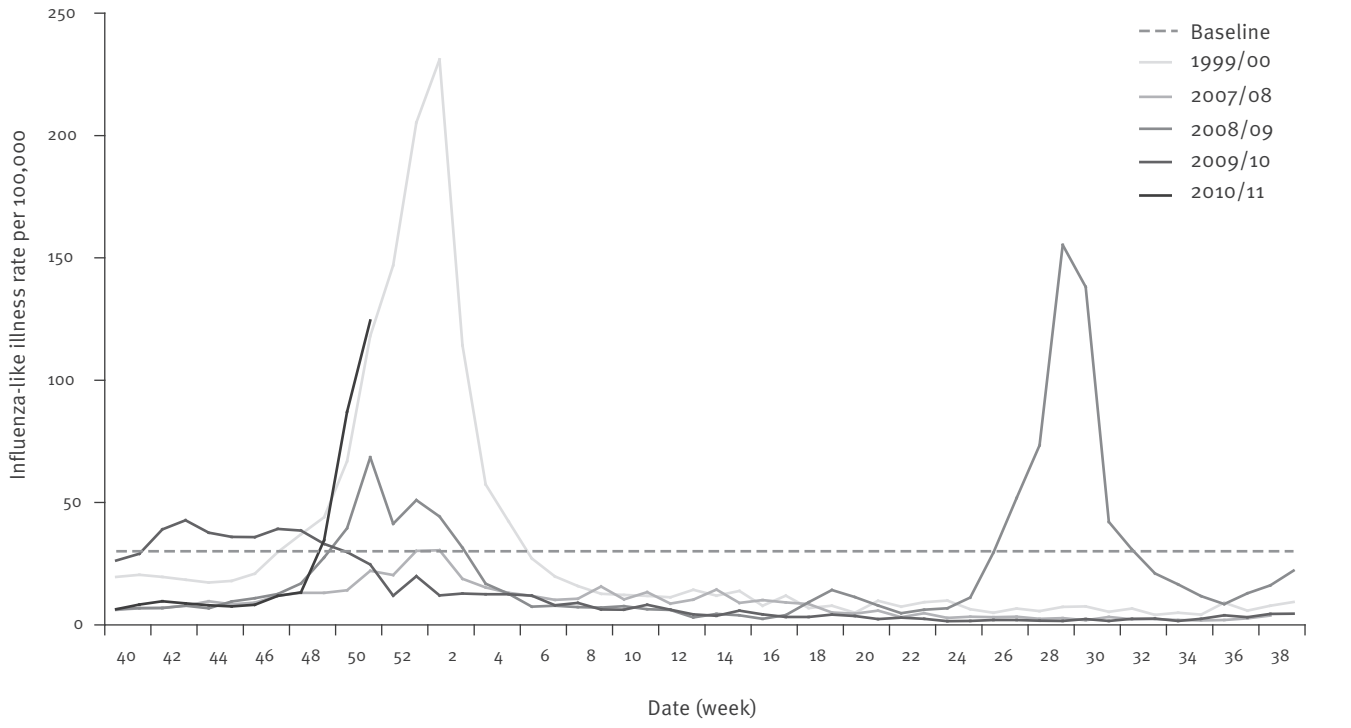
The 2010/11 winter influenza season is underway in the United Kingdom, with co-circulation of influenza A(H1N1)2009 (antigenically similar to the current 2010/11 vaccine strain), influenza B (mainly B/Victoria/2/87 lineage, similar to the 2010/11 vaccine strain) and a few sporadic influenza A(H3N2) viruses. Clinical influenza activity has been increasing. Severe illness, resulting in hospitalisation and deaths, has occurred in children and young adults and has predominantly been associated with influenza A(H1N1)2009, but also influenza B viruses.

Introduction

The onset of this winter season in the northern hemisphere is associated with more uncertainty than usual about which influenza viruses are likely to circulate and predominate, given the varying proportions of different virus strains circulating in the southern hemisphere between June and September 2010 [1]. Notably, influenza A(H3N2) predominated over influenza A(H1N1)2009 in several countries, e.g. South Africa and Chile. The second wave of the pandemic in the United Kingdom (UK) during the winter season of 2009/10 was almost exclusively associated with circulation of influenza A(H1N1)2009 [2]. Serological evaluation in the UK of population immunity to the pandemic strain after the second wave suggested that susceptibility was lowest in younger age groups (<15 years), with significant remaining susceptibility in the age group of 15–44 year-olds [3]. In view of the importance of children in the transmission of influenza A(H1N1)2009 [4], and the limited remaining susceptibility within this group, the

Figure 1

Royal College of General Practitioners influenza like illness consultation rates, England and Wales, current and past seasons



probability of extensive morbidity in this age group associated with this strain in winter 2010/11 was considered unlikely in the absence of significant antigenic change in the pandemic virus. The extent, however, to which influenza A(H1N1)2009 would predominate over influenza A(H3N2) and cause illness in the remaining susceptible children and younger adults was unknown.

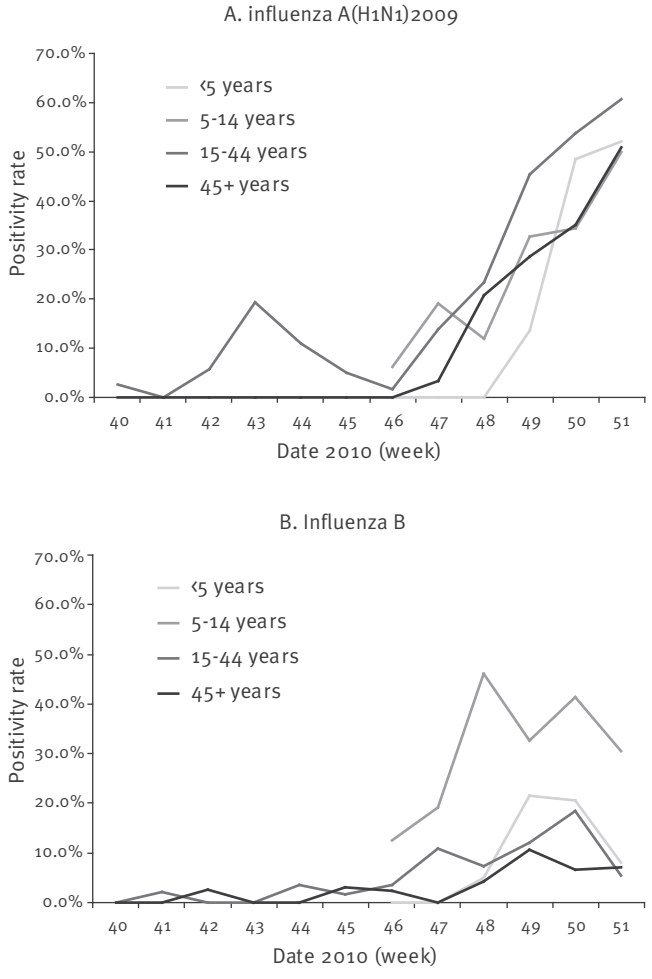
Investigations

Virological surveillance in the UK operates through hospital laboratories in secondary care and community-based schemes. Specimens containing influenza virus from community, hospitalised and fatal cases are forwarded to the UK National Influenza Centre for further characterisation. Samples are also received directly from sentinel primary care physicians participating in virological surveillance schemes in the community [5]. An antigenic typing profile is developed for each virus isolate and compared with influenza vaccine and reference strains. Genotypic and, where appropriate, phenotypic antiviral susceptibility analyses are performed on influenza-positive clinical material and/or virus isolates. Genetic characterisation is performed by targeted haemagglutinin (HA) sequence analysis and/or whole genome sequencing for a subset of isolates (primer sequences available on request).

We describe here observations undertaken as part of routine national surveillance. These are carried out under National Health Service (NHS) Act 2006 (section 251), which provides statutory support for disclosure of such data by the NHS, and their processing by the Health Protection Agency (HPA) for communicable disease control [6].

Figure 2

Influenza positivity rates from community sentinel virological surveillance in England by age, 4 October-26 December 2010



Rates with sample number less than 10 are not presented. Recent weeks' data may not be complete due to reporting time lag.

Epidemiological findings

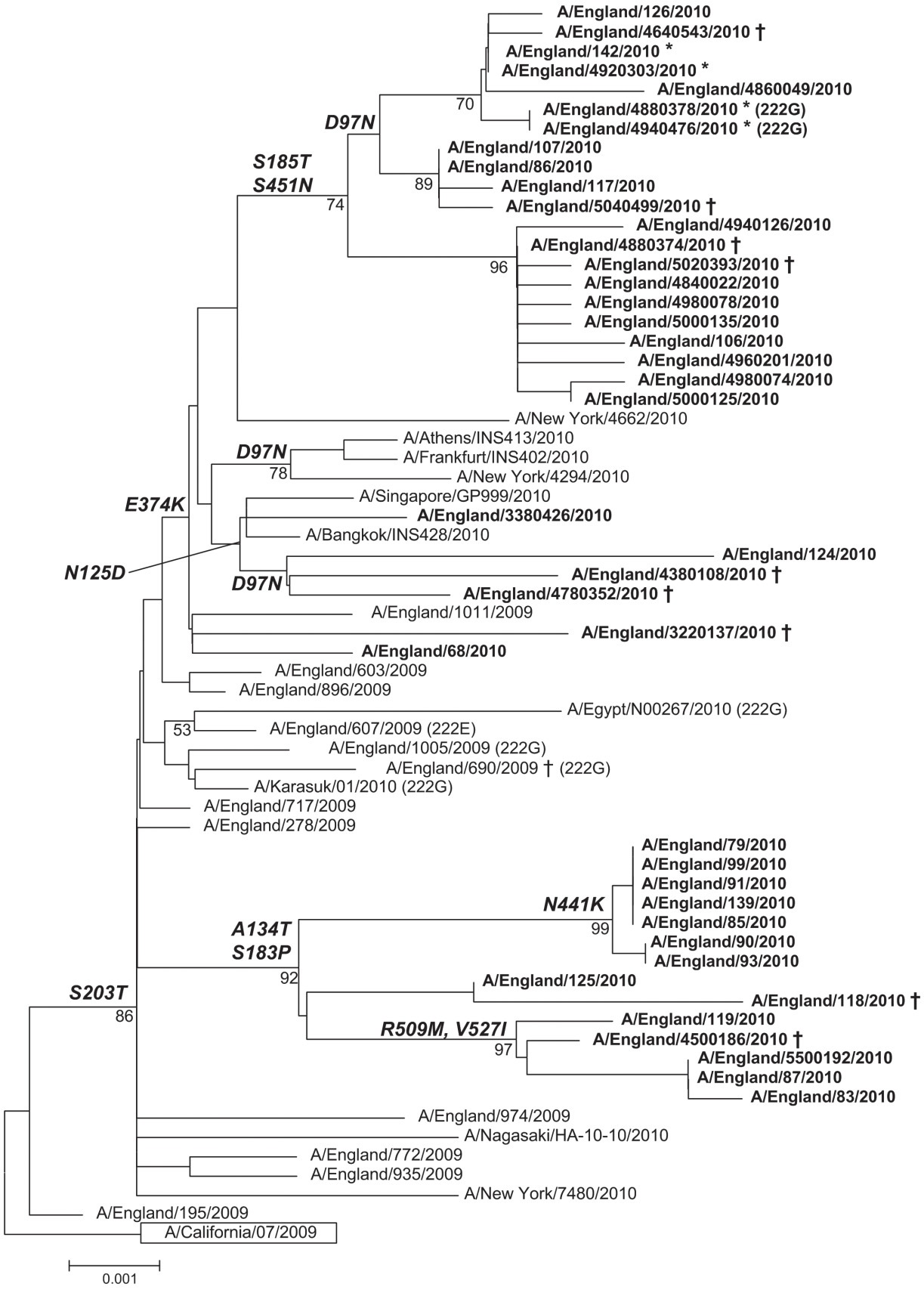
Early detections of influenza A(H1N1)2009 virus were first reported in weeks 40–42 from cases in the community. Indicators of clinical activity began to rise in week 47 crossing the traditional baseline threshold level indicating generalised influenza activity in the community in week 49, and have continued to increase up to week 52 (Figure 1).

Influenza A(H1N1)2009 viruses, followed by influenza B, have been the predominant influenza viruses circulating in the community in the period from October to the end of December 2010. Of 3,959 respiratory specimens reported to the English Data Mart system as taken in week 51, 1,711 (43.2%, increased from 38.9% in week 50) were positive for influenza, namely 1,402 influenza A(H1N1)2009, 41 not subtyped influenza A and 268 influenza B [7]. Since the beginning of the season, over 120 institutional outbreaks of respiratory illness have been reported, primarily from schools: 112 (93%) outbreaks from schools, four from care homes, two from hospitals, one from a military base, one from a nursery and two from prisons. Both influenza B and influenza A(H1N1)2009 have been detected in the few outbreaks that have been virologically investigated and confirmed: 22 outbreaks (44%) with influenza A(H1N1)2009 detected, 16 with influenza B, four with a mixture of influenza A(H1N1)2009 and influenza B, one with influenza A(H3N2) and seven with other respiratory viruses.

Admissions to hospital with severe illness have been reported. As of 30 December 2010, there were 738 patients with confirmed or suspected influenza in NHS critical care beds in England (42 cases under five years of age, 24 cases between five and 15 years, 586 cases between 16 and 64 years, and 86 cases 65 years and above) [8]. Thirty-nine deaths were reported between weeks 36 and 52 associated with confirmed influenza infection [7]. Four of the fatal cases were under five years of age, seven were 5-14 years of age, 27 cases were 15-64 years of age, and one fatal case was older than 64 years. The majority (36/39) of these deaths were associated with influenza A(H1N1)2009 infection, and three with influenza B infection. Underlying chronic conditions were reported in 23 of the 38 fatal cases for whom this information was available, with neurological disease such as cerebral palsy (n=9) and asthma

Figure 3

Phylogenetic relationship of full-length HA sequences of influenza A(H1N1)2009 viruses from fatal, severe and mild cases in the United Kingdom during 2010



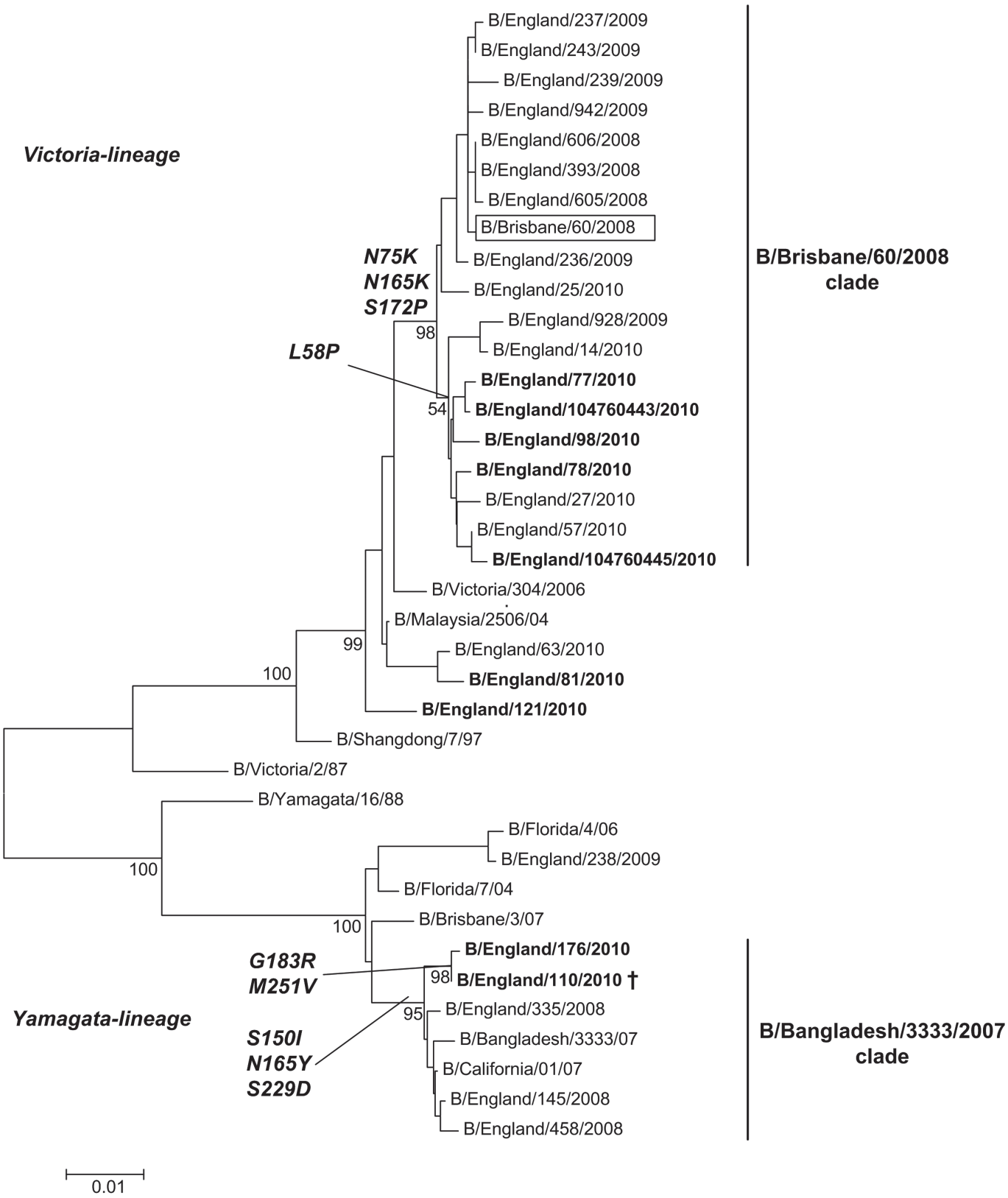
HA: haemagglutinin.

† Fatal case; * severe case.

Sequences downloaded from the NCBI Influenza Virus Resource (http://www.ncbi.nlm.nih.gov/genomes/FLU/) representative of globally circulating viruses during 2010 and, in bold, UK sequences from the first and second pandemic wave of 2009 were included. The tree was rooted with the vaccine strain A/California/07/2009 (boxed) as outgroup. Branch lengths are drawn to scale. Signature amino acid changes (H1 numbering) are annotated at the nodes of each cluster. Viruses with 222G or 222E changes are marked in the tree.

Figure 4

Phylogenetic relationship of HA1 sequences of influenza B viruses from fatal and mild cases in the United Kingdom during 2010



HA: haemagglutinin.

† Fatal case.

Branch lengths are drawn to scale. Amino acid changes characteristic of clades are marked in the tree. Sequences from UK 2010 viruses are in bold, and the 2010/11 vaccine strain is boxed.

(n=8) the most frequently reported underlying risk factors for vaccination [9]. Very few of the fatal cases (2/33) had received the 2010/11 trivalent influenza vaccine. A third of the cases (8/22) had not received antiviral therapy.

The proportion of samples from patients with influenza-like illness in sentinel general practitioner surveillance schemes in the community reported positive for influenza virus (A(H1N1)2009 or B) has risen rapidly to over 50% in week 49. The proportion of samples positive for influenza A(H1N1)2009 virus was highest in young adults (15-44 years), and for influenza B in children aged 5-14 years (Figure 2).

By week 50, the proportion of the population in England aged under 65 years in a risk group who had received the 2010/11 influenza vaccine was 43% [7].

Virological investigations

Influenza A(H1N1)2009 isolates characterised to date, in samples from the community, hospitalised patients and fatal cases, are antigenically homogeneous and similar to the A(H1N1)2009 virus included in the 2010/11 seasonal influenza vaccine, A/California/7/2009. Only minor genetic drift has been noted in influenza A(H1N1)2009 viruses circulating in 2010 compared with the earliest isolates in April 2009, and this observed genetic diversity has been consistent with expected patterns of virus evolution (Figure 3). Phylogenetic analysis shows that HA sequences from nine fatal and four severe cases in the UK in 2010 were interspersed with sequences from mild cases in 2010 from the UK and elsewhere. All UK 2010 viruses cluster in two main branches, characterised by either E374K with additional mutations in minor subclusters such as D97N, S185T, S451N and N125D, some of which have been recently described [10], or by A134T and S183P, with additional substitutions such as N441K, R509M and V527I. Almost all viruses from winter 2010 analysed to date from fatal and non-fatal cases had 222D in the HA gene (39/41).

Preliminary analyses from a limited number of whole genome sequences including some from fatal cases, indicate that these are consistent with observations from seasonal influenza and from the first and second waves of the recent pandemic: so far no unique mutations have been associated with severe or fatal cases of influenza A(H1N1)2009, but further comprehensive analysis is required.

Between October and December 2010, antiviral resistance monitoring was undertaken on 156 community and 159 hospital isolates. Six cases of oseltamivir resistance associated with the H275Y mutation in the neuraminidase (NA) gene have been detected.Only one of these cases has had known exposure to oseltamivir, Two of them have been identified from community surveillance of uncomplicated infections, three cases have been detected before treatment in individuals hospitalised with underlying risk factors, and the sixth case has been detected after oseltamivir treatment in a hospitalised individual.

Over 98% of influenza B viruses isolated in the UK since week 40 in 2010 have been from the B/Victoria/2/87 lineage, with most showing good reactivity to antisera raised against reference viruses from this lineage. The HA sequences group within the genetic clade represented by the current vaccine strain, B/Brisbane/60/2008, characterised by amino acid substitutions L58P N75K, N165K and S172P (Figure 4). A separate small cluster of three viruses from the antigenically distinct B/Yamagata/16/88 lineage have also been detected in one region of England: one fatal case and two hospitalised cases. The three known fatal influenza B cases were distributed across both lineages. The HA segment of the influenza B/Yamagata lineage virus isolated from a fatal case in week 46 belonged to a clade represented by influenza B/Bangladesh/3333/2007, with amino acid substitutions S150I, N165Y and S229D relative to a previous vaccine strain, B/Florida/4/06. This HA sequence contained two additional substitutions, G183R and M251V, which had been sporadically detected in influenza B viruses isolated in several countries in 2009/10.

Antigenic characterisation of the few influenza A(H3N2) viruses detected since week 38 indicates that these viruses are closely related to A/Perth/16/2009, the influenza A(H3N2) 2010/11 vaccine strain.

Conclusions

Influenza virus circulation is underway in the UK and is contributing to seasonal winter pressures in the health system. The circulation of other winter viruses such as respiratory syncytial virus (RSV) and the particularly cold weather are also contributing. The virological picture is complex, with many strains of influenza virus circulating but no antigenic change in the influenza A(H1N1)2009 virus, and no immediately obvious genetic differences between viruses recovered from fatal cases and those causing mild illness. The picture of the illness associated with influenza A(H1N1)2009 infection is consistent with what was seen in the 2009 pandemic, with a similar demographic impact, particularly affecting children and young adults. Whilst young age groups have the least experience of influenza and are recognised as important in the transmission of influenza, it is also possible that propensity to consult a doctor is greatest in younger age groups. Although the remaining susceptibles in the age group under 15 year account for high rates of positivity in peak weeks in community samples (as is often the case during seasonal influenza), it is notable that overall, sustained high rates of positivity are most marked in the age group between 15 and 44 years. This is in contrast to earlier pandemic waves in 2009 when highest rates of positivity in the community were observed in the 5-14 year-olds. The age group of 15-44 year-olds is also clearly the major group contributing to hospital admissions and deaths. The increase in requirement for

critical care in the current season reflects the impact of influenza A(H1N1)2009 illness in the remaining susceptible young adults (15-44 years) and risk groups in the population.

Most of those with severe illness, and those dying, have not previously been vaccinated against influenza and have not had the benefit of the early use of antiviral drugs. Countries in Europe yet to experience substantial influenza activity this winter may wish to take all reasonable measures to increase the uptake of seasonal influenza vaccine in those at high risk of the complications of influenza and to ensure that antiviral drugs are readily available for those who are either severely ill or at increased risk of severe illness from influenza.

Further analysis of the antigenic and genetic properties of all influenza viruses from hospitalised patients, outbreaks and community cases is ongoing.

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Continued emergence and changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus, United Kingdom, winter 2010/11

A Lackenby (angie.lackenby@hpa.org.uk)[1], J Moran Gilad[1], R Pebody[2], S Miah[1], L Calatayud[2], S Bolotin[2], I Vipond[3], P Muir[3], M Guiver[4], J McMenamin[5], A Reynolds[5], C Moore[6], R Gunson[7], CI Thompson[2], M Galiano[2], A Bermingham[2], J Ellis[2], M Zambon[2]

1. Health Protection Agency, Microbiology Services Colindale, London, United Kingdom
2. Health Protection Agency, Health Protection Services Colindale, London, United Kingdom
3. Health Protection Agency, Microbiology Services Bristol, United Kingdom
4. Health Protection Agency, Microbiology Services Manchester, United Kingdom
5. Health Protection Scotland, Glasgow, United Kingdom
6. Public Health Wales Microbiology Cardiff, University Hospital of Wales, Cardiff, United Kingdom
7. West of Scotland Specialist Virology Centre, Glasgow, United Kingdom

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During the winter period 2010/11 27 epidemiologically unlinked, confirmed cases of oseltamivir-resistant influenza A(H1N1)2009 virus infection have been detected in multiple, geographically dispersed settings. Three of these cases were in community settings, with no known exposure to oseltamivir. This suggests possible onward transmission of resistant strains and could be an indication of a possibility of changing epidemiology of oseltamivir-resistant influenza A(H1N1)2009 virus.

To date, during the winter period 2010/11, 27 confirmed cases of oseltamivir-resistant influenza A(H1N1)2009 virus infection have been detected. Three of these cases with resistant strains were in community settings. While the number of cases infected with a resistant strain who have been detected in the community is small, it is likely to have epidemiological significance given that no such cases were detected in 2009/10.

The 2010/11 winter season in the northern hemisphere has been characterised by co-circulation of different influenza strains, primarily influenza A(H1N1)2009, influenza B and, sporadically, influenza A(H3N2) [1]. Residual population susceptibility to influenza A(H1N1)2009 virus has led to severe and fatal illness among children and young adults, with many of the fatal cases having underlying risk factors associated with severe disease outcomes such as debilitating neurological conditions and chronic respiratory diseases. This emphasises the need for early antiviral therapy, which has proved successful in reducing viral shedding and severity of illness [2]. Neuraminidase inhibitors (NI) (oseltamivir and zanamivir), the most common antiviral drugs used for treatment and prophylaxis of patients with all influenza subtypes, were widely used in the first and second wave of the pandemic in the United Kingdom (UK) during 2009, and were available through the National Pandemic Flu Service (NPFS) telephone helpline [3] to all sections of the population, irrespective of whether the patient belonged to a risk group. In the winter of 2010/11 the use of NI has been restricted to those in recognised clinical risk groups, consistent with National Institute for Health and Clinical Excellence (NICE) guidance [4].

Resistance to NI is determined by mutations in the viral neuraminidase (NA) [5]. During the first 10 years post licensure, oseltamivir resistance, when it was observed and investigated, was associated with a loss of viral fitness and reduction in transmissibility [6]. Mutations giving rise to NI resistance are both influenza subtype-specific and drug-specific, with a histidine to tyrosine mutation at position 275 (H275Y) of the viral NA being the most common in influenza A(H1N1) viruses [5]. Unexpectedly, during the winter season 2007/08, the emergence of a transmissible, drug-resistant influenza A(H1N1) strain rendered the use of oseltamivir ineffective against this subtype [7,8]. This strain, with H275Y in the viral NA likely arose as a result of additional compensatory mutations elsewhere in the viral NA gene or elsewhere in the viral genome.

During the 2009 influenza A(H1N1) pandemic, oseltamivir was used extensively globally for both treatment and prophylaxis. A total of 319 cases infected with oseltamivir-resistant influenza viruses have been recognised globally, from more than 20,000 influenza-positive samples tested [9].

Resistance to oseltamivir was mainly detected in severely immunosuppressed individuals or hospitalised patients sampled post-treatment, although several clusters involving limited person-to-person

transmission were recognised. While this indicated a low prevalence of oseltamivir resistance, the continual evolution of influenza viruses emphasises the necessity for close surveillance of antiviral resistance. Here we report on our findings during winter 2010/11.

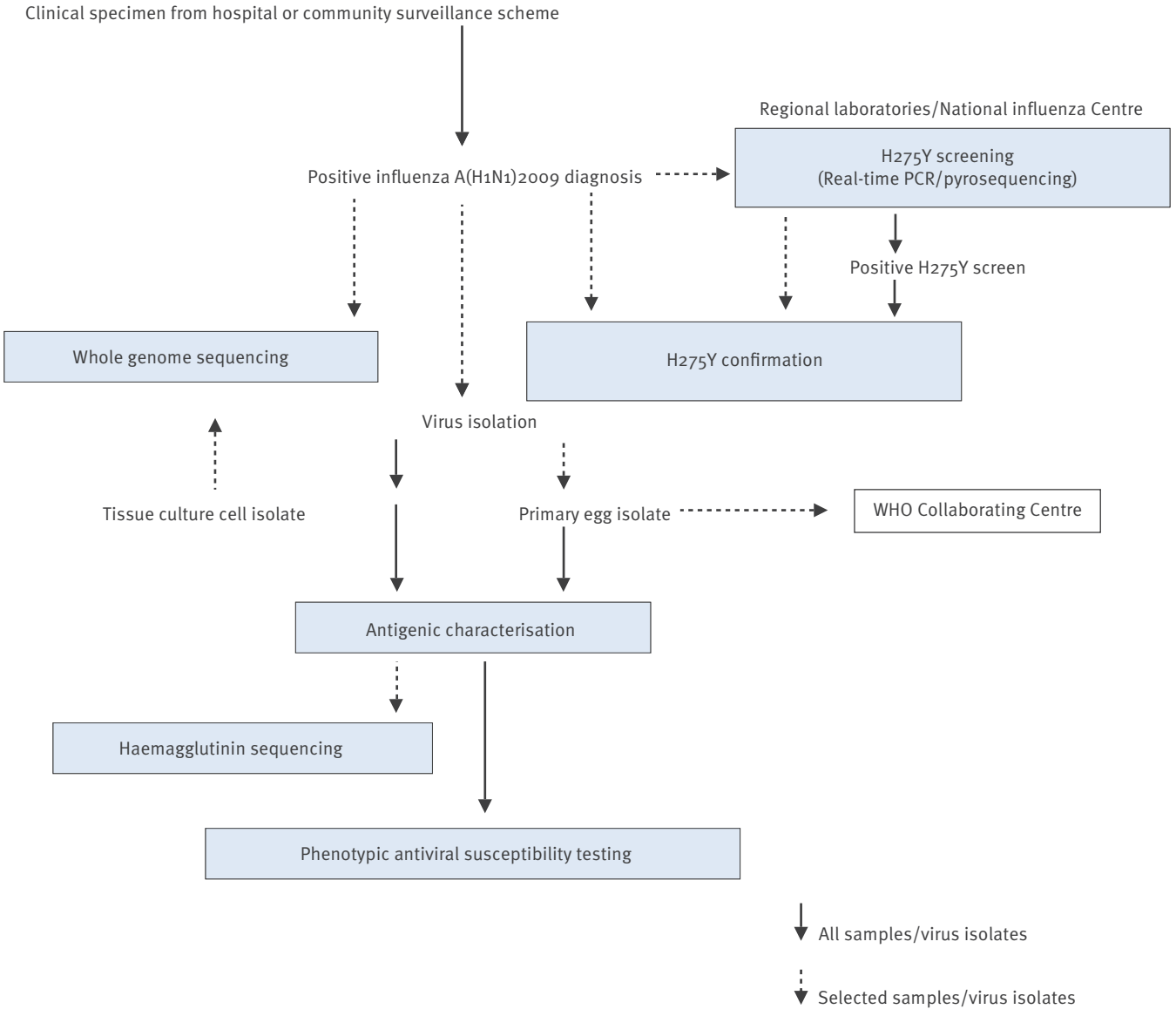
Methods

Monitoring of antiviral drug susceptibility in the UK circulating influenza strains, among hospitalised and primary care patients, is performed as part of influenza virological strain surveillance and is integrated with antigenic and genetic analyses at the National Influenza Centre (NIC) at the Health Protection Agency (HPA), Colindale (Figure 1) [1]. Rapid genotypic screening of influenza A(H1N1)2009 strains for the H275Y single-nucleotide polymorphism (SNP) by regional laboratories, beginning in England and Wales in October 2010 (and in Scotland in 2009), allows rapid detection of resistant strains closer to the point of care and supports a national enhanced surveillance programme for antiviral drug susceptibility. This screening is performed by SNP analysis on clinical specimens using a real-time polymerase chain reaction (PCR) method that differentiates between wild-type and resistant viruses. The HPA methodology is available on request, as the manuscript is in preparation. Resistance is confirmed by pyrosequencing at the NIC, where additional viral genotypic and phenotypic surveillance and characterisation is performed to identify additional alterations in drug susceptibility and any other associated mutations [10].

Clinically and epidemiologically relevant resistance (>50% of viral quasi-species in the original clinical material harbour the H275Y mutation) are reported weekly in HPA weekly influenza reports, to the

Figure 1

Influenza A(H1N1)2009 antiviral drug testing strategy in the United Kingdom



Source: Health Protection Agency, laboratories/National influenza Centre, United Kingdom.
PCR: polymerase chain reaction; WHO: World Health Organization.

European Centre for Disease Prevention and Control (ECDC) via the European Surveillance System (TESSy) and to the World Health Organization (WHO) headquarters and the WHO Regional Office for Europe. Clinical specimens with quasi-species harbouring <50% resistant virus are reported back to clinicians as resistant for patient management but not internationally, according to the agreed WHO strategy (Technical consultation meeting (8 September 2010) proceedings paper under preparation by the WHO).

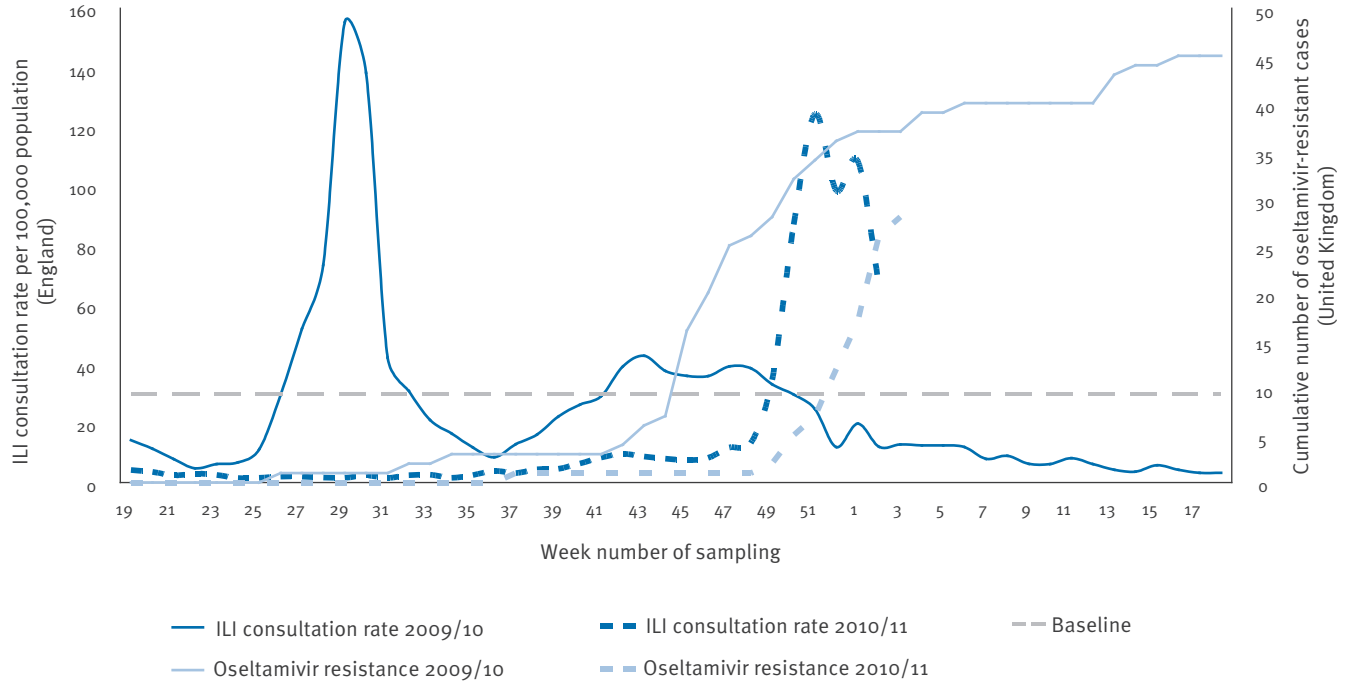
Written informed consent and explicit ethical approval was not sought as this was an observational study undertaken as part of routine pandemic surveillance. It was carried out under UK legislation NHS Act 2006 (section 251), which provides statutory support for disclosure of data by the NHS, and their processing by the Health Protection Agency (HPA) for communicable disease control. Health Protection Scotland remains a constituent part of the NHS and coordinates the investigation and management of all national outbreaks in Scotland. Additional clinical and laboratory data on influenza cases with resistant strains were collected via national databases and by contacting attending physicians where appropriate. Frequencies were compared using the chi-square or Fisher's exact test as appropriate.

Virological findings

To date, during the winter period 2010/11, 27 confirmed cases of oseltamivir-resistant influenza A(H1N1)2009 virus infection have been detected up to week 3 of 2011 (Figure 2). Similar rates of oseltamivir resistance (1%) due to the H275Y mutation were detected in 2010/11 as in 2009/10 (Table 1). During 2009/10, resistance was detected exclusively from hospital-based surveillance. However, three of 27 cases with resistant strains detected in 2010/11 were in community settings, with no known exposure to oseltamivir (p=0.05). While the number of cases infected with a resistant strain who have been detected in the community is small, it is likely to have epidemiological significance given that no such cases have been previously detected in 2009/10 despite a large sample size (1,098 cases analysed).

Figure 2

Influenza-like illness consultation rates in primary care and cumulative cases infected with oseltamivir-resistant influenza A(H1N1)2009, United Kingdom, week 19 of 2009 to week 3 of 2011 [12]*



ILI: influenza-like illness.

Table

Incidence rates of oseltamivir-resistant influenza A(H1N1)2009 virus infection, United Kingdom, 2009/10 (n=45) and 2010/11 (n=27)

Setting	May 2009-April 2010			May 2010-January 2011		
	Total tested	Number resistant	Percentage resistant	Total tested	Number resistant	Percentage resistant
Community	1,098	0	0.0	364	3	0.8
Hospital	4,489	45	1.0	2,500	24	1.0
Total	5,587	45	0.8	2,864	27	0.9

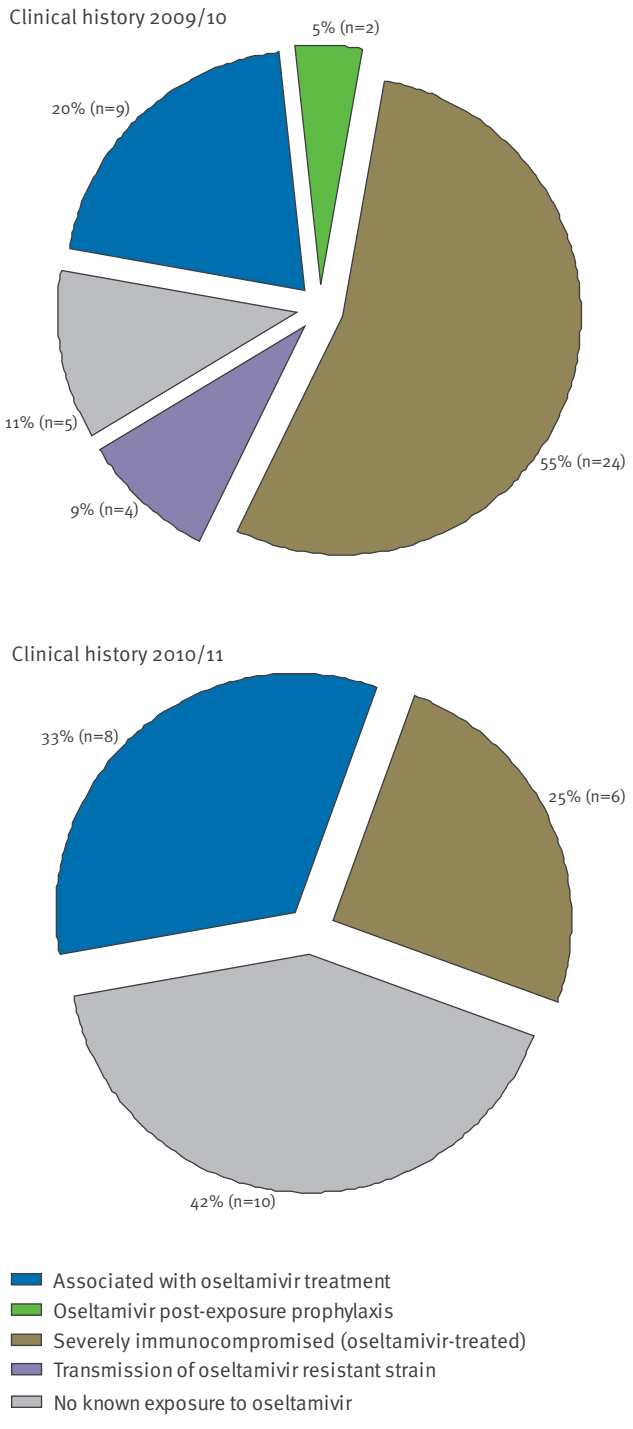
All oseltamivir-resistant viruses in 2010/11 were wild type (isoleucine) at position 223 in NA, a site at which mutations can increase the phenotypic impact of resistance due to the H275Y mutation.

Analysis of influenza A(H1N1)2009-positive material taken from both hospitalised and community cases during the first and second waves of the pandemic in the UK found that the earliest UK detection of oseltamivir resistance due to the H275Y mutation occurred in June 2009. A total of 45 resistant cases were detected between week 19 of 2009 and week 18 of 2010 (Figure 2), eight of whom were associated with a nosocomial outbreak among severely immunocompromised individuals [11].

During 2009/10 the majority of sporadic resistance (80%) was detected in individuals with a history of exposure to antiviral drugs or immunosuppression (Figure 3). Whole genome sequencing of 10 of 45 resistant strains and phenotypic analysis of 15 of 45 resistant strains did not reveal any other known drug-resistant variants.

Figure 3

Patient characteristics associated with oseltamivir-resistant influenza A(H1N1)2009 virus infection in the United Kingdom during 2009/10 (n=44) and 2010/11 (n=24)



Clinical and epidemiological findings

In 2010/11, the mean age of all cases (n=27) infected with oseltamivir-resistant influenza A(H1N1)2009 virus was 32 years (median: 37; range: nine months to 75 years); in 2009/10, the mean age of such cases (n=45) was 38 years (median: 43 years; range: four months to 95 years). In 2010/11, 10 of the 27 cases were male and the corresponding figure for 2009/10 was 33 of the 45 cases (p=0.01).

Clinical and epidemiological features were available for 24 of 27 cases infected with oseltamivir-resistant influenza A(H1N1)2009 virus in 2010/11 and 44 of 45 such cases in 2009/10 (Figure 3).

Most notably, 10 of 24 of cases with resistant strains in 2010/11 had no known exposure to oseltamivir or contact with known cases of resistance (including three otherwise healthy individuals sampled in the community as part of virological surveillance) as compared with five cases of 44 in 2009/10 (p=0.01). The cases with resistant strains were distributed throughout England, Scotland and Wales. The frequency of these cases in both 2009/10 and 2010/11 increased with a 1–2-week delay (using sample date) of the increase in influenza-like illness (ILI) consultation rates (Figure 2), possibly reflecting that testing volume sufficient to detect infrequent resistance has been attained. ILI is defined as the presence of four of the following ICHPPC criteria i) sudden onset ii) cough iii) rigors/chills iv) fever v) prostration and weakness vi) myalgia vii) no significant respiratory physical signs other than redness of nasal mucous membrane and throat viii) influenza in a close contact.

Seven patients (of 24) in 2010/11 were immunosuppressed (six were treated with oseltamivir and one had no known oseltamivir exposure), compared with 34 of 44 immunosuppressed patients in 2009/10 (p=0.001). Of the 2009/10 cases, 24 were treated, two were given post-exposure prophylaxis, four were infected with the resistant strain and four had no known exposure to oseltamivir in 2010/11. To date in 2010/11, there has been no documented onward transmission of resistant strains, whereas in 2009/10, transmission was documented for four of 44 cases with resistant strains (p=0.3).

Conclusions

In 2010/11, cases infected with oseltamivir-resistant influenza A(H1N1)2009 virus have emerged sporadically in the community, some of whom have had no known exposure to oseltamivir, in addition to such cases occurring in hospitalised patients. Although clustering has not been formally ascertained, it is considered unlikely, which therefore suggests the likelihood of low-level onward transmission of resistant strains. In 2007/8 oseltamivir-resistant seasonal influenza A(H1N1) harbouring the H275Y mutation emerged, unrelated to antiviral drug use, and spread at varying rates globally, quickly becoming dominant over the sensitive strain in most countries by the end of 2008 [13]. The emergence of oseltamivir-resistant influenza A(H1N1)2009 virus is of concern and, despite the current low levels, requires vigilance.

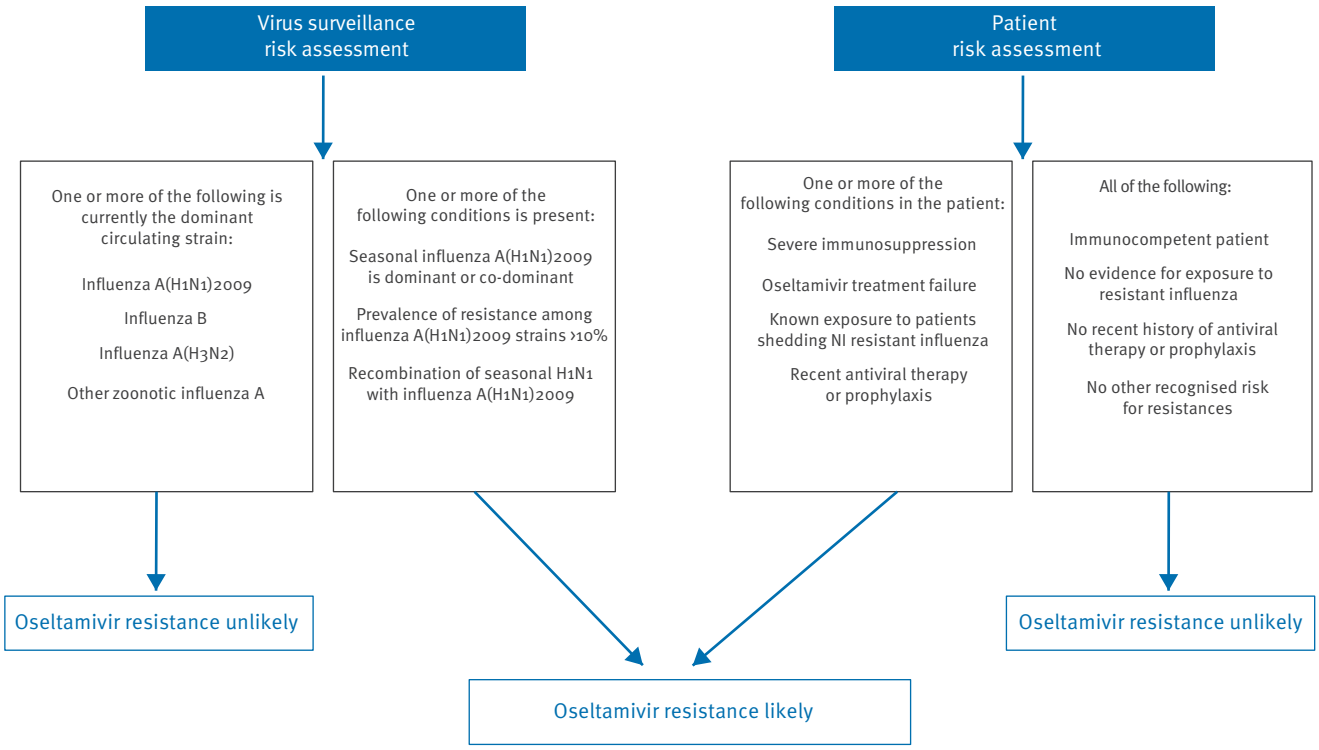
The frequency of immunosuppression as an underlying risk factor is lower among cases with resistant strains in 2010/11, which may be explained in part by the high index of suspicion for the emergence of resistance due to the H275Y mutation, resulting in increased and timely use of zanamivir in this patient population, as advocated by national UK guidance. The HPA revised guidance for managing influenza in the era of emerging oseltamivir resistance emphasises the necessity of active surveillance for antiviral drug resistance, particularly among high-risk groups such as those who are immunosuppressed [14,15].

In the light of the varying rates of oseltamivir resistance among different influenza subtypes and across geographical locales, the choice of antiviral agent is often difficult. Clinical decisions should therefore be based on the perceived risk for resistance both at the individual level and global (population) level, using current local virological and epidemiological data wherever possible. A proposed model for such risk assessment is outlined in Figure 4. Ongoing incidence of oseltamivir resistance in the community in patients without evident risk factors will influence antiviral prescribing recommendations if the overall frequency of resistance rises above 10%. Decisions about antiviral therapy for patient management will increasingly require risk assessment and national and international antiviral policies.

Observational data produced through surveillance provide the crude rates of oseltamivir resistance among currently circulating influenza subtypes. Assessing risk factors for antiviral resistance and propensity for onward transmission are also important and assist in recognition of new resistance mechanisms. Current *in vitro* and *in vivo* studies of the fitness of resistant influenza A(H1N1)2009 strains are conflicting. In human airway cultures the resistant variant was shown to have a fitness deficit in comparison to its wild-type counterpart [16] and Duan *et al*. found that the drug resistant virus only transmitted via the contact route, not the respiratory droplet route and was outgrown by its wild-type counterpart in co-infected animals [17]. In contrast however, Hamelin *et al*. found that oseltamivir-resistant

Figure 4

A decision-support tool for guiding the choice of antivirals through risk assessment[a]



[a] For patients requiring prophylaxis or antiviral therapy for suspected or proven influenza A(H1N1)2009

A(H1N1) virus was equally virulent as its wild-type counterpart in mice and ferrets and did transmit [18].

Our surveillance findings imply the need for urgent studies to evaluate possible underlying compensatory mutations among resistant strains.

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* Erratum: The title of Figure 2 was corrected after publication of the article, on 4 February 2011.

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Effectiveness of seasonal 2010/11 and pandemic influenza A(H1N1)2009 vaccines in preventing influenza infection in the United Kingdom: mid-season analysis 2010/11

R Pebody (richard.pebody@HPA.org.uk)[1], P Hardelid[1], D M Fleming[2], J McMenamin[3], N Andrews[1], C Robertson[3,4], D R Thomas[5], P SebastianPillai[6], J Ellis[6], W Carman[7], T Wreghitt [8], M Zambon[6], J M Watson[1]

1. Health Protection Agency Health Protection Services – Colindale, London, United Kingdom
2. Royal College of General Practitioners Research and Surveillance Centre, Birmingham, United Kingdom
3. Health Protection Scotland, Glasgow, United Kingdom
4. University of Strathclyde, Glasgow, United Kingdom
5. Public Health Wales, Cardiff, United Kingdom
6. Health Protection Agency Microbiology Services – Colindale, London, United Kingdom
7. West of Scotland Specialist Virology Centre, Glasgow, United Kingdom
8. Health Protection Agency Microbiology Services, Cambridge, United Kingdom

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This study provides mid-season estimates of the effectiveness of 2010/11 trivalent influenza vaccine and previous vaccination with monovalent influenza A(H1N1)2009 vaccine in preventing confirmed influenza A(H1N1)2009 infection in the United Kingdom in the 2010/11 season. The adjusted vaccine effectiveness was 34% (95% CI: -10 - 60%) if vaccinated only with monovalent vaccine in the 2009/10 season; 46% (95% CI: 7 - 69%) if vaccinated only with trivalent influenza vaccine in the 2010/11 season and 63% (95% CI: 37 - 78%) if vaccinated in both seasons.

Introduction

Following the emergence of pandemic influenza A(H1N1)2009 virus and the development of several monovalent pandemic influenza A(H1N1)2009 vaccines, a number of observational studies have since demonstrated the clinical effectiveness of these vaccines in various settings during the 2009/10 influenza A(H1N1)2009 pandemic [1-3]. Uncertainty exists, however, about their duration of protection.

Vaccination with the 2010/11 northern hemisphere seasonal trivalent influenza vaccine, which includes the influenza A(H1N1)2009 strain, was started in autumn 2010. The United Kingdom (UK) target populations for vaccination were individuals aged six months to under 65 years in clinical risk groups at elevated risk of severe disease (including pregnant women) and individuals aged 65 years and over [4]. Approximately 35% of those under 65 years of age in a clinical risk group had already received monovalent pandemic influenza vaccine in 2009/10 [4].

In the period December 2010-January 2011, the UK experienced widespread influenza A(H1N1)2009 transmission. Using the established swab-negative case-control approach in primary care [5,6], this study sets out to provide in-season interim estimates of the effectiveness of the 2010/11 seasonal influenza vaccine in preventing confirmed influenza infection in the UK in 2010/11 and the potential effect of previous vaccination with monovalent A(H1N1)2009 vaccine.

Methods

Study population and period

This study uses data from four influenza sentinel surveillance schemes in England, Scotland and Wales. Details of the Royal College of General Practitioners (RCGP), Health Protection Agency (HPA) Regional Microbiology Network (RMN) and Health Protection Scotland (HPS) swabbing schemes have been described previously [3]. Public Health Wales operates a sentinel general practitioner (GP) swabbing scheme with 44 practices covering a population of 355,705, 12 per cent of the population in Wales.

This study covers samples collected in the period from 1 September 2010 to 11 January 2011. Cases were individuals presenting with an acute influenza-like illness (ILI) in a participating practice in the study period who were swabbed and tested positive for influenza regardless of type or subtype. ILI was defined as an acute respiratory illness with fever or complaint of feverishness. Controls were individuals presenting with ILI in the same period that were swabbed and tested negative for influenza. A standard specimen request form provided demographic and clinical information on cases and controls including date of birth, sex, risk

group, date of onset of illness, date of specimen collection, influenza vaccination status for the current and previous season and vaccination dates.

Laboratory methods

Samples in England were sent to the HPA Microbiology Services (RCGP scheme) or one of the local HPA Regional laboratories (RMN scheme). Samples in Wales were sent to the Public Health Wales Specialist Virology Centre and in Scotland to the West of Scotland Specialist Virology Centre (HPS scheme) for molecular testing. Laboratory confirmation was undertaken using reverse transcription polymerase chain reaction (RT-PCR) assays for circulating influenza A viruses, influenza B viruses and other respiratory viruses [7,8].

Statistical methods

In order to assess vaccine effectiveness (VE) against influenza A(H1N1)2009 infection, a four-level variable was defined with the following four categories:

1. Unvaccinated in both years (not in receipt of either pandemic influenza A(H1N1)2009 vaccine in 2009/10 or trivalent vaccine in 2010/11);
2. Receipt of pandemic influenza A(H1N1)2009 vaccine in 2009/10 but not in receipt of 2010/11 trivalent vaccine;
3. Receipt of either pandemic influenza A(H1N1)2009 vaccine in 2010/11 (provided to certain risk groups) or trivalent vaccine in 2010/11 or both, but not vaccinated in 2009/10;
4. Receipt of pandemic influenza A(H1N1)2009 vaccine in 2009/10 and trivalent vaccine in 2010/11, or received first dose of pandemic influenza A(H1N1)2009 vaccine in 2009/10 and second dose in 2010/11.

Persons who had received two doses of pandemic influenza A(H1N1)2009 vaccine in 2009/10 were not analysed separately from those who received only one dose as the numbers were low.

Individuals were considered vaccinated if their date of seasonal or pandemic influenza A(H1N1)2009 vaccination was 14 days or more before the date of onset of illness. Persons for whom the interval between vaccination and onset of illness was less than 14 days were excluded, as their immunity status was considered unknown. If a person's trivalent vaccination status was known but not their pandemic influenza A(H1N1)2009 vaccination status or vice versa, they were excluded from the estimation of VE for influenza A(H1N1)2009 vaccine. For the estimation of VE for influenza A(H3) or B, pandemic vaccination status was not considered of interest. If the date of trivalent vaccination was missing, it was assumed that the person was vaccinated more than 14 days before the onset date, and for pandemic influenza A(H1N1)2009 vaccine it was assumed the person was vaccinated in 2009/10.

The same approach was used if date of onset was missing in a vaccinated individual. Respiratory samples with a delay greater than 29 days between onset of illness and sample collection were excluded as the sensitivity of the PCR test reduces for long intervals between onset and sampling. A sensitivity analysis was undertaken censoring at seven days between onset of illness and sample collection.

Vaccine effectiveness was estimated as 1-[odds ratio] using multivariable logistic regression models with influenza A(H1N1)2009 or influenza B PCR results as outcomes and seasonal or pandemic vaccination status

Table 1

Inclusion and exclusion criteria of participants for specimens submitted, United Kingdom, 1 September 2010 –11 January 2011

Criteria	Excluded	Included
1. Original participants		4,554
- Excluded as no PCR results available	538	
- Remaining participants		4,016
2. Influenza A(H1N1)2009 endpoint		
- Excluded as confirmed influenza B or A(H3)	535	
-Excluded as no result for influenza A(H1N1) 2009	1	
- Excluded as missing vaccination history	553[a]	
Interval between onset of illness and sample longer than 29 days	36	
- Final remaining study participants		*2,891*
3. Influenza A(H3)/B endpoint		
- Excluded as confirmed A(H1N1)2009	1,251	
-Excluded as not tested/no result for influenza B	8	
- Excluded as missing vaccination history	236	
Interval between onset of illness and sample longer than 29 days	34	
- Final remaining study participants		*2,487*

[a] Including eight people with sample taken later than 29 days after onset of illness.
PCR: Polymerase chain reaction.

as the linear predictor. Age (coded into five standard age groups, <5 years, 5-14 years, 15-44 years, 45-64 years and ≥65 years), surveillance scheme (HPS, RCGP or RMN) and date of sample collection (month) were investigated as potential confounding variables.

All statistical analyses were carried out in R version 2.10.1.

Results

This report has information on 4,554 individuals from whom samples were collected during the study period. Of these, 3,204 samples were collected through the RCGP surveillance scheme, 469 through the RMN scheme, 743 through the HPS scheme and 138 through the Public Health Wales scheme.

Table 2

Details for pandemic influenza A(H1N1)2009 cases and controls, United Kingdom, September 2010 – January 2011 (n=3,480)[a]

	Number of controls (%) (n=2,229)	Number of cases (%) (n=1,251)
Age group (years)		
<5	224 (10.0)	93 (7.4)
5-14	217 (9.7)	130 (10.3)
15-44	1,030 (46.2)	734 (58.7)
45-64	526 (23.6)	272 (21.7)
≥65	215 (9.6)	16 (1.3)
Missing	17 (0.8)	6 (0.5)
Sex		
Male	843 (37.8)	514 (41.1)
Female	1,324 (59.4)	668 (53.4)
Missing	62 (2.8)	69 (5.5)
Month of sample collection		
September 2010	67 (3.0)	0 (0)
October 2010	436 (19.6)	24 (1.9)
November 2010	629 (28.2)	51 (4.1)
December 2010	934 (41.9)	1,096 (87.6)
January 2011	163 (7.3)	80 (6.4)
Missing	0 (0)	0 (0)
Interval from onset of illness to sampling (days)		
0-1	245 (11.0)	193 (15.4)
2-4	847 (38.0)	598 (47.8)
5-7	462 (20.7)	197 (15.7)
8-14	283 (12.7)	97 (7.8)
15-29	85 (3.8)	18 (1.4)
>29	36 (1.6)	8 (0.6)
Missing	271 (12.2)	140 (11.2)
Vaccination status		
Unvaccinated	1,567 (70.3)	1,022 (81.7)
Vaccinated 2009/10 season only	105 (6.7)	26 (2.1)
Vaccinated 2010/11 season only	78 (3.5)	22 (1.8)
Vaccinated in both seasons	86 (3.9)	21 (1.7)
Vaccination status missing (either 2009/10 season, 2010/11 season or both)	393 (17.6)	160 (12.8)
Surveillance scheme		
RCGP	1,529 (68.6)	775 (34.8)
RMN	239 (10.7)	171 (7.7)
HPS	410 (18.4)	250 (11.2)
Wales	51 (2.3)	55 (2.5)
Missing	0 (0)	0 (0)

HPS: Health Protection Scotland; RCGP: Royal College of General Practitioners' surveillance scheme; RMN: Health Protection Agency Regional Microbiology Network.

[a] Includes those with missing vaccination history and/or interval from onset of illness to sample longer than 29 days.

Those excluded from the study because of missing information (including PCR results and available vaccination history) are summarised in Table 1. Date of onset of illness was missing for 521 persons (11.4%): these were still included in the analyses. In the analyses evaluating VE in preventing influenza A(H1N1)2009 infection, samples positive for influenza A(H3) or influenza B were excluded and vice versa. There were therefore 2,891 persons for whom data on both vaccination status (for both vaccines) and pandemic influenza A(H1N1)2009 infection was available. Similarly, there were 2,487 persons included in the estimation of trivalent vaccine for prevention of influenza B or A(H3).

Table 2 shows the distribution and completeness of the baseline characteristics of the study participants according to whether they were influenza A (H1N1)2009 cases or controls. Age group, surveillance scheme and time period were found to be significantly associated with a confirmed influenza A(H1N1)2009 infection (Table 2).

Vaccine effectiveness in prevention of influenza A(H1N1)2009 infection

Table 3 shows the number and proportion of samples positive for influenza A(H1N1)2009 virus according to vaccination status (three categories). Crude vaccine effectiveness is also shown.

Age group, time period and surveillance scheme were adjusted for in a multivariable logistic regression model. These were all significantly associated with having a positive swab result. Risk group was missing for 1,316 of 4,554 samples (29%), and this variable was therefore not included in the model. The total number of observations included was 2,872.

The adjusted VE estimates (Table 3) increased from 34% (95% CI: -10 - 60%) for vaccination only in 2009/10 to 46% (95% CI: 7 - 69%) for vaccination only in 2010/11 to 63% (95% CI: 37 - 78%) if vaccinated in both seasons. Persons who had received vaccination in both 2009/10 and 2010/11 seasons did not have a significantly higher VE compared to persons who received vaccine only 2009/10 (Wald test p=0.06). Persons vaccinated only in 2010/11 also did not have a significantly different VE compared to those vaccinated only in 2009/10 (Wald test p=0.45). The VE for 2010/11 trivalent vaccination, irrespective of previous pandemic vaccination status, was 51% (95% CI: 29 - 66%). Censoring samples taken more than seven days after symptom onset did not significantly change the VE estimates: the adjusted VE for those vaccinated last season was 44% (95% CI: 0 - 68%), for those vaccinated only this season was 63% (95% CI: 32 - 79%) and for those vaccinated both seasons was 64% (95% CI: 36 - 80%).

The adjustment for month had a large effect on the VE point estimate for the group vaccinated in 2009/10; it decreased from 62% (crude) to 34% after adjustment. This is because the number of people vaccinated in 2009/10 only decreases across months (whilst influenza A(H1N1)2009 incidence is increasing), whereas the number of people vaccinated in 2010/11 is increasing over time.

There was no evidence of significant effect modification of vaccine by age group (using the same five age groups, likelihood ratio test p=0.21), although some of the vaccine-age sub-groups did not have any PCR positive results among them.

Vaccine effectiveness in prevention of H3 or influenza B infection

Twenty-one of 216 persons vaccinated with trivalent influenza vaccine (9.7%) were positive for influenza B or A(H3) compared to 478 of 2,271 persons unvaccinated with trivalent influenza vaccine (21%). This gives a crude VE of 60% (95% CI: 36 - 75%). If adjusted for age group, surveillance scheme and time period (month), adjusted VE was reduced to 50% (95% CI: 17 - 70%). There was no evidence of significant age–vaccine interaction (likelihood ratio test p=0.37).

Discussion

The swab-negative case -control study design is an established approach to estimate influenza vaccine effectiveness. A number of studies have recently been published on the methodology [9,10]. The potential limitations of the approach presented in this paper have been outlined previously and relate to convenience sampling; the potential for selection bias; missing data items and lack of information on risk status. The likely impact of each of these on VE estimates has been addressed earlier [3].

Table 3

Number and proportion of samples positive for influenza A(H1N1)2009 according to vaccination status, United Kingdom, September 2010 – January 2011

Vaccination status	Influenza A(H1N1)2009 positive/n (%)[a]	Crude vaccine effectiveness	Adjusted vaccine effectiveness
Unvaccinated	1,014/2,554 (39.7%)	-	-
Vaccinated season 2009/10 only	26/130 (20.0%)	62% (95% CI: 41 - 75%)	34% (95% CI: -10 - 60%)
Vaccinated 2010/11 season only	22/100 (22.0%)	57% (95% CI: 31 - 73%)	46% (95% CI: 7 - 69%)
Vaccinated in both seasons	21/107 (19.6%)	63% (95% CI: 40 - 77%)	63% (95% CI: 37 - 78%)

[a] Chi-square test p<0.001 on three degrees of freedom.

This study demonstrates three key findings: vaccination with this current season's trivalent influenza vaccine provides protection against both confirmed influenza A(H1N1)2009 and influenza B infection and immunisation with A(H1N1)2009 vaccine in 2009/10 followed by trivalent influenza vaccine this season provides better protection against confirmed influenza A(H1N1)2009 infection. Finally vaccination only last season with A(H1N1)2009 vaccine, seems to provide the least protection against confirmed influenza A(H1N1)2009 infection.

This study provides some of the first evidence that this season's trivalent influenza vaccine is effective in reducing confirmed influenza A(H1N1)2009 and B infection in persons consulting in primary care. This level of protection is consistent with several studies undertaken with trivalent influenza vaccines in the pre-pandemic era and is congruent with moderately good matching between the vaccine and the circulating influenza strain [5,6]. We found no evidence that protection was significantly different by age group; however it is likely that the study size was not sufficiently large to address this point specifically.

Although recently published work has demonstrated in several geographical settings, that the pandemic influenza A(H1N1)2009 vaccine was highly effective last season in preventing confirmed influenza A(H1N1)2009 infection that season [2,3], this study indicates that pandemic vaccine protection may not last across seasons. This corroborates recent findings from a longitudinal sero-epidemiological survey, which suggests that population A(H1N1)2009 antibody levels may start to reduce in the post-pandemic period, particularly in the 5-14-years old age-band [11]. Further work needs to be undertaken in this area. Our paper does suggest that within the data available at present there is a dose-response relationship and, that vaccination with this season's trivalent influenza vaccine of individuals who have already received monovalent A(H1N1)2009 vaccine last season produced the highest effectiveness compared to vaccination only in the 2010/11 season or vaccination with A(H1N1)2009 vaccine alone in the 2009/10 season. This reinforces the importance of the UK policy for vaccination of those who had received the monovalent vaccine in the previous season.

In conclusion, this study undertaken mid-season provides evidence that this season's trivalent influenza vaccine does provide protection against infection to both strains of influenza circulating this season (A(H1N1)2009 and influenza B) in Europe. It is important to note that more precision in this estimate will be available at the end of the season. The findings seem to provide some of the first published evidence that protection might wane following vaccination with influenza A(H1N1)2009 vaccine after 12 months and reinforces the recommendation that annual re-immunisation of target groups is required regardless of vaccination the previous season (including those vaccinated with an adjuvanted vaccine).

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Conflicts of interest
All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare that DM Fleming has received funding to attend influenza related meetings and has received consultancy fees from influenza vaccine manufacturers who might have an interest in the submitted work in the previous 3 years. In addition, The Virus Reference Department of the Health Protection Agency receives funding from a variety of vaccine manufacturers who might have an interest in the submitted work. All other authors declare they have no conflicts of interest.

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Effectiveness of the 2010/11 seasonal trivalent influenza vaccine in Spain: preliminary results of a case–control study

C Savulescu (csavulescu@isciii.es)[1,2], S Jiménez-Jorge[1,3], S de Mateo[1,3], J Ledesma[4], F Pozo[4], I Casas[4], A Larrauri[1,3], cycEVA Study Team[5]

1. National Centre of Epidemiology, Institute of Health Carlos III, Madrid, Spain
2. EpiConcept, Paris, France
3. Ciber Epidemiología y Salud Pública (CIBERESP), Ministry of Science and Innovation, Institute of Health Carlos III, Spain
4. National Influenza Centre-Madrid, National Centre for Microbiology, Institute of Health Carlos III, Madrid, Spain
5. Members of the team are listed at the end of the article

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We present preliminary results of a case–control study to estimate influenza vaccine effectiveness in Spain, from week 50 of 2010 to week 6 of 2011. The adjusted effectiveness of the vaccine in preventing laboratory-confirmed influenza due to any type of influenza virus was 50% (95% CI: –6 to 77%) for the trivalent seasonal vaccine and 72% (95% CI: 7 to 92%) for both trivalent seasonal and monovalent pandemic vaccines, suggesting a protective effect of seasonal vaccination lower than that reported for the previous season.

Background

After the 2009 influenza A(H1N1) pandemic, the World Health Organization (WHO) in February 2010 recommended the trivalent influenza vaccine for the northern hemisphere for the 2010/11 influenza season. The vaccine included the pandemic strain A/California/07/2009 (H1 subtype), the A/Perth/16/2009 (H3 subtype) and the B/Brisbane 60/2008 viruses. The influenza A(H1) strain is the same as that used in the monovalent 2009/10 pandemic vaccine, which showed good effectiveness in preventing influenza A(H1N1)2009 infection in the 2009/10 season [1,2].

In Spain, influenza vaccination is offered free of charge each year to people in high-risk groups. In the 2010/11 season, it was recommended to persons over six months old with chronic conditions, elderly people aged over 60 years (65 years in some regions), healthcare workers and caregivers. The vaccination campaign lasted between September and November 2010 and several vaccine brands were used [3]. The monovalent pandemic vaccine was only offered in the 2009/10 season: the vaccine brands were mainly adjuvanted, except those used for pregnant women, for whom a non-adjuvanted vaccine was recommended. The pandemic vaccine was also not recommended for elderly people aged over 64 years without underlying diseases.

Since the 2008/09 influenza season, Spain has been participating in the Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network, established by the European Centre for Disease Prevention and Control (ECDC) [4]. Various study designs were tested: the test-negative case–control design proved suitable for such studies in Spain [5,6]. One of the objectives of this network is to provide early intraseasonal estimates of influenza vaccine effectiveness. The importance of having such estimates early in the season was highlighted during 2009/10, when intraseasonal estimates were needed in order to evaluate the impact of vaccination with the monovalent pandemic influenza vaccine [7].

The study presented here aims at providing an intraseasonal estimate of the seasonal trivalent vaccine 2010/11 effectiveness in preventing laboratory-confirmed influenza in Spain, in order to guide public health policies.

Methods

We conducted an observational case–control study (cycEVA) using the test-negative design described previously for the study of influenza vaccine effectiveness in elderly people [5]. Our study was carried out between week 50 of 2010 (12–18 December 2010) – when the influenza-like illness (ILI) threshold was first passed in the participating regions – and week 6 of 2011 (6–12 February 2011). Of the 17 regions of the Spanish Influenza Sentinel Surveillance System, eight participated in the study. In these eight regions, 246 of 325 (76%) sentinel general practitioners (GPs) and paediatricians agreed to take part in the study, covering a population of 313,734 inhabitants, representing 2.1% of the total population in these regions [8]. Of the 246 GPs and paediatricians, 159 (65%) recruited at least one patient in the study.

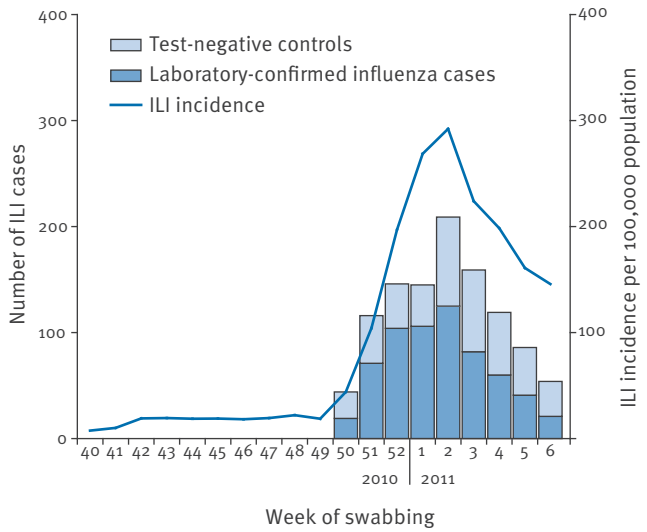
Each week, participating GPs and paediatricians systematically swabbed the first two patients presenting with ILI according to the European Union case definition [8]. A case of confirmed influenza was defined as an ILI patient with laboratory confirmation of influenza virus infection. Three outcomes were used in the study: infection with any type of influenza virus, influenza A(H1N1)2009 virus and influenza A(H3) or influenza B viruses. The controls were ILI patients whose laboratory results were negative for any influenza strain.

Data collection

Using a standardised questionnaire, participating GPs and paediatricians collected the following data for the recruited patients: age, sex, clinical symptoms, date of symptom onset, date of swabbing, vaccination status for 2010/11 seasonal influenza vaccine, influenza vaccination status for the previous season (seasonal and pandemic vaccines), laboratory result, chronic conditions, pregnancy, morbid obesity (defined as body mass index greater than 40), smoker status (current versus previous or non-smoker), functional status, any hospitalisation for chronic conditions in the previous year and the number of outpatient visits for any reason in the previous year. The patients were defined as having a chronic condition if they had any of the following: diabetes mellitus, cardiovascular disease, chronic pulmonary disease, renal disease, hepatic disease, congenital or acquired immunodeficiency, and chronic treatment with acetylsalicylic acid (in children). Poor functional status was defined as needing help for walking or bathing. Individuals were considered vaccinated if they had received the seasonal influenza vaccine 14 days or more before the date of symptom onset. Vaccinated individuals whose date of vaccination was missing (n=7) were considered vaccinated if the date of onset was two weeks after the end of the vaccination campaign.

Figure 1

Laboratory-confirmed influenza cases (n=629) and test-negative controls (n=449) among ILI patients by week of swabbing, cycEVA study, week 50 (2010)–week 6 (2011) and weekly ILI incidence, week 40 (2010)–week 6 (2011), Spain



ILI: influenza-like illness.

Source: cycEVA study and Spanish Influenza Surveillance System, National Centre of Epidemiology, Institute of Health Carlos III, Spain.

Data analysis

We restricted all analyses to patients with an interval between symptom onset and swabbing of less than eight days. Logistic regression was used to calculate the crude and adjusted odds ratios (ORs) and their corresponding 95% CIs. Vaccine effectiveness was calculated as (1–OR) multiplied by 100. All variables collected in the study were checked for possible confounding: we included in the regression model those that changed the crude OR by >10%. Thus, the final model included age group (0–4, 5–14, 15–44, 45–64 and ≥65 years), week of swabbing and previous vaccination status (seasonal or pandemic vaccine, according to the analysis performed).

We first carried out the analysis with all eligible patients, as some previously healthy people might have been vaccinated in an occupational setting or in private clinics. Then we restricted the analysis to those eligible for vaccination (people in high-risk groups) [3]). To check the effect of being vaccinated with both vaccines when using influenza A(H1N1)2009 virus infection as the outcome, we also carried out the analysis using a categorical variable for vaccination (unvaccinated, vaccinated with only seasonal trivalent vaccine 2010/11, only monovalent 2009/10 pandemic vaccine and both vaccines) [10]. We conducted all statistical analyses using STATA/IC 11.

The surveillance-affiliated laboratories or the National Centre of Microbiology (WHO National Influenza Centre-Madrid) confirmed influenza infection using real-time polymerase chain reaction (PCR). A number of laboratory-confirmed cases were genetically studied by sequencing the viral haemagglutinin gene. Phylogenetic analysis was carried out in order to characterise the specific strains of influenza A and B viruses.

The cycEVA study was included as part of influenza surveillance activities in Spain: therefore no ethical approval was needed for the study. No personal data were collected and patients gave verbal informed consent to be swabbed.

Results

From the beginning of the 2010/11 season in Spain, influenza A(H1N1)2009 virus has been predominant, with an increasing contribution of influenza B virus after the week 2 of 2011 when the peak of influenza activity was registered [11]. A similar viral circulation pattern and influenza activity evolution has been observed in the eight cycEVA regions. The incidence of ILI peaked in week 2 of 2011 (294 ILI cases per 100,000 population in the participating regions) (Figure 1). The

highest incidence was recorded in children under 15 years, with a maximum weekly incidence of 543 and 533 ILI cases per 100,000 population in the age group 5–14 years and 0–4 years, respectively. During the study period, the proportion of influenza virus-positive samples increased from 40.3% in week 50 of 2010 to 64.3% in the epidemic peak and then decreased to 48.4% in week 06 of 2011 [11].

A total of 1,078 patients were recruited. Of these, 1,061 (98%), comprising 618 cases and 443 controls, were included in the analysis where the outcome was laboratory confirmation of any type of influenza virus. For the analysis in which influenza A(H1N1)2009 infection was the outcome, we included 983 patients: 540 were laboratory-confirmed cases. When influenza A(H3) virus or influenza B virus infection was the outcome, 513 patients were included: six were laboratory-confirmed cases of influenza A(H3) infection and 64 were laboratory-confirmed cases of influenza B infection (Figure 2).

The number of patients recruited in the study peaked in week 2 of 2011 and decreased thereafter during the study period, following the weekly ILI incidence in the eight participating regions (Figure 1).

Laboratory-confirmed influenza cases and test-negative controls did not differ regarding the covariates collected, except for age group and eligibility for vaccination (Table 1). Among cases, 53.9% belonged to the age group 15–44 years compared with 47.6% of controls, and 3.6% of cases belonged to the age group ≥65 years compared with 8.6% of controls. A higher proportion of patients were eligible for vaccination among controls (11.5%) than among cases (7.9%).

Figure 2

Flowchart of data exclusion and analysis outcomes, cycEVA study, Spain, week 50 (2010)–week 6 (2011)

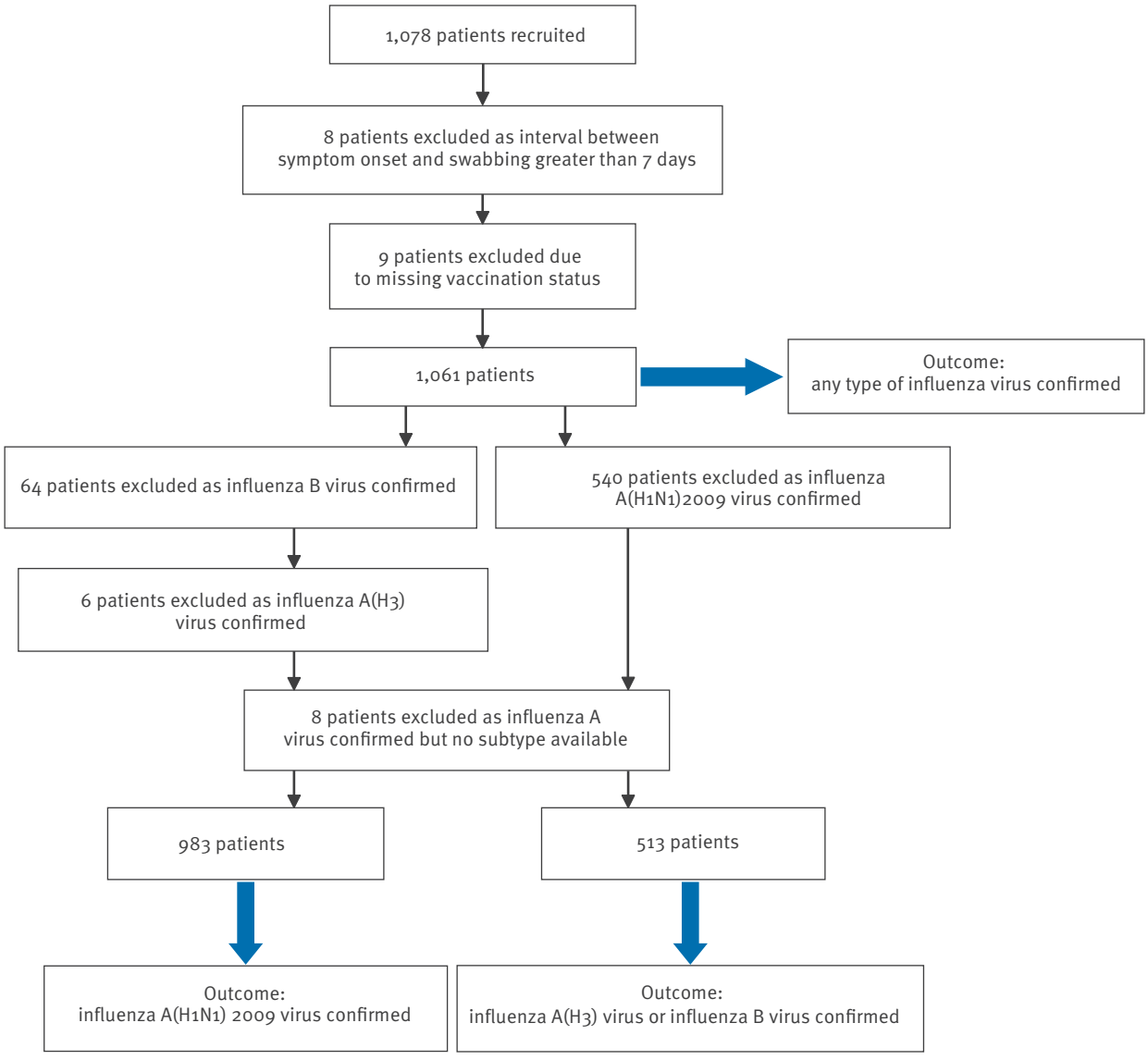


Table 1

Characteristics of influenza cases with any type of influenza virus (n=618) and test-negative controls (n=443), cycEVA study, Spain, week 50 (2010)–week 6 (2011)

Characteristic	Cases[a] No./total no. (%)[b]	Controls[a] No./total no. (%)[b]	P value[c]
Vaccination status			
Vaccinated with trivalent 2010/11 seasonal vaccine	26/618 (4.2)	49/443 (11.1)	<0.0001
Vaccinated with monovalent 2009/10 pandemic vaccine	12/594 (2.0)	24/398 (6.0)	0.001
Age group (years)			
0–4	44/618 (7.1)	32/443 (7.2)	0.007
5–14	101/618 (16.3)	80/443 (18.1)	
15–44	332/618 (53.9)	211/443 (47.6)	
45–64	118/618 (19.1)	82/443 (18.5)	
≥65	22/618 (3.6)	38/443 (8.6)	
Male	300/618 (48.6)	204/443 (46.0)	0.422
Any chronic condition	67/450 (14.9)	61/330 (18.5)	0.180
Pregnancy	1/255 (0.4)	5/217 (2.3)	0.065
Obesity[d]	4/475 (0.8)	3/349 (0.9)	0.978
Any hospitalisation for chronic conditions in the previous year	4/611 (0.6)	8/431 (1.9)	0.073
Number of visits to a GP in the previous year			
None	164/610 (26.9)	96/432 (22.2)	0.107
1–4	256/610 (42.0)	178/432 (41.2)	
>4	190/610 (31.2)	158/432 (36.6)	
Smoking	47/532 (8.8)	38/366 (10.4)	0.436
Poor functional status	2/571 (0.3)	4/393 (1.0)	0.195
Eligible for vaccination	49/618 (7.9)	51/443 (11.5)	0.049

GP: general practitioner.

[a] Cases and controls recruited with an interval between symptom onset and swabbing of less than eight days.

[b] Unless otherwise indicated.

[c] Chi-square test or Fisher's exact test, when appropriate.

[d] Defined as body mass index greater than 40.

Table 2

Intraseasonal estimates of trivalent 2010/11 seasonal influenza vaccine and monovalent 2009/10 pandemic vaccine in preventing influenza A(H1N1) 2009 infection, Spain, week 50 (2010)–week 6 (2011)

Patients	Vaccination status	Number of cases	Number of controls	Crude vaccine effectiveness, as percentage (95% CI)	Adjusted vaccine effectiveness[a], as percentage (95% CI)
All[b]	Unvaccinated	494	344	Reference	Reference
	Seasonal 2010/11 vaccine only	18	30	58 (24 to 77)	52 (6 to 75)
	Pandemic 2009/10 vaccine only	5	9	61 (–16 to 87)	67 (–5 to 90)
	Seasonal and pandemic vaccines	4	15	82 (44 to 94)	72 (7 to 92)
Eligible for vaccination[c]	Unvaccinated	27	20	Reference	Reference
	Seasonal 2010/11 vaccine only	9	17	61 (–6 to 86)	52 (–53 to 85)
	Pandemic 2009/10 vaccine only	2	0	ND	ND
	Seasonal and pandemic vaccines	3	10	78 (9 to 95)	83 (15 to 97)

CI: confidence interval; ND: not determined.

[a] Adjusted for age group and week of swabbing.

[b] Includes 521 cases and 398 controls.

[c] Includes 41 cases and 47 controls.

Estimates of the effectiveness of the seasonal trivalent influenza vaccine 2010/2011

The crude effectiveness of the vaccine in preventing influenza caused by any type of influenza virus was 65% (95% CI: 41–79%). Adjusting for age group, monovalent pandemic vaccination, previous seasonal vaccination in 2009/10 and week of swabbing, the effectiveness was 50% (95% CI:–6 to 77%). In the group eligible for vaccination (n=91), the adjusted vaccine effectiveness was 66% (95% CI: –1 to 89%).

In the analysis with influenza A(H1N1)2009 virus infection as the outcome, the crude vaccine effectiveness was 66% (95% CI:41–81%) and the adjusted effectiveness estimate, taking into account age group, monovalent pandemic vaccination and week of swabbing, was 49% (95% CI: 3–73%). For those eligible for seasonal vaccination (n=88), the adjusted vaccine effectiveness was 63% (95%CI: –15 to 88%).

Crude vaccine effectiveness in preventing influenza A(H3) virus or influenza B virus infection was 51% (95% CI: –40 to 88%), which increased when adjusted for age group, previous seasonal vaccination in 2009/10 and week of swabbing to 84% (95% CI:16–97%). For those eligible for vaccination, the adjusted vaccine effectiveness was 90% (95% CI: –80 to 100%).

In the analysis with the four-level vaccination variable in preventing influenza A(H1N1)2009 infection, in patients who received 2010/11 seasonal trivalent vaccine only, the vaccine effectiveness, adjusted for age group and week of swabbing, was 52% (95% CI: 6–75%) (Table 2). For patients receiving both seasonal trivalent and monovalent pandemic vaccines, the adjusted vaccine effectiveness was 72% (95% CI: 7–92%). In the analysis including patients eligible for vaccination, the adjusted effectiveness when vaccinated with both vaccines was (83%; 95% CI: 15–97%). Point estimates for patients vaccinated only with the pandemic vaccine were higher than for the patients vaccinated only with the 2010/11 seasonal vaccine, but the difference was not statistically significant (Table 2).

Laboratory findings

A total of 56 specimens were sent for genetic characterisation of the virus. In 40 specimens, there was sufficient PCR-amplified product for sequencing of the viral haemagglutinin gene: 33 were influenza A(H1N1)2009, one was influenza A(H3) and six were influenza B viruses. Phylogenetic analysis of the 33 A(H1N1)2009 sequences showed a genetic similarity to the influenza virus of the pandemic vaccine since neither specific mutations 94N, 125D and 250A defining the A/Christchurch/16/2010 clade, nor 128P, 199A and 295V defining the A/Hong Kong/2213/2010 clade were found. Nevertheless, three of the 33 sequenced viruses showed other amino acid changes compared with the vaccine strain. The six influenza B viruses were similar to the vaccine strain. Specific mutations 53N, 94H, 230V and 280A, defining the clade A/Hong Kong 2121/2010 were identified for the patient with influenza A(H3) virus.

Discussion

Our results suggest a protective effect of the seasonal trivalent vaccine in preventing influenza due to infection of any type of influenza virus, including influenza A(H1N1)2009 virus and influenza A(H3) or influenza B viruses. Similar results were obtained when we restricted the analysis to those eligible for vaccination. These are preliminary results and should be interpreted with caution, taking into consideration the sample size.

However, the effectiveness of the trivalent seasonal vaccine in preventing influenza A(H1N1)2009 infection in both analyses (49% and 52%) is lower than that reported for the monovalent pandemic vaccine in the 2009/10 season in the same study population, which reached 75% (unpublished data). Several factors might have contributed to this finding. Firstly, the monovalent pandemic vaccine used in the 2009/10 season was adjuvanted (with the exception of that used for pregnant women), while the current seasonal trivalent vaccine used in all participating regions is non-adjuvanted. Secondly, the monovalent pandemic vaccine was not recommended for elderly people aged over 64 years without underlying diseases, resulting in a vaccinated population that was younger and more immunocompetent. Last, but not least, the lower effectiveness of the seasonal vaccine might suggest that there may have been some genetic changes in the influenza A(H1N1)2009 virus. Most influenza A(H1) viruses circulating in Spain remained closely related genetically to the vaccine virus; however, there have been observed some amino acid changes in the haemagglutinin gene of a small proportion of studied strains that could be reasonably be attributable to genetic drift, since these mutations are different from those defining new clades observed in September 2010 [12]. Notably, the only influenza A(H3) virus characterised in our study falls within a subgroup represented by the influenza A/Hong Kong/2121/2010 virus.

We also observed a higher protective effect in preventing infection due to influenza A(H1N1)2009 virus in patients who had received both seasonal trivalent and monovalent pandemic vaccines, consistent with other early reports [10,13].This might suggest a type of cumulative protection, which should be confirmed by immunological studies, and highlights the need for routine annual influenza vaccination for people in the recommended groups.

In the same analysis, we also found that the monovalent pandemic vaccine had a higher point estimate than that for the seasonal vaccine, but this difference was not statistically significant due to the low number who were vaccinated. These findings might be related again to the type of the vaccine used (adjuvanted ver-

sus non-adjuvanted) or to the population targeted for vaccination.

Interestingly, we found a good protective effect of the seasonal trivalent vaccine against influenza A(H3) and influenza B viruses, although this effect was higher than that reported in another study [10]. This is consistent with the good match between the vaccine and circulating influenza B strain. The difference in the estimates could be related to different confounding factors that the effectiveness calculations were adjusted for.

This is the third season in which we have used the test-negative case–control design in the cycEVA study. The experience of the two previous seasons [1,5] was reflected in increased participation of GPs and paediatricians, compliance with the protocol and completeness of data collection (less than 10% data were missing for important variables). The introduction of systematic swabbing for ILI patients might have reduced the selection bias toward vaccinated patients, which is known to occur in surveillance-based studies [14].

In conclusion, the cycEVA study was able to provide an early intraseasonal estimate of the effectiveness of the seasonal vaccine nine weeks since the epidemic started. It suggests a protective effect of the vaccine against all types of influenza viruses. This effect was also seen in the group eligible for vaccination; however, the effect was lower than that reported in the previous season [1]. It also demonstrates that intraseasonal vaccine effectiveness estimates are possible by conducting observational studies, with an acceptable additional effort, within the framework of a well-organized influenza surveillance system meeting the criteria of the European Influenza Surveillance Network.

The cycEVA study is ongoing in Spain and ILI cases are still being recruited while sporadic circulation of influenza viruses is registered in the participating regions. Therefore we expect that at the end of the season the sample size will allow more precise estimates of vaccine effectiveness and will enable us to control for other confounding factors known to influence vaccine effectiveness. In addition, the I-MOVE multicentre study, pooling data from eight European countries including Spain, will be able to present even more precise estimates.

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Members of the cycEVA Study Team
Jaume Giménez, Juana M. Vanrell (Service of Epidemiology, General Directorate of Public Health, Baleares), Carolina Rodriguez, Tomás Vega (General Directorate of Public Health, Research and Development. Castilla y León), Ana Martínez, Nuria Torner (Department of Health, Generalitat of Catalonia. CIBERESP), Julián M. Ramos, Maria C. Serrano (Sub-directorate of Epidemiology, Public Health Directorate. Extremadura), Jesús Castilla, Manuel García Cenoz (Institute of Public Health of Navarra. CIBERESP), Jone M. Altzíbar (Sub-directorate of Public Health. País Vasco. CIBERESP), Jose M. Arteagoitia (Public Health Service, Department of Health, Basque Government. País Vasco), Carmen Quiñones, Milagros Perucha (General Directorate of Public Health and Consumption, Consejería de Salud. La Rioja), Daniel Castrillejo (General Directorate of Public Health and Consumption of Melilla).

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Early estimates of seasonal influenza vaccine effectiveness in Europe, 2010/11: I-MOVE, a multicentre case–control study

E Kissling (e.kissling@epiconcept.fr)[1], M Valenciano[1], I-MOVE case–control studies team[2]
1. EpiConcept, Paris, France
2. Members of the team are listed at the end of the article

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We present early estimates (up to week 4 of 2011) of the 2010/11 seasonal influenza vaccine effectiveness in preventing medically attended influenza-like illness (ILI) laboratory confirmed as influenza. Practitioners from seven European sentinel networks systematically swabbed ILI patients. We included patients meeting the European Union ILI case definition and swabbed less than eight days after symptom onset. Laboratory-confirmed influenza cases were compared with negative controls. The adjusted vaccine effectiveness was 42.3% (95% CI: –7.3 to 69.0%), suggesting moderate protection of the seasonal vaccine.

Background

The Influenza Monitoring Vaccine Effectiveness in Europe (I-MOVE) network was established in 2007 by the European Centre for Disease Prevention and Control (ECDC) to monitor seasonal and pandemic influenza vaccine effectiveness [1-3]. In the 2010/11 season, to estimate the effectiveness of the seasonal vaccine in preventing medically attended influenza-like illness (ILI) laboratory confirmed as influenza we undertook a multicentre case–control study based on sentinel practitioner surveillance networks from eight study sites (France, Hungary, Ireland, Italy, Romania, Poland, Portugal and Spain). We report the preliminary results from seven study sites (data from France are not included in this preliminary analysis as data collection is ongoing).

Data collection and analysis

We used similar methods to those used in the first two seasons of I-MOVE [1,3]. The studies were conducted within the context of the existing European Influenza Surveillance Network (EISN) [4].

The study population consisted of patients consulting a participating practitioner for ILI within eight days after symptom onset. Practitioners systematically selected ILI patients to swab.

A case of confirmed influenza was an ILI patient (defined according to the European Union case definition [5]) who was swabbed and tested positive for influenza using real-time polymerase chain reaction (PCR) or culture. Controls were ILI patients who were swabbed and tested negative for any influenza virus.

Individuals were considered vaccinated if they had received a dose of the seasonal vaccine more than 14 days before the date of onset of ILI symptoms. Participating sentinel practitioners interviewed ILI patients to collect information on ILI signs and symptoms, date of onset of symptoms, current vaccination status (including date of vaccination), prior seasonal and pandemic influenza vaccination status and a list of potential confounding factors: age, sex, presence of chronic condition(s), severity of chronic disease(s) using the number of hospitalisations for the chronic disease(s) in the previous 12 months as a proxy, smoking history (non-smoker, past, current smoker), number of practitioner visits in the previous 12 months. We included in the study patients recruited up to the end of week 4 of 2011, meeting the European ILI case definition with onset of symptoms more than 14 days after the start of national 2010/11 influenza vaccination campaigns. In each study, we excluded controls with symptom onset in the weeks before the week of symptom onset of the first confirmed influenza case of the season and individuals with missing information on laboratory results. In addition, for effectiveness of the vaccine in preventing influenza A(H1N1)2009 virus infection, we excluded any individual positive for other influenza virus types and excluded controls with symptom onset in the weeks before the week of symptom onset of the first case of influenza A(H1N1)2009 virus infection recruited in the 2010/11 season.

We estimated the pooled seasonal influenza vaccine effectiveness as one minus the odds ratio (OR) (expressed as a percentage) using a one-stage method with the study site as fixed effect in the model. To estimate adjusted vaccine effectiveness, we used logistic regression models including all potential confounding factors.

We first conducted the analysis excluding all individuals with at least one missing value (complete case analysis). We then estimated missing data for vaccination status and covariates using the multiple multivariate imputation by chained equations procedure in Stata [6]. We used missing at random assumptions. We used all predictors together to impute the missing values and independently analysed 20 copies of the data using 30 cycles of regression.

Estimates of seasonal influenza vaccine effectiveness

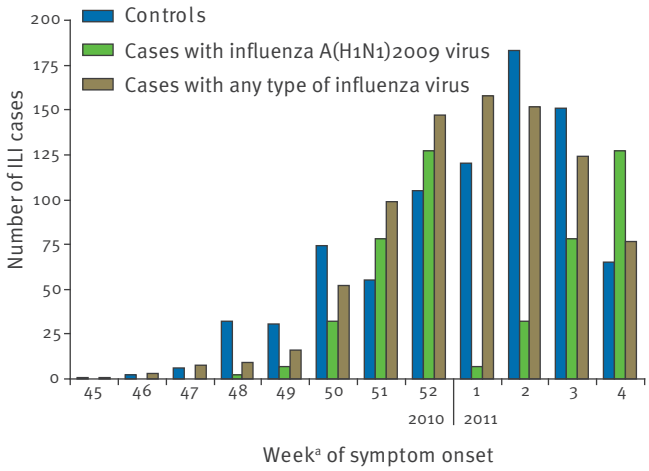
A total of 585 practitioners agreed to participate in the study; 352 of them (60%) recruited at least one ILI patient (Table 1). After excluding 71 individuals with missing information on laboratory results, a total of 1,671 ILI patients were included in the analysis: 846 cases and 825 controls (Figure 1). Among the cases, 649 (76.7%) were positive for influenza A(H1N1)2009 virus, nine (1.1%) for influenza A(H3N2) virus, 15 (1.8%) were positive for influenza A virus that could not be subtyped and 173 (20.5%) were positive for influenza B virus.

Among 1,658 individuals with information on vaccination status and vaccination date for seasonal vaccination in 2010/11, 116 (7.0%) were vaccinated (ranging from 2.2% in Poland and Ireland to 19.9% in Italy).

The median age was lower in cases (29 years, standard deviation (SD): 18 years) than in controls (34 years, SD: 21 years) (Table 2). The delay between onset of symptoms and swabbing was slightly shorter in cases (mean: 1.8 days, range: 0–7 days) than in controls (mean: 1.9 days, range: 0–7 days).The proportion of individuals presenting with fever, malaise, headache, myalgia or cough was higher among cases than among controls (Table 2). Compared with cases, a higher proportion of controls had diabetes, heart disease or were hospitalised at least once for their chronic disease in the previous 12 months. A higher proportion of controls were current or past smokers, vaccinated with the 2009/10 seasonal influenza vaccine, and vaccinated with the 2009/10 pandemic influenza vaccine. The median number of practitioner visits in the previous 12 months was two for cases (ranging from 0 to 26) and three for controls (ranging from 0 to 60) (Table 2).

Figure

Influenza A(H1N1)2009 cases (n=649), all influenza cases (n=846) and influenza-negative controls (n=825) recruited by week of symptom onset, multicentre case–control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)



ILI: influenza-like illness.

[a] International Organization for Standardization (ISO) definition of a week.

Table 1

Practitioners' participation, influenza-like illness (ILI) patients recruited by case–control status, vaccination status and study site, multicentre case–control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Study site	Number of practitioners accepting to participate in the study	Number of practitioners recruiting at least one ILI patient[a]	Number of ILI patients[a] recruited by practitioners	Inclusion period for the study	Number of ILI patients included in the study positive for any influenza virus[c]		Number of ILI patients included in the study negative for any influenza virus[c]	
				ISO week number (year)[b]	Total	Vaccinated	Total	Vaccinated
Hungary	98	64	242	50 (2010)–4 (2011)	47	1	195	11
Ireland	22	17	160	48 (2010)–4 (2011)	84	0	54	3
Italy	38	31	220	48 (2010)–4 (2011)	40	7	126	26
Poland	34	16	46	48 (2010)–4 (2011)	24	0	21	1
Portugal	58	30	186	45 (2010)–4 (2011)	117	5	69	11
Romania	89	40	69	52 (2010)–4 (2011)	32	2	37	5
Spain	246	154	819	49 (2010)–4 (2011)	498	19	314	25
Total	**585**	**352**	**1,742**	–	**842**	**34**	**816**	**82**

ISO : International Organization for Standardization.

[a] ILI patients meeting the European Union case definition, swabbed less than eight days after onset of symptoms within the study period.

[b] From 15 days after the start of the seasonal influenza vaccination campaign to the week of symptom onset of the last case recruited. Controls with an onset of symptoms in the weeks before the first case were excluded.

[c] ILI patients in the study after excluding those with missing information on laboratory results, vaccination status or date of vaccination.

A total of 34 cases were vaccinated with the 2010/11 seasonal vaccine. In two of the seven studies there were no vaccinated individuals among the recruited cases.

In the pooled complete case analysis the adjusted vaccine effectiveness was 35.1% (95% CI: −23.0 to 65.8) in preventing influenza caused by all types of influenza viruses and 34.9% (95% CI: −37.5 to 69.2%) in preventing influenza A(H1N1)2009 virus infection (Table 3).

In the pooled analysis with imputed data, the adjusted vaccine effectiveness against all influenza strains was 42.3% (95% CI: −7.3 to 69.0%), and 44.1% (95% CI: −14.3 to 72.7%) against influenza A(H1N1)2009 virus (Table 3).

Discussion

Our early pooled estimates suggest that the 2010/11 seasonal vaccine conferred moderate protection against medically attended laboratory-confirmed influenza. These results should be interpreted with caution, however, for reasons including low vaccine coverage and potential biases due to the test-negative design, confounding factors, missing values and small sample size due to the early estimation in the season. Those biases have been described elsewhere in detail [3,7].

Our estimates of the 2010/11 seasonal vaccine effectiveness apply to the study period (until the end of week 4 of 2011). They are based on data from seven European study sites sharing the same protocol and definition of variables. The pooled point estimates of

Table 2

Characteristics of influenza cases (n=846) and test-negative controls (n=825) included, multicentre case-control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Characteristic	Influenza cases No./total no. (%)[a]	Test-negative controls No./total no. (%)[a]	P value
Median age	29 years	34 years	< 0.001[b]
Age group (years)			
0–4	49/845 (5.8)	57/825 (6.9)	< 0.001[c]
5–14	146/845 (17.3)	88/825 (10.7)	
15–64	621/845 (73.5)	591/825 (71.6)	
≥65	29/845 (3.4)	89/825 (10.8)	
Female	443/844 (52.5)	433/825 (52.5)	1.000[c]
Symptoms			
Fever	818/845 (96.8)	763/819 (93.2)	0.001[c]
Malaise	791/846 (93.5)	745/822 (90.6)	0.037[c]
Headache	653/830 (78.7)	596/809 (73.7)	0.020[c]
Myalgia	683/827 (82.6)	626/806 (77.7)	0.013[c]
Cough	797/846 (94.2)	686/818 (83.9)	<0.001[c]
Number of days between symptom onset and swabbing			
0	49/846 (5.8)	39/825 (4.7)	0.327[c]
1	376/846 (44.4)	352/825 (42.7)	
2	247/846 (29.2)	242/825 (29.3)	
3	108/846 (12.8)	105/825 (12.7)	
≥4	66/846 (7.8)	87/825 (10.5)	
Seasonal vaccination, 2010/11	34/842 (4.0)	82/816 (10.0)	<0.001[c]
Pandemic vaccination, 2009/10	53/826 (6.4)	88/784 (11.2)	0.001[c]
Seasonal vaccination, 2009/10	58/825 (7.0)	109/780 (14.0)	<0.001[c]
Diabetes	15/741 (2.0)	38/774 (4.9)	0.003[c]
Heart disease	24/ 740 (3.2)	84/774 (10.9)	<0.001[c]
Smoker status			
Current	88/822(10.7)	123/786 (15.6)	<0.001[c]
Former	52/822 (6.3)	79/786 (10.1)	
Never	682/822 (83.0)	584/786 (74.3)	
Median number of GP visits in the previous 12 months	2	3	0.005[b]
Any hospitalisation in the previous 12 months for chronic diseases	1/846 (1.1)	23/823 (2.6)	0.026[c]

GP: general practitioner.

[a] Unless otherwise indicated.

[b] Non-parametric test of the median.

[c] Two-sided Fisher's exact test.

vaccine effectiveness were between 35% (adjusted) and 61% (crude).

We adjusted for most of the confounding factors described in the literature (see, for example, [7]). The adjusted vaccine effectiveness was lower than the crude vaccine effectiveness (absolute differences ranging from 16.2% to 24.7%), suggesting some positive confounding. The main confounders identified were seasonal influenza vaccination in the previous season and age group.

This is the third season the I-MOVE programme has estimated influenza vaccine effectiveness using laboratory-confirmed outcomes. Compared with the I-MOVE estimates of last season, the 2010/11 seasonal vaccine seems to have a lower effectiveness against influenza A(H1N1)2009 virus infection than the monovalent pandemic vaccine of 2009/10 [3]. This may be explained by antigenic drift, by a different distribution of adjuvanted versus non-adjuvanted vaccines in some study sites [8] or by a different study population. The ILI cases included in the 2009/10 I-MOVE multicentre case–control study were younger (mean age: 12 years for cases and 24 for controls) than those included in this 2010/11 early analysis.

The pooled early estimates are similar to those observed in the United Kingdom [9], the Navarre region in Spain [8] and the cycEVA study in Spain [10]. Later in the season, the larger sample size per country will allow us to conduct precise pooled and stratified analyses and to further explore the difference in effectiveness of the seasonal vaccine with that of the 2009/10 pandemic vaccine. In addition, the use of validation subsets in France, in which we collect more accurate and additional information in a subsample of the ILI patients, will enable to base our estimates on data from eight countries.

I-MOVE is a unique network in Europe able to measure seasonal and pandemic vaccine effectiveness. The early estimates presented here suggest that the seasonal vaccine has a lower effectiveness than that observed with the monovalent pandemic vaccine [3].

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Table 3

Pooled crude and adjusted 2010/11 seasonal vaccine effectiveness, by type of outcome and type of analysis, multicentre case–control study, seven European Union country study sites, week 45 (2010)–week 4 (2011)

Outcome	Crude vs adjusted	Complete vs imputed data analysis	Number of ILI cases included	Vaccine effectiveness	
				%	95% CI
Infection with any influenza virus	Crude[a]	Complete case analysis[b]	1,390	56.9	32.2 to 72.6
		Imputed data[c]	1,671	58.5	35.7 to 73.2
	Adjusted model[d]	Complete case analysis[b]	1,390	35.1	−23.0 to 65.8
		Imputed data[c]	1,671	42.3	−7.3 to 69.0
Infection with influenza A(H1N1)2009 virus	Crude[a]	Complete case analysis[b]	1,158	59.6	32.6 to 75.8
		Imputed data[c]	1,407	60.5	35.3 to 75.8
	Adjusted model[d]	Complete case analysis[b]	1,158	34.9	−37.5 to 69.2
		Imputed data[c]	1,407	44.1	−14.3 to 72.7

ILI: influenza-like illness.

[a] Study site included in the model as fixed effect.

[b] Excluding individuals with missing values.

[c] Missing data imputed using imputation by chained equations.

[d] Model adjusted for 2009/10 seasonal and pandemic influenza vaccination, presence of at least one chronic disease, sex, at least one hospitalisation for chronic disease in the previous 12 months, current smoker, age group, visits to a general practitioner in previous 12 months (0–1, 2–4 and ≥5 visits) and week of symptom onset.

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Members of the I-MOVE case–control studies team
ECDC, Stockholm, Sweden: BC Ciancio, P Kramarz, A Nicoll; EpiConcept, Paris, France: E Kissling, A Moren, C Savulescu, M Valenciano; Hungary: B Oroszi; K J Horváth, Á Csohán; S Caini, M Rózsa; Ireland: A S Barret, A O´Malley,J O´Donnell, J Moran, S Coughlan, M Joyce; C Collins, Italy: C Rizzo, A Bella, P D'Ancona, S Giannitelli, M C Rota, S Puzelli, I Donatelli; Poland: I P Stankiewicz, P Stefanoff, M Gluchowska, L Brydak, M Romanowska; Portugal: B Nunes, A Machado, I Batista, P Pechirra, P Gonçalves, P Conde, I Falcão; Romania: D Pitigoi, A E Baetel, E Lupulescu; Spain: S Jiménez-Jorge, S de Mateo, F Pozo, J Ledesma,I Casas, A Larrauri.

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Beyond the influenza-like illness surveillance: The need for real-time virological data

J S Casalegno (jean-sebastien.casalegno@chu-lyon.fr)[1], E Frobert[1], V Escuret[1], M Bouscambert-Duchamp[1], G Billaud[1], Y Mekki[1], I Schuffenecker[1], B Lina[1], F Morfin[1], M Valette[1]
1. Hospices Civils de Lyon, National Influenza Centre, Laboratory of Virology, Lyon, France

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To the editor: We read with great interest your special issue on the Experiences with the pandemic in Europe (Vol. 15, issue 49, 9 December 2010). The reports in that issue clearly highlight the importance of surveillance and monitoring of both emergence and spread of influenza outbreaks through syndromic and laboratory surveillance networks [1]. We would however like to highlight that, in medical practice, it is hardly possible to determine the aetiology of viral respiratory infections by using only clinical symptoms as a basis for diagnosis. For example the correlation between the influenza and influenza-like illnesses (ILI) presentation and the diagnosis of influenza may vary considerably depending on the definition of ILI, the accuracy of the clinician, the epidemiological context, and the presence of co-circulating confounding respiratory viruses. Collecting virological data is mandatory for such networks.

The early phase of the A(H1N1)2009 pandemic in France is an interesting example of this risk of confusion. In France, two independant surveillance networks are involved in influenza surveillance: the 'réseau sentinelle' or sentinel network and the Groupes Régionaux d'Observation de la Grippe (GROG). The sentinel network [2] declared the A(H1N1)2009 pandemic in France the first week of September 2009 (week 36), based on the increase in ILI reports. At the same time, GROG [3] and the laboratory network linked to the National Influenza Centre reported a low incidence of pandemic influenza A(H1N1)2009 [4]. From week 36 to week 43, the GROG network reported a limited pandemic influenza A(H1N1)2009 activity. The pandemic started only mid-October (week 44), according to clinical and virological data. This discrepancy is explained by the difference in the surveillance methods of the two networks. The sentinel network uses clinical surveillance of ILI based on reports from general practitioners (GPs),

Table

Percentage of clinical symptoms observed in paediatric patients with a positive influenza or rhinovirus laboratory-confirmed nasal sample, week 36 to 46, France 2009[a] (n=415)

Symptom	Influenza A(H1N1)	Rhinovirus	Odds ratio, 95% confidence interval	p
Cough	87,9	59,2	(0,12;0,32)	p<0,001
Asthenia	24,6	13,8	(0,29;0,81)	p<0,001
Myalgia	22,2	6,4	(0,11;0,47)	p<0,001
Diarrhoea	9,8	5,3	(0,90;4,10)	Not significant
Vomiting	21,8	15,7	(0,40;1,10)	Not significant
Hyperthermia	81,7	79,2	(0,50;1,38)	Not significant
Temperature ≥ 39,5°C	28	25,3	(0,53;1,51)	Not significant
Swollen lymph nodes	12,1	11,8	(0,53;1,76)	Not significant
Nasal secretion	36,1	45,1	(0,98;2,16)	p<0,05
Bronchitis	3,4	5,4	(0,62;4,30)	Not significant
Dyspnoea	8,2	24,1	(17,7;41,30)	p<0,001
Otitis	8,2	2,5	(0,10;0,78)	p<0,01
Pharyngitis	32,2	8,7	(0,11;0,35)	p<0,001
Cutaneous rash	7,8	4,9	(0,27;1,39)	Not significant
ILI diagnosed	36,5	35	(0,62;1,39)	Not significant

[a] Results are presented as the likelihood of the presence of symptoms and rhinovirus detection (Odds ratio, 95% confidence interval)

whereas the GROG network associates virological diagnoses to the clinical surveillance of ILI reported by GPs. The latter network could ascertain that non-influenza respiratory viruses, mainly rhinoviruses and other respiratory viruses such as parainfluenza viruses, were responsible for the increase in reported ILI from week 36 to week 43 [4,5].

To investigate this point further, we reviewed 415 emergency paediatric medical records collected between week 36 and week 46 (mean age 4.8 years +/- 7.1 standard deviation). We compared the clinical symptoms of 208 laboratory-confirmed A(H1N1)2009 influenza virus-positive and 207 rhinovirus-positive patients (Table). It was clear that there were differences between the clinical presentations. Cough, asthenia, myalgia, pharyngitis and otitis were more frequent in the A(H1N1)2009 influenza group whereas nasal secretion and dyspnea were more frequent in the rhinovirus group. However, all these symptoms were noticed in both groups. Temperature did not differ significantly between the A(H1N1)2009 influenza and rhinovirus groups. The conclusion of ILI in the emergency paediatric medical report was not predictive for either laboratory-confirmed influenza or rhinovirus cases. The pandemic context, the expectation of influenza to spread with the start of the school year in September, massive media coverage of the pandemic and the general level of anxiety made the presumptive clinical diagnosis of influenza a real challenge in the early pandemic phase.

These data highlight the fact that viral respiratory infections can easily be clinically confused. It is important to keep in mind these limitations and that ILI and other respiratory symptoms can account for the presence of different respiratory viruses. As reported by Thomson and Nicoll [1], clinical surveillance of upper respiratory tract infection is required but the link of non-specific surveillance data (including surveillance of ILI, schools or work absenteeism, analysis of search engine query data) with a reliable virus surveillance system is mandatory for optimal surveillance and epidemic or pandemic management

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Letter to the editor. Virological analysis of fatal influenza cases in the United Kingdom during the early wave of influenza in winter 2010/11

F Baldanti (f.baldanti@smatteo.pv.it)[1], A Zanetti[2]
1. Molecular Virology Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
2. Department of Public Health, Microbiology and Virology, University of Milan, Milan, Italy

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To the editor: In response to the paper by Ellis *et al.* [1], published in Eurosurveillance Volume 16, issue 1, we would like to make a few observations.

D222G/N substitutions in the haemagglutinin of influenza A(H1N1)2009 strains have been associated with increased virulence [2-4].

An enhanced binding affinity of the mutated haemagglutinin to the α-2,3 sialic acid receptor rather than to the α-2,6 sialic acid receptor has been postulated to be the basis of the increased virulence of D222G/N mutants [3]. The α-2,3 sialic acid receptor is present at higher density on the surface of the cells of the lower respiratory tract tissues whereas the α-2,6 sialic acid receptor is present at higher density on the surface of cells of the upper respiratory tract tissues.

In surveillance reports from different countries, the overall presence of such mutants ranged from 2.0% to 5.6%, while it was significantly higher (up to 22.9%) in severe or in fatal cases [2-4]. Interestingly, the paper by Kilander *et al.*, analysing both nasal swabs and bronchoalveolar lavage, showed the highest rate of D222G/N mutants in patients with severe and fatal infections [2]. In a multicenter study, we analysed paired nasal swabs and bronchoalveolar lavage samples from patients admitted to intensive care units for mechanical ventilation or extracorporeal membrane oxygenation. The samples were compared with samples from patients with pneumonia not requiring mechanical ventilation and from community patients. Our data showed that D222G/N mutants were more frequently detected in lower respiratory tract secretions than in secretions from the higher respiratory tract [5]. In addition, by combining data from nasal swabs and bronchoalveolar lavage samples, the frequency of D222G/N mutants in patients with severe infections increased to 43.0%, as compared to 7.8% and 0% in patients with moderate and mild infections, respectively [5]. In agreement with the pathogenetic hypothesis considering the lower respiratory tract as the more favorable environment for replication of such mutants, viral RNA levels were significantly higher in bronchoalveolar lavage samples than in nasal swabs [5].

Ellis *et al.* reported that almost all viruses derived from fatal and non-fatal cases analysed (39/41) in the United Kingdom during the early wave of the 2010/11 influenza winter season showed the wild-type 222D haemagglutinin residue [1]. Thus, in the paper by Ellis *et al.*, severe and fatal influenza cases were not associated with the emergence of D222G/N mutants, even though the role of other aminoacid substitutions remains to be determined [1]. The authors of this study do not specify the type of clinical samples used for analysis. In the case they used nasal swabs only, on the basis of the above-referenced studies, the rate of D222G/N mutants might have been underestimated.

For a better understanding of the mechanisms of influenza A pathogenicity and the epidemiology of severe and fatal events, the analysis of bronchoalveolar lavage specimens in parallel with nasal swab specimens from patients admitted to intensive care units for severe infections should be envisaged. Additionally, a post-mortem analysis of tissues and/or secretions from the lower respiratory tract from deceased patients, in the event they had not been previously analysed, is important.

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Authors' reply. Virological analysis of fatal influenza cases in the United Kingdom during the early wave of influenza in winter 2010/11

J Ellis (joanna.ellis@hpa.org.uk)[1], M Galiano[1], R Pebody[1], A Lackenby[1], CI Thompson[1], A Bermingham[1], E McLean[1], H Zhao[1], S Bolotin[1], O Dar[1], J M Watson[1], M Zambon[1]
1. Health Protection Agency, Centre for Infections, London, United Kingdom

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To the editors: Our Italian colleagues provide commentary on an important question, as yet unresolved, regarding the relationship between pathogenesis of influenza A(H1N1)2009 infection and mutation in particular viral genes contributing to virulence. Viral haemagglutinin (HA) is the key virulence determining gene for influenza in birds, and a major determinant for host cell tropism in mammalian influenza [1]. The link between cell tropism and virulence in humans remains unclear; many different approaches to this question conclude that virulence is associated with multiple viral genes, including genes determining replication efficiency (polymerase genes) and non-structural genes governing the interaction with the host immune response.

The emergence of animal viruses into the human population is associated with adaptive mutations [2-3] and tracking substitutions at residues known to be associated with such adaptive changes is an important surveillance function. The commentary highlights the opportunities arising from surveillance to develop and apply hypothesis generating questions from observational data sets.

During the 2009 pandemic, attention has focussed on amino acid substitutions at position 222 in the HA of influenza A(H1N1)2009 viruses, which has been observed to vary [4], with aspartic acid (D), glutamic acid (E), asparagine (N) and glycine (G) residues being present at this position. There is a clear correlation between enhanced binding to α2-3-linked sialyl receptor sequences by 222G variants and increased infection of ciliated epithelial cells in vitro models [5].

Our rapid communication of data obtained during the early phase of the epidemic in winter 2010 in the United Kingdom, using available material predominantly derived from swabs taken at the point of diagnosis from the upper respiratory tract (URT), was intended to provide a comprehensive update from all available sources, to give as full a picture as possible. We agree that wherever possible, when URT and lower respiratory tract (LRT) samples are available from individual cases, analysis in parallel is important, as well as sequential sampling from individuals who are hospitalised with severe illness. The ability to link both of these observations to clinical outcome and "within host" variation or evolution is important. We recognise that there is an inherent bias in such an approach, as individuals in the community are almost never sampled from the LRT, leading to the possibility of over interpretation of the importance of a single mutation, by focussing only on severe cases, but analysis of clinical outcome and its relationship to whole genome genetic composition of influenza viruses is underway in several different centres internationally.

The selection and emergence of the D222G mutation as a cause or consequence of more severe lower respiratory tract infection is still to be resolved. Emergence of this mutant is likely to exacerbate severity of disease, but by itself, may be neither necessary nor sufficient to account for a severe disease outcome, which is invariably a balance between virus virulence factors and host immune response capability. Further work is needed, both at the level of reductionist experimental pathology work in the animal model, and at the observational level in human populations. Detailed studies such as the Mechanisms of Severe Acute Influenza Consortium (MOSAIC) study [6], which focus on analysis of viral virulence and host immune response in severe illness, are likely to provide insights useful to understanding pathogenesis in humans. We thank our colleagues for raising this comment and for the opportunity to broaden the commentary in more detail than was possible in the original article.

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Letter to the editor. Group A streptococcal infections during the seasonal influenza outbreak 2010/11 in South East England

P Parola[1], P Colson[2], G Dubourg[2], M Million[1], R Charrel[2], P Minodier[3], D Raoult (didier.raoult@gmail.com)[1]
1. Infectious Diseases and Tropical Medicine Unit, University Hospitals of Marseille, Marseille, France
2. Fédération de Bactériologie-Hygiène-Virologie, Pôle des Maladies Infectieuses et Tropicales Clinique et Biologique, University Hospitals of Marseille, Timone Hospital, Marseille France
3. Urgences Pédiatriques, North University Hospital, Marseille, France

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To the editor: We read with great interest the recent article about invasive Group A *Streptococcus* (GAS) infections associated with influenza B in England by Scaber et al. [1]. Indeed, since 2002 the Clinical Microbiology Laboratory of University Hospitals in Marseille, France, has implemented a tool for the weekly surveillance of microbiological data (called EPIMIC), which consists in a simple warning program using Microsoft Excel software. Both the numbers of samples received and of pathogens diagnosed are compared to historical data as soon as they are entered. Any significant increase beyond the critical threshold, defined by the mean of historical data plus two standard deviations (SDs), generates a signal allowing to detect abnormal and seasonal events in infectious diseases [2].

Recently, we have been alerted by an abnormal increase of invasive Group A *Streptococcus* (GAS) infections detected at the Point Of Care Laboratories of two main Marseille University hospitals (Timone and North hospitals), using rapid antigen detection (RAD) tests on throat swabs. In these two sites and during the three past years (2008-2010), the mean weekly number of GAS detection was six and four, respectively. Between 15 January, and 15 February, 143 RAD tests for GAS infections were positive in patients consulting at the emergency wards, including 98 at La Timone (69%) and 44 at Hospital Nord (31%). These patients had a mean age of 8.6 years (median, 5 years). At the beginning of February 2011, the number of positive GAS was higher than the critical threshold in both sites (mean +2 SDs), being about three times higher compared to the mean value. The number of samples to be tested also increased about the critical threshold.

When this alert was transmitted to the pediatricians working at the emergency wards of both hospitals, they reported to have examined an unusual number of children presenting with both influenza-like symptoms, in the context of seasonal influenza outbreak in France, and pharyngitis with GAS RAD positive testing. At the same time, Scaber et al. reported their series of cases of invasive GAS co-infection with influenza B [1]. Therefore, we investigated retrospectively the association of GAS detection using the RAD test with influenza virus detection by the rapid influenza diagnostic test (RIDT) and real-time RT-PCR assays (rtRT-PCR) in naso-pharyngeal specimens [3]. From 1 January to 28 February, a total of 227 samples tested positive for GAS, and influenza tests were requested by clinicians in 74 of them. A total of 23 co-infections with influenza virus were identified (31%), including 15 with influenza B virus, six with influenza A (not subtyped) and two with influenza A(H1N1)2009. We also investigated the number of invasive GAS by checking the number of GAS positive blood cultures. From January 2007 through February 2011, 30 GAS positive blood cultures were identified in our laboratory, including 10 between 1 October, 2010 and 28 February, 2011 ($p<0.05$; Fisher and Yates tests, considering the number of blood culture samples received at the laboratories). As it can be considered that our laboratories cover a population of 600,000 persons living in Marseille and the surroundings, the incidence of invasive GAS in the last five months could be estimated at 1.6 per 100,000 population.

We provide here microbiological evidence of concurrent influenza viral infection in almost a third of children with GAS infections. It was a remarkable finding that over half of the 23 samples testing positive for influenza were influenza B. The high proportion of confirmed influenza B in our series, even if in a small sample size, is striking, regarding the potential morbidity and mortality associated with influenza B virus in the context of co-infection with invasive GAS, as recently reported [1].

Our warning and investigation resulted from the implementation of a surveillance tool to detect abnormal events in infectious disease. This method of surveillance may lead to other surprising discoveries.

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Influenza vaccine effectiveness, 2010/11

A Steens[1], W van der Hoek (Wim.van.der.Hoek@rivm.nl)[1], F Dijkstra[1], M van der Sande[1]
1. Epidemiology and Surveillance Unit, Centre for Infectious Disease Control, National institute for Public Health and the Environment, Bilthoven, the Netherlands

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To the editor: The editorial [1] and the articles related to it published on 17 March 2011 in *Eurosurveillance* provide important information on preliminary mid-season influenza vaccine effectiveness (VE) estimates for the 2010/11 season. Reliable VE estimates are essential for effective communication and planning of scarce resources. It is important to assess concordance between pooled European data [2] and national estimates, to evaluate on the one hand whether pooling indeed provides more robust estimates, and on the other hand, to explore potential geographical variation in such estimates.

In the Netherlands, we have been estimating effectiveness of the influenza vaccine in preventing medically attended laboratory-confirmed influenza-like illness (ILI) using the test-negative case-control approach for several years. While incorporating this in the routine ILI/influenza surveillance in primary care limits the possibility to optimise the design, to avoid bias, and to adjust for potential confounding, it ensures sustainability and assessment of annual variation. Unfortunately, our limited sample sizes do not allow strain-specific estimates, result in large confidence intervals, and make adjustment for age and underlying conditions challenging. Therefore, to increase power and obtain more valid VE estimates, we very much support pooled European analysis [2].

We estimated the VE using logistic regression on all medically attended ILI patients in the sentinel surveillance system with disease onset between the week in which influenza virus was encountered for the first time in the season and the end of April, the following year. For the current season, we included cases up to 21 March 2011. For 2009/10 and 2010/11, we excluded cases if the period between disease onset and date of swabbing was greater than seven days.

The crude effectiveness of the trivalent seasonal influenza vaccine in 2006/07, 2007/08 [3], 2008/09 [4], and of the monovalent 2009 influenza A(H1N1) pandemic vaccine in 2009/10 ranged from 20% to 60%. Adjustment for age lowered the VE estimates and widened the confidence intervals (Table).

The crude VE estimate for the 2010/11 vaccine was 46% (95% confidence interval: 9–67), which is similar to what has been reported in other European studies [2]. The 2010/11 VE estimate was lower when only individuals with an indication for vaccination (underlying condition or aged 60 years or older) were included.

It is worrying that patterns similar to those observed in the Netherlands are observed on a European scale. In particular, the consistent pattern of reduced VE estimates following correction for potential confounding by age or underlying conditions warrant further studies to develop methodologies for robust, non-biased VE estimates.

Table

Influenza vaccine effectiveness estimates per season, the Netherlands, 2006/07 – 2010/11

Influenza season	Vaccinated / total positive	Vaccinated / total negative	Crude VE (95% CI)	Age-adjusted VE (95% CI)
2006/07	9/72	25/144	32% (-55 to 70)	6% (-132 to 62)
2007/08	10/141	38/236	60% (17 to 81)	59% (7 to 82)
2008/09	20/167	45/311	20% (-41 to 54)	19% (-56 to 58)
2009/10[a]	6/36	72/258	48% (-29 to 79)	35% (-76 to 76)
2010/11	26/217	52/260	46% (9 to 67)	5% (-80 to 49)

CI: confidence interval; VE: vaccine effectiveness.
[a] Vaccine effectiveness calculated for the adjuvanted MF-59TM 2009 influenza A(H1N1) pandemic vaccine.

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