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

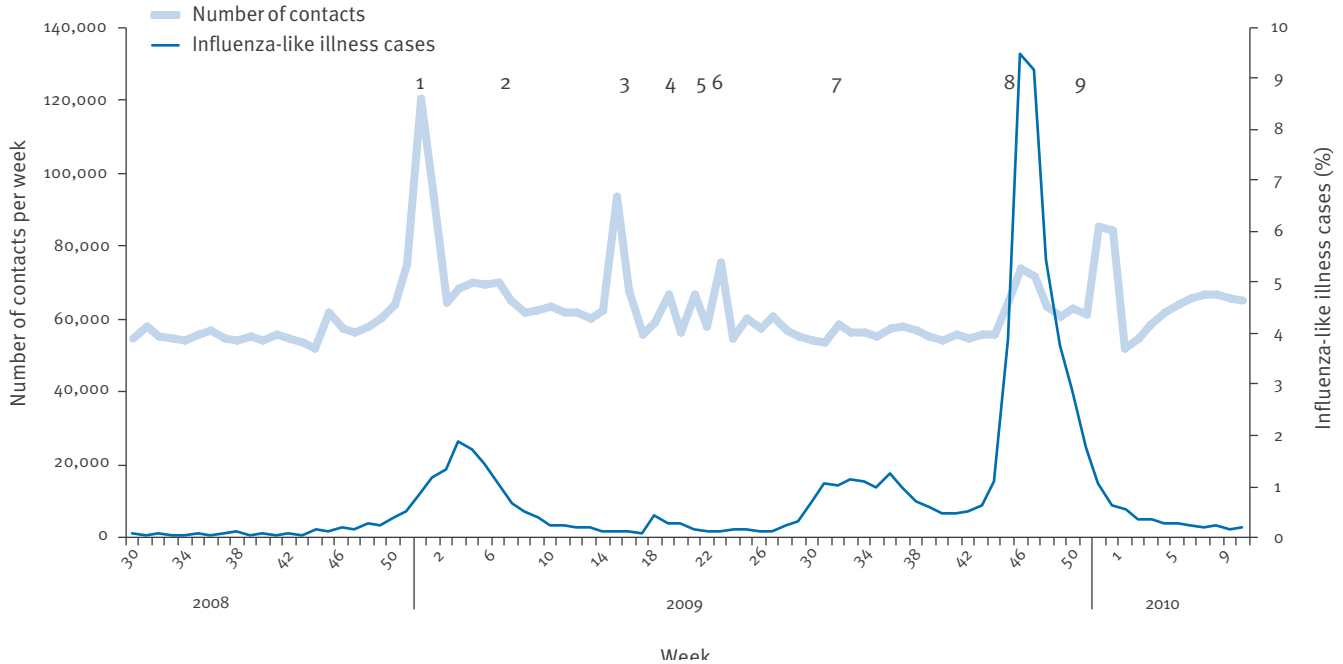
All contacts are registered in a single national computer system. In the electronic health record, demographic data are registered in a structured format, but the medical history, diagnosis and actions taken are recorded in a free text format. In agreement with the on-call physicians and the Danish Medical 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

Figure 1

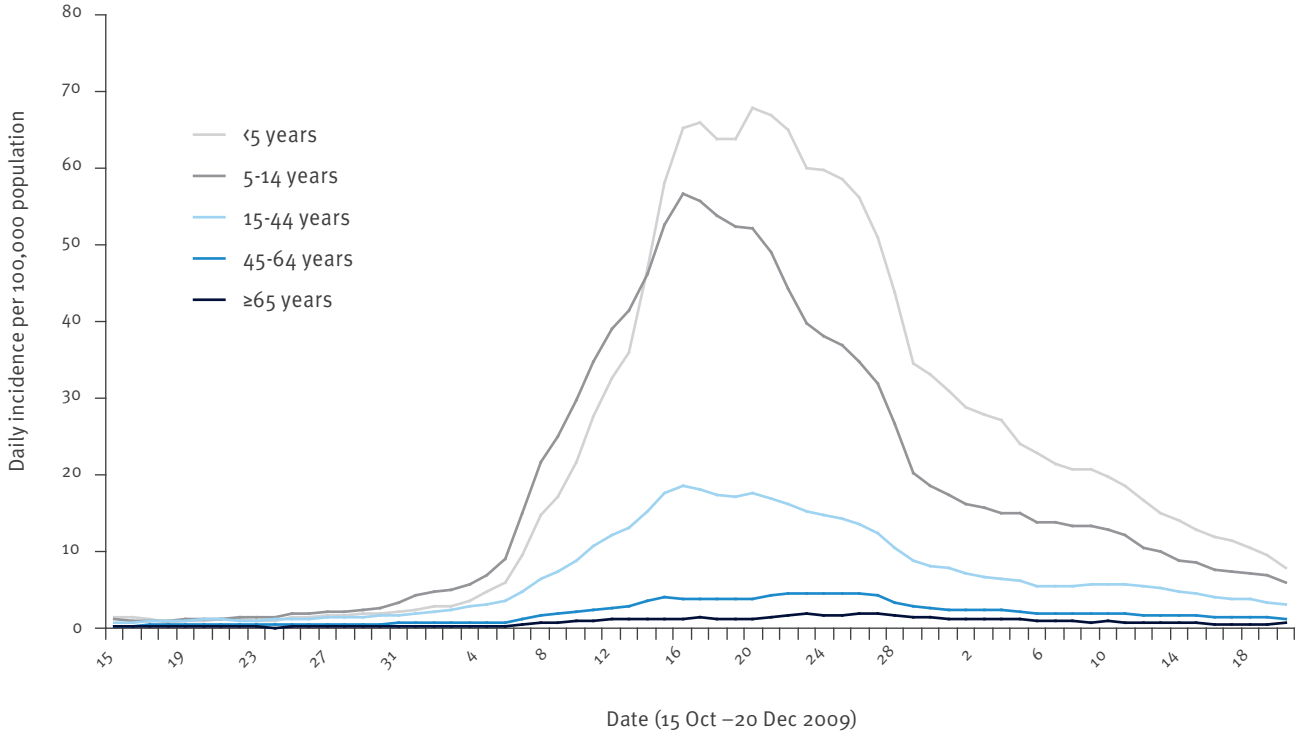
Contacts to the on-call medical service and influenza-like illness cases, per week, Denmark, 2008-2010



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.

Figure 2

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



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

Table

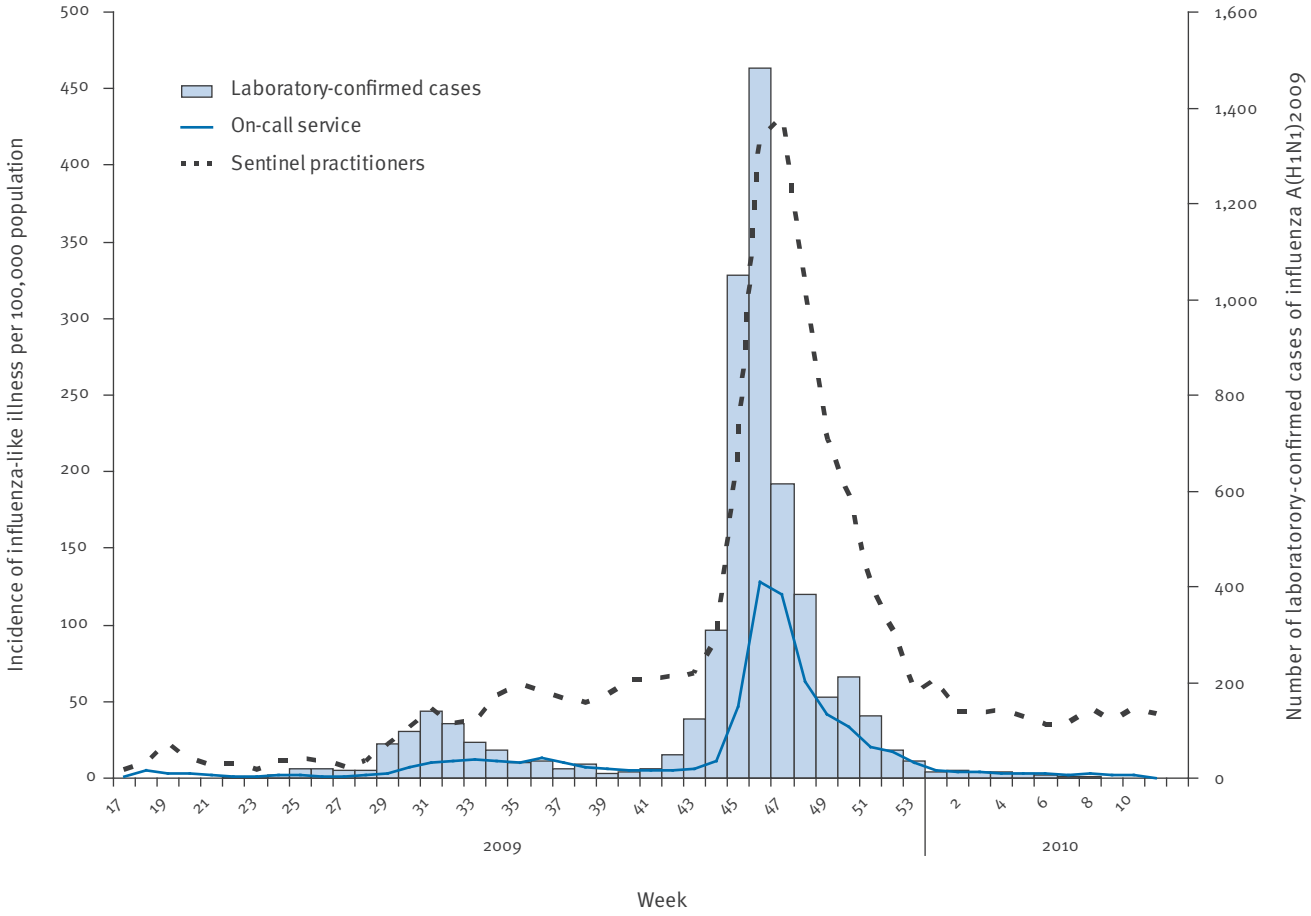
Referral of patients with influenza-like illness to consultation at a clinic or hospital during seasonal influenza 2008/09 and summer and autumn waves of influenza A(H1N1)2009, Denmark, 2008–2010

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.

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 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).

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

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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.

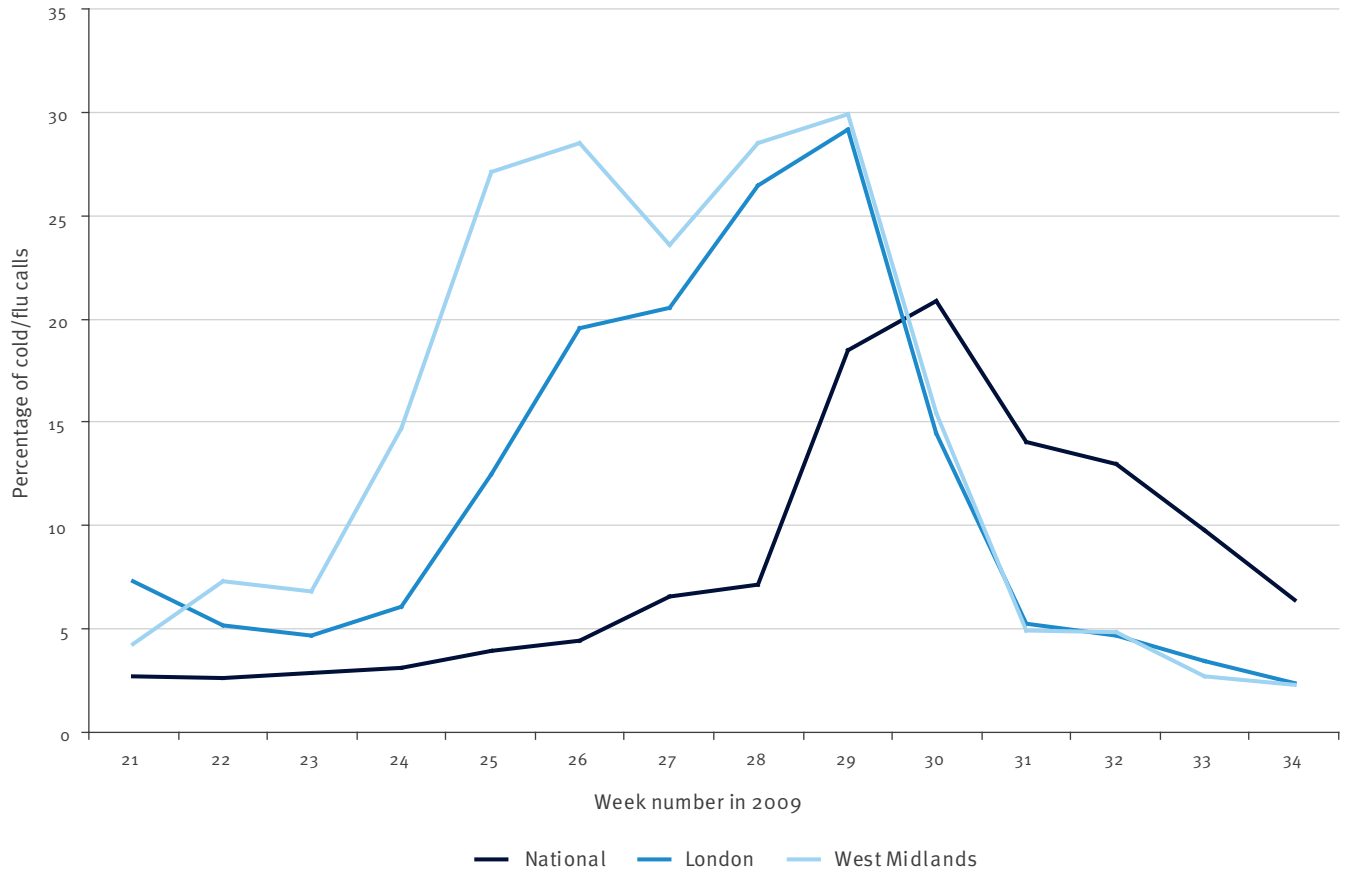
HPA/QSurveillance system

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

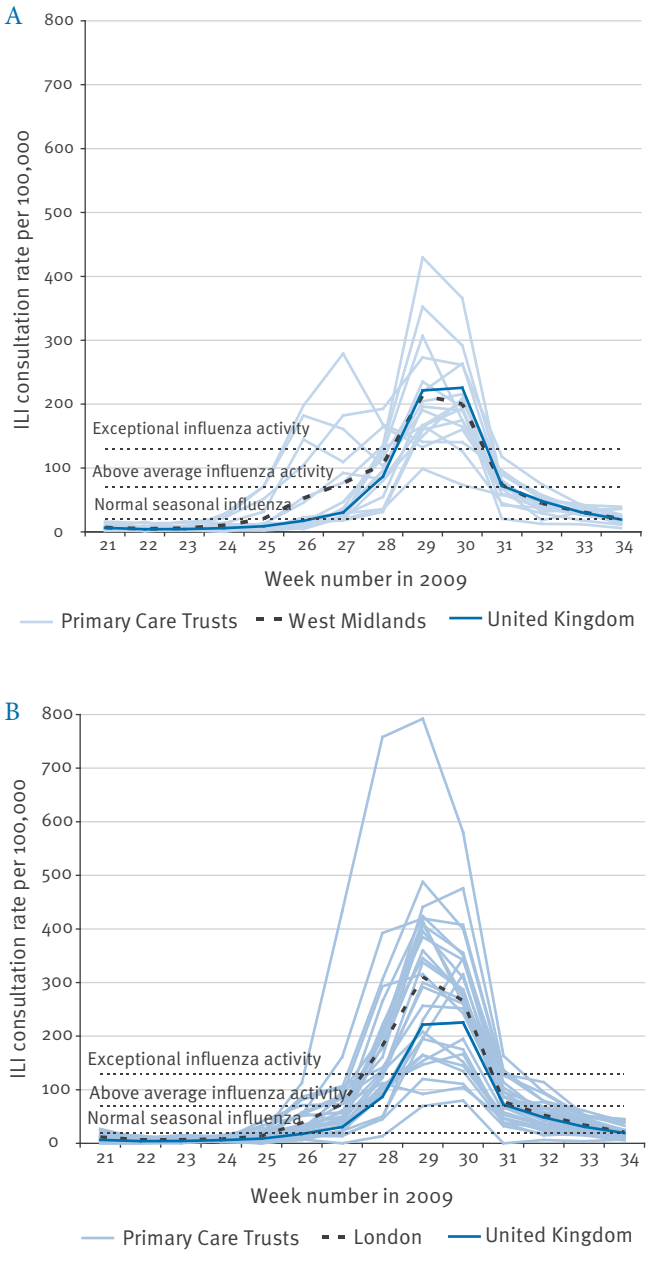
NHS Direct cold/flu calls for West Midlands and London, summer 2009



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.

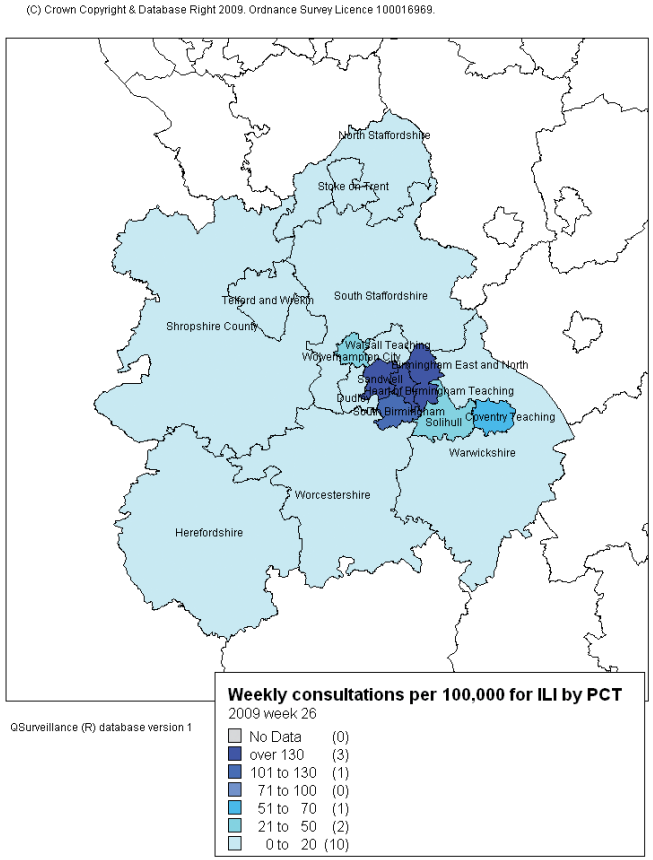
Community transmission in London started slightly later and showed a different pattern, with HPA/NHS Direct and HPA/QSurveillance systems both showing a single peak in week 29, the same week as the West Midlands peak, one week ahead of the national peak (Figures 1 and 2). HPA/QSurveillance ILI rates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

Figure 3

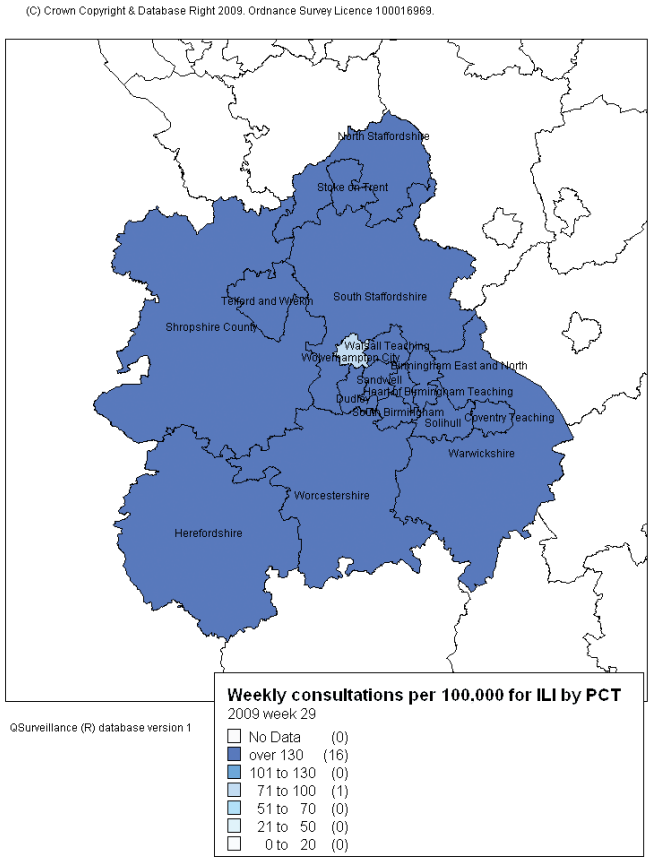
Weekly HPA/QSurveillance consultation rates for influenza-like illness by PCT and cold/flu calls to the HPA/NHS Direct Syndromic Surveillance System by postcode district for West Midlands and London, summer 2009

West Midlands, QSurveillance

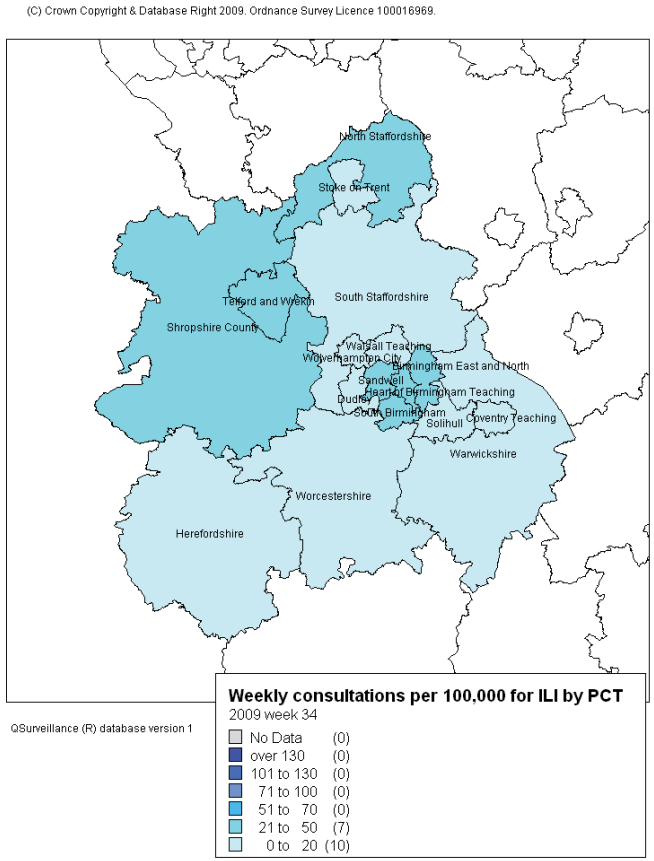
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)

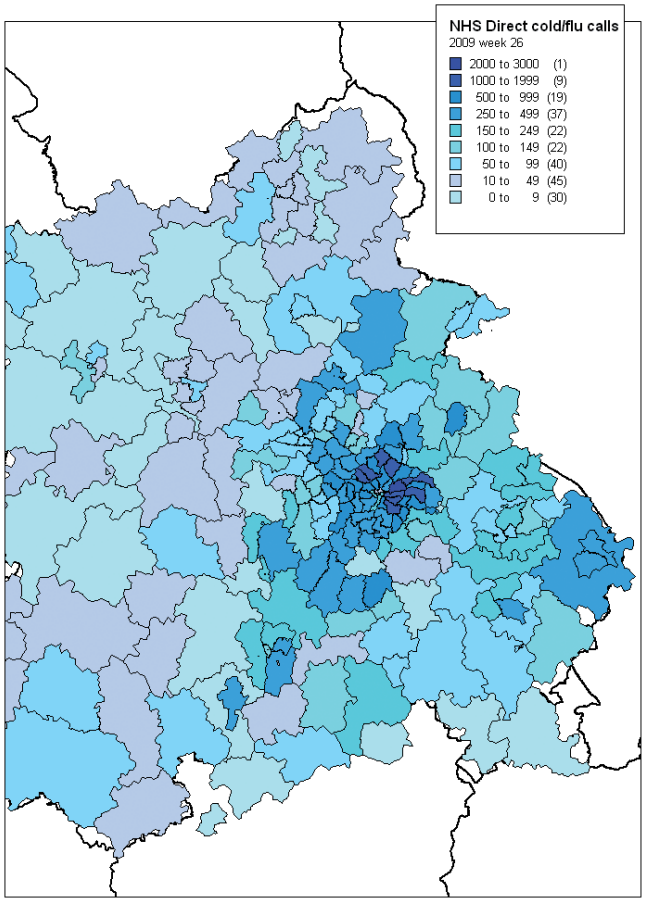


Week 34 (17-23-August 2009)

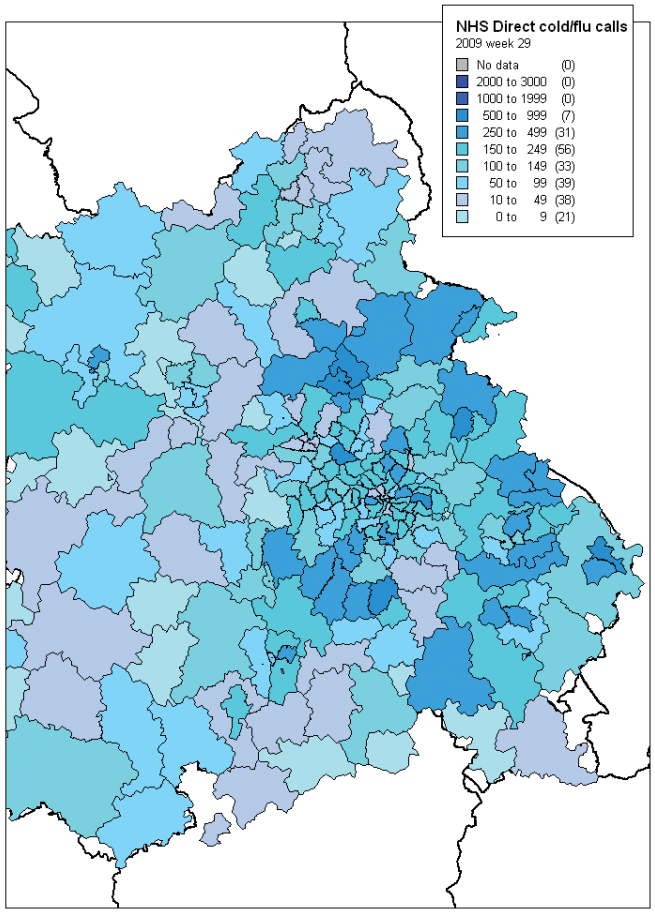


West Midlands, NHS Direct

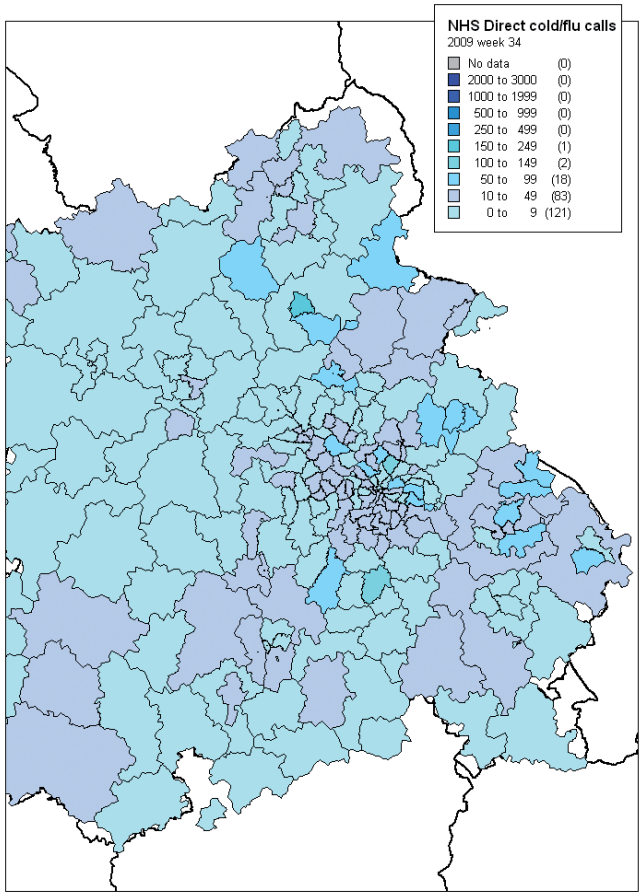
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)

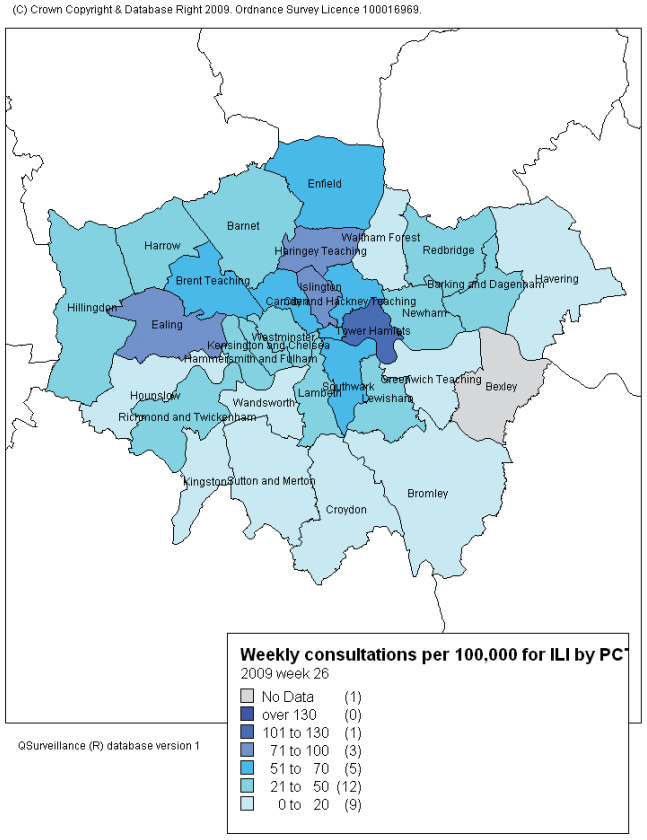


Week 34 (17-23-August 2009)

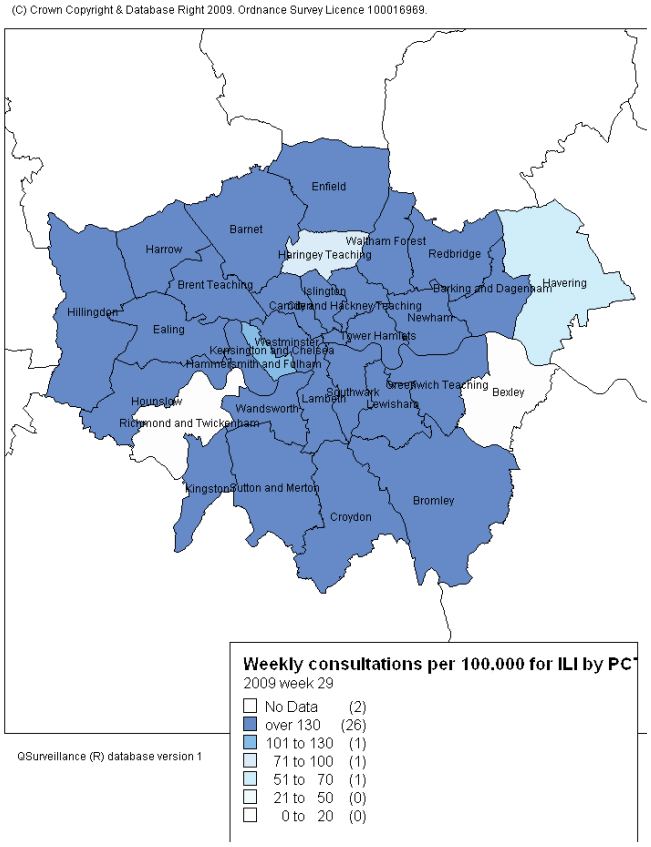


London, QSurveillance

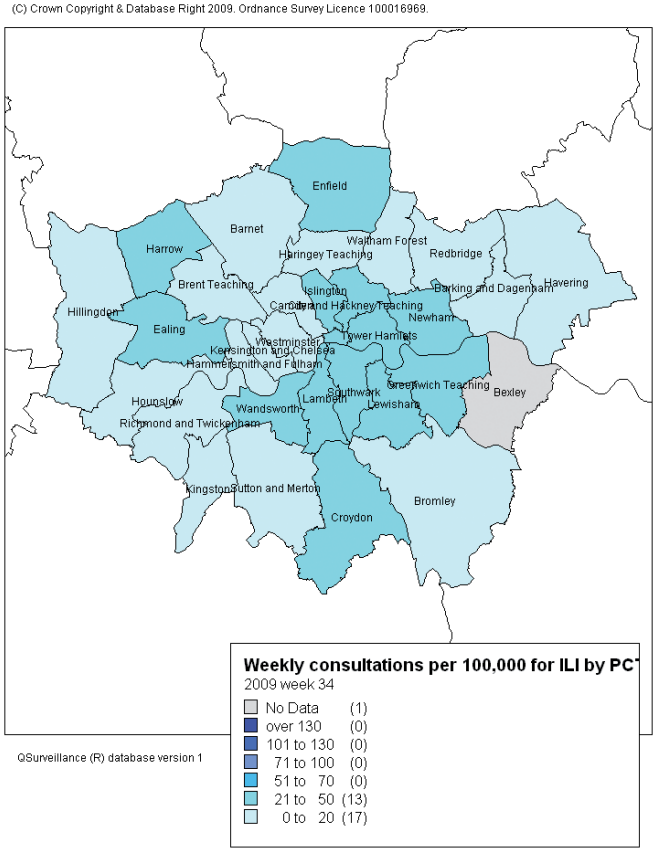
Week 26 (22-28 June 2009)



Week 29 (13-19 July 2009)

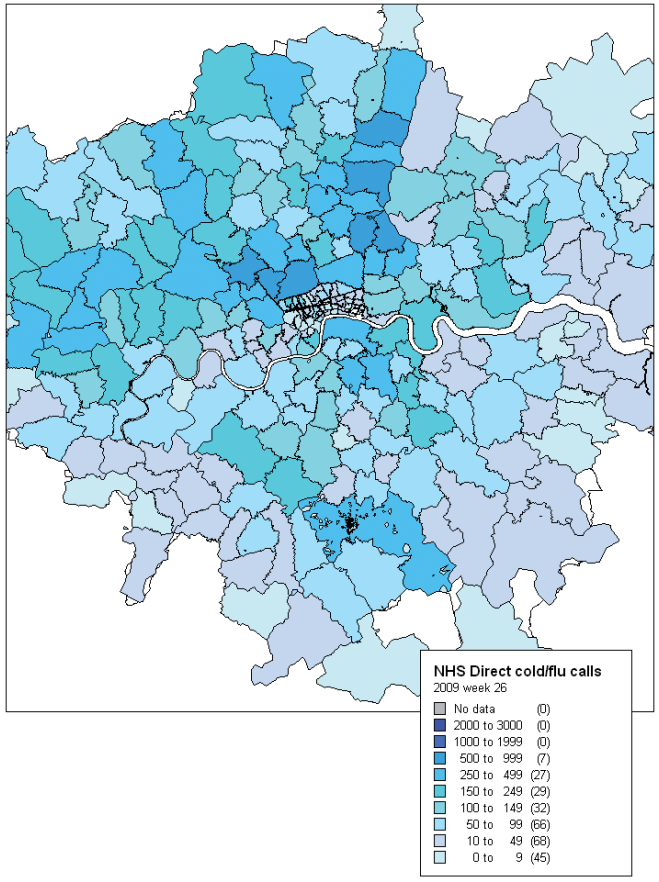


Week 34 (17-23-August 2009)

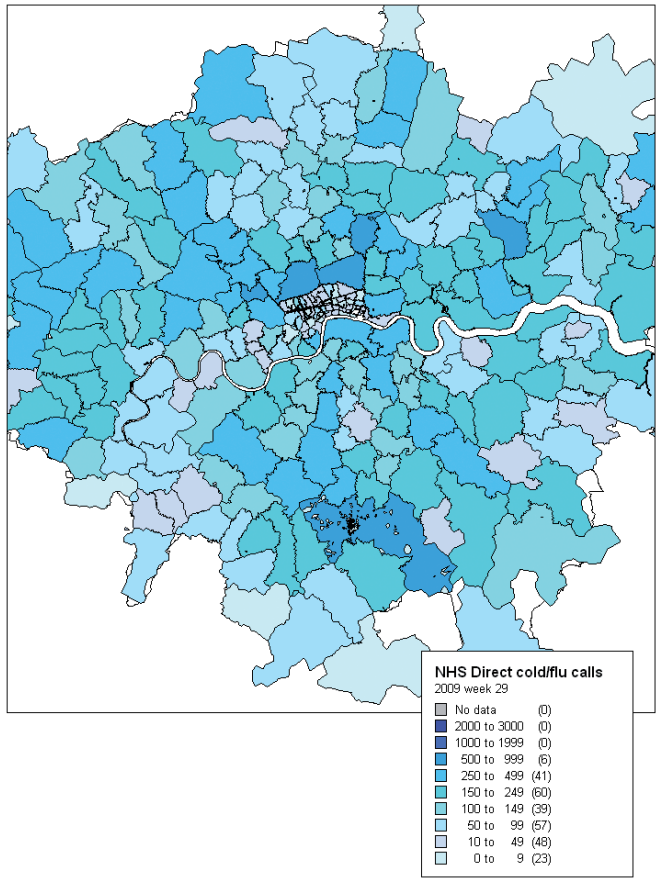


London, NHS Direct

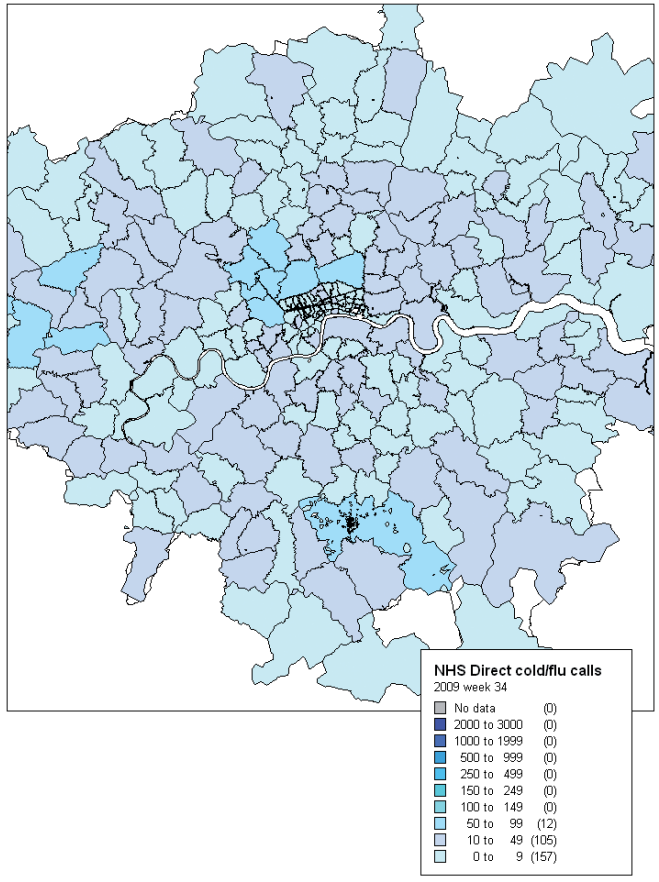
Week 26 (22-28 June 2009)



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

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Article published on 20 January 2011

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

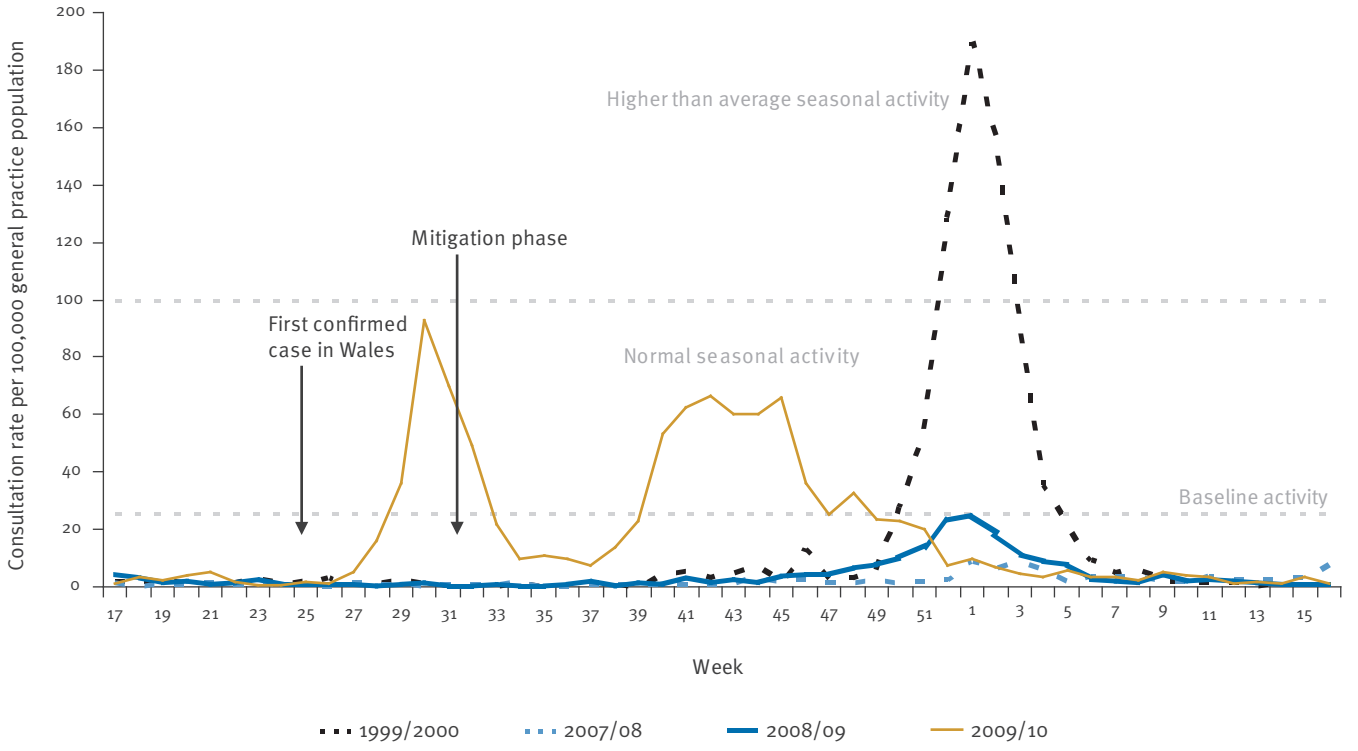
During the first wave, there were 44 hospital admissions and one patient died from confirmed influenza A(H1N1)2009. By contrast, the second wave resulted in substantially more hospital admissions (n=379), despite lower ILI consultation rates in GP, including over 60 admissions to intensive care units 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

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.

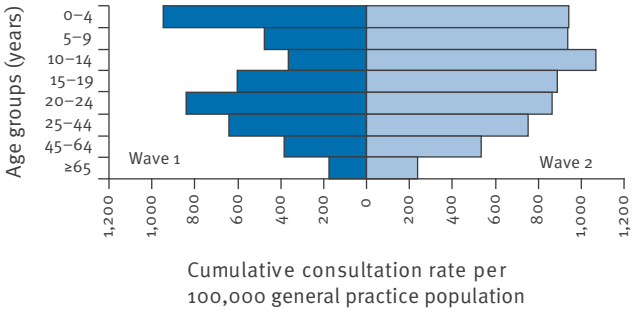
Source: Public Health Wales (general practitioner sentinel surveillance scheme).

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.

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.

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



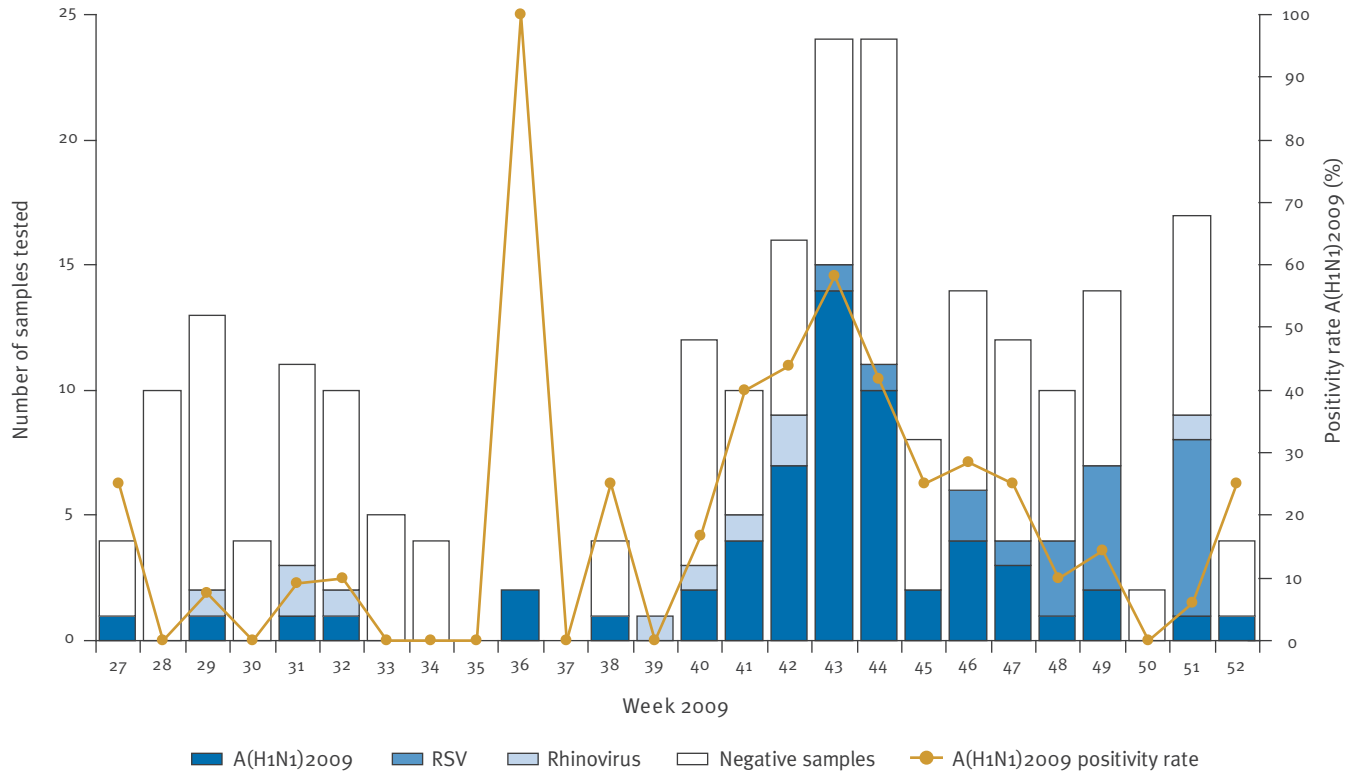
Source: Public Health Wales (Rapid general practitioner surveillance of influenza using Audit+).

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

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.

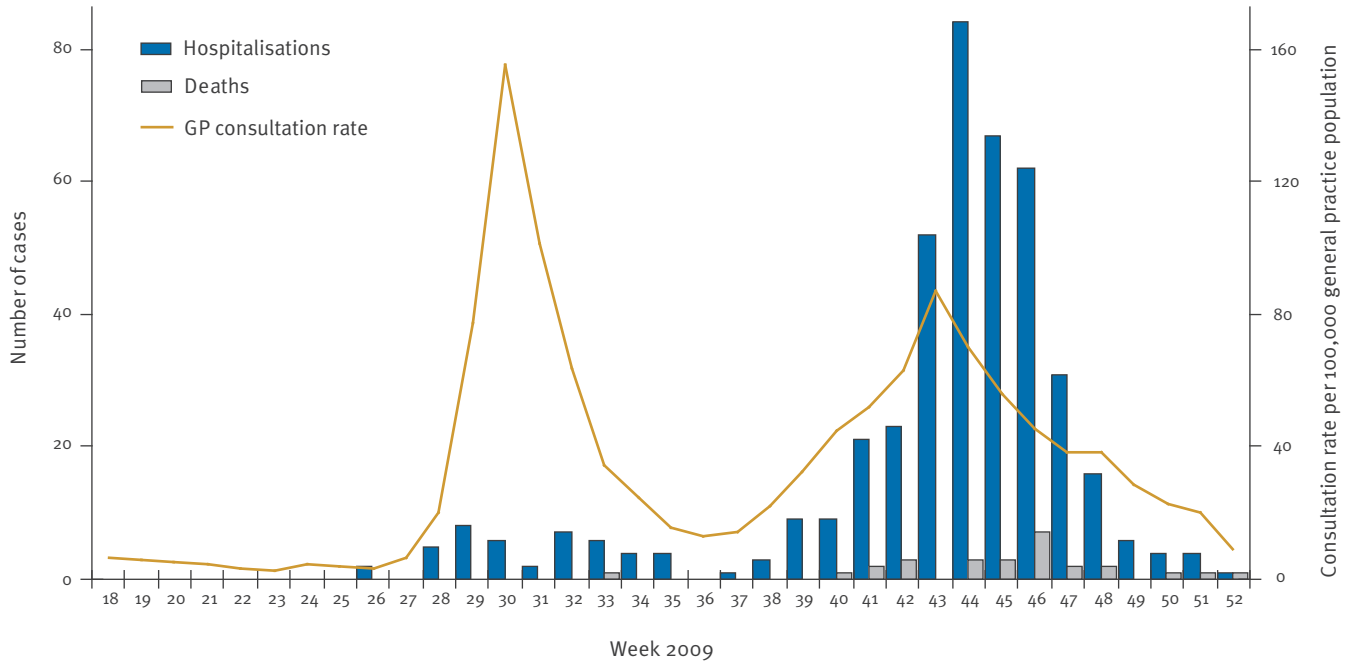
[a] In week 36 only two samples were tested, both were positive.

Source: Public Health Wales (regional virus laboratory).

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

Figure 4

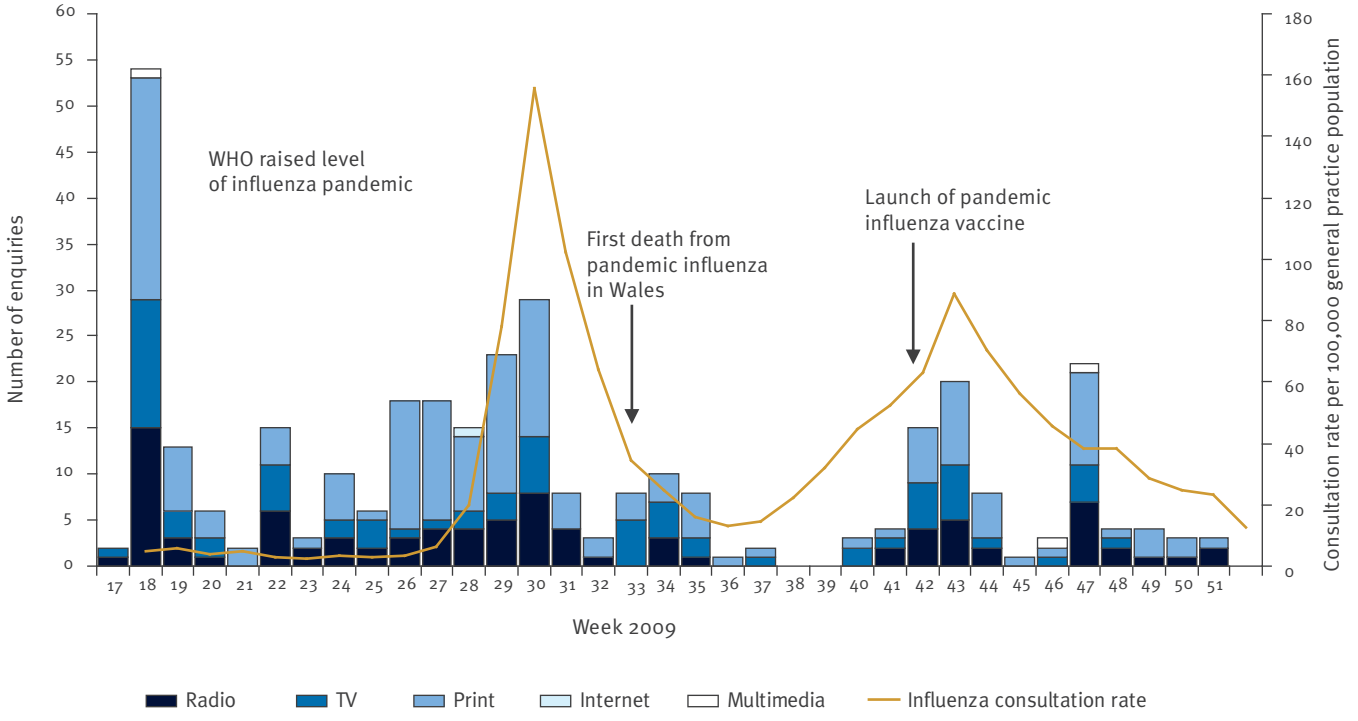
Consultation rates for influenza-like illness, and admissions to hospital and deaths from influenza A(H1N1)2009, Wales, United Kingdom, weeks 18–52, 2009



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+).

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.

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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

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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 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.

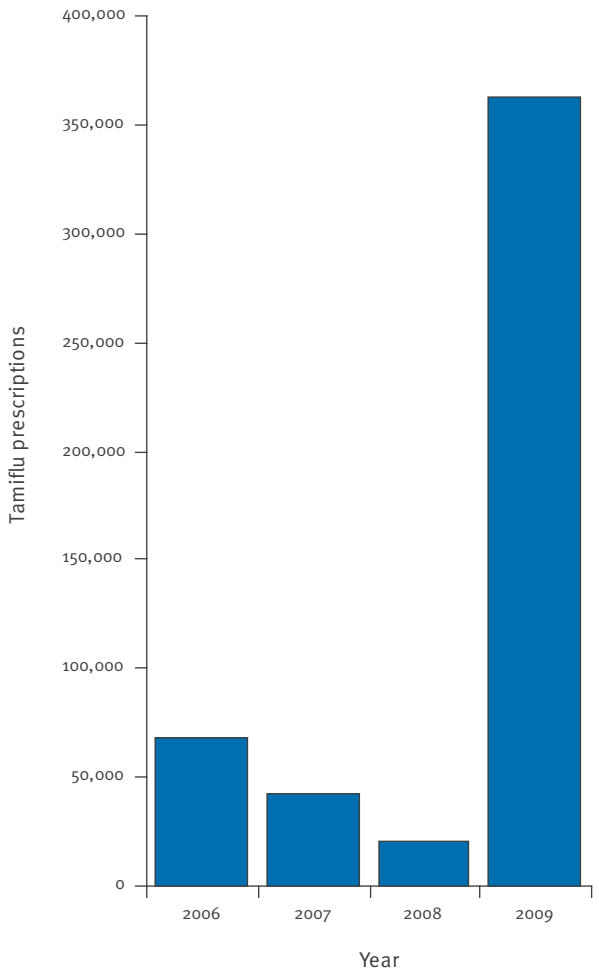
Early analysis of the pandemic influenza A(H1N1)2009 strain revealed that it was susceptible to the NAIs but was resistant to the adamantanes, an older class of anti-influenza drugs that inhibit the M2 ion channel [7]. In the early months of the pandemic and prior to the production and availability of 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 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.

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.

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 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 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.

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).

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 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

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.

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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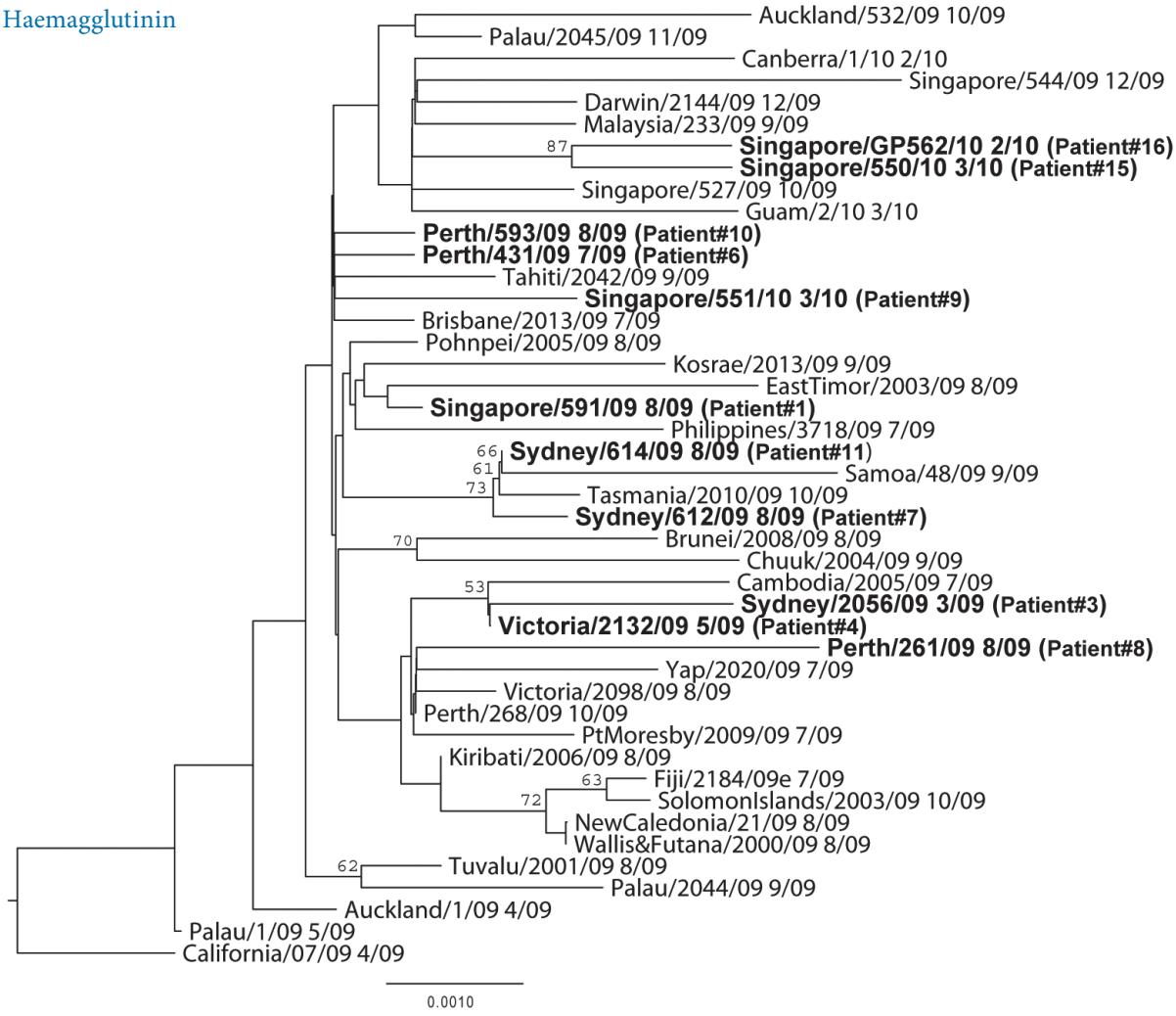
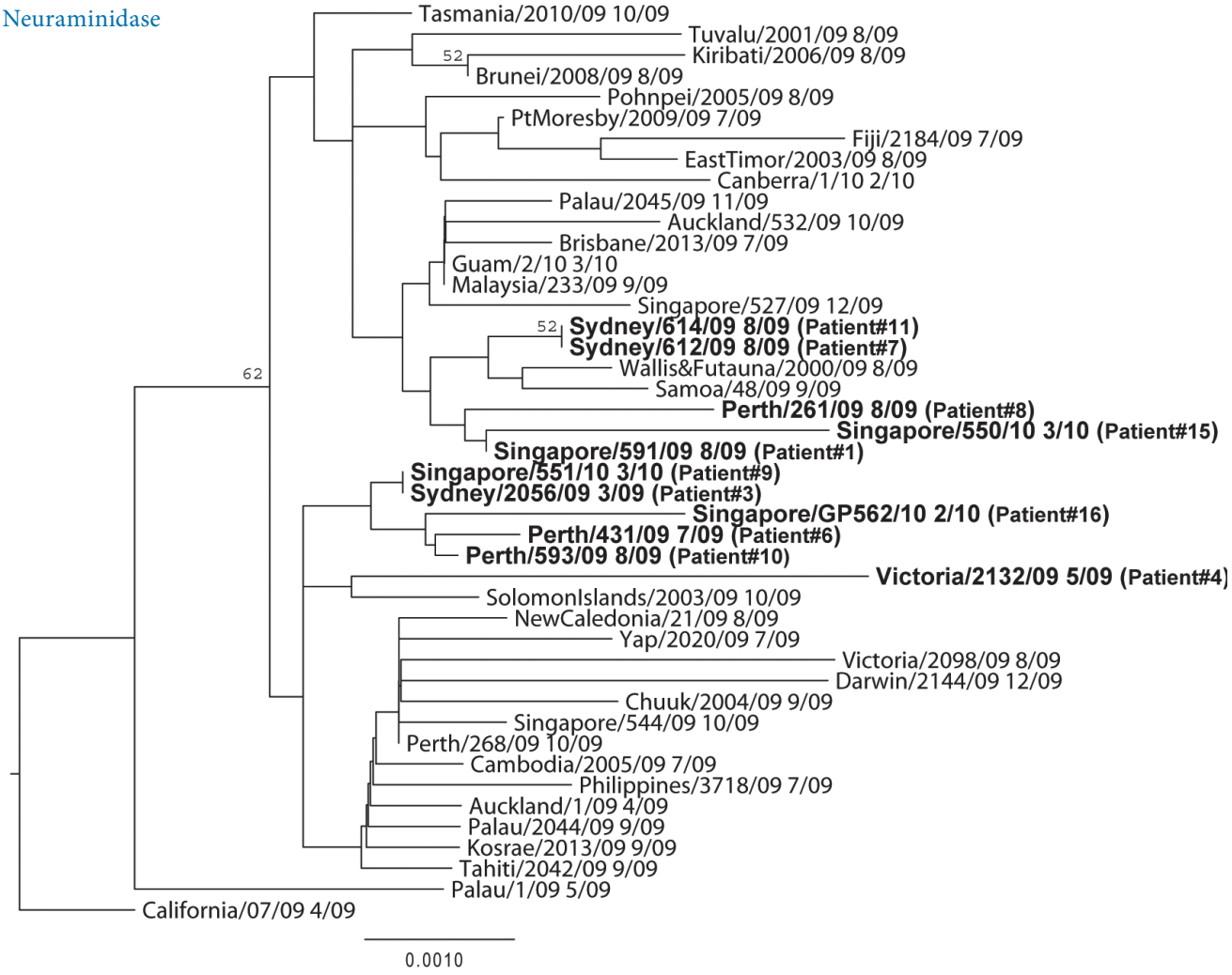
Figure 2

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



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.

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

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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

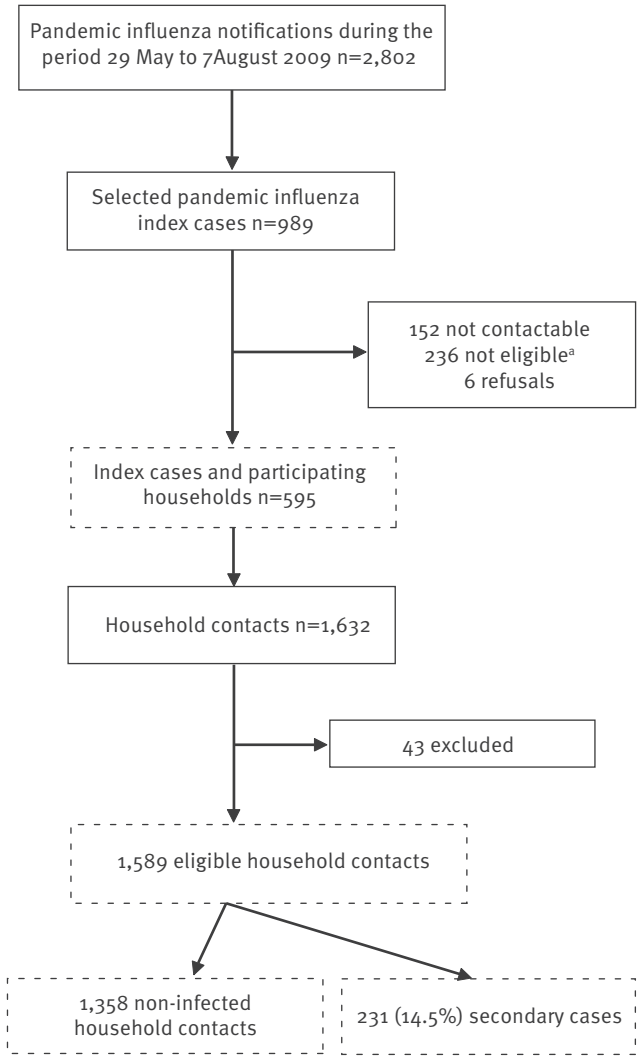
Pandemic influenza index cases and their household contacts were recruited during a ten-week period encompassing the peak of pandemic influenza activity, from 29 May 2009 (four days after notification of the first confirmed case in WA), to 7 August 2009 [13]. Influenza is a notifiable disease in Australia, 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 investigation (Figure 1). Participating index cases were

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.

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).

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.

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.

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)

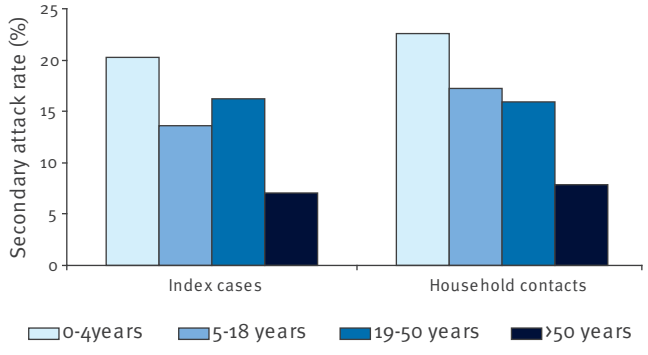
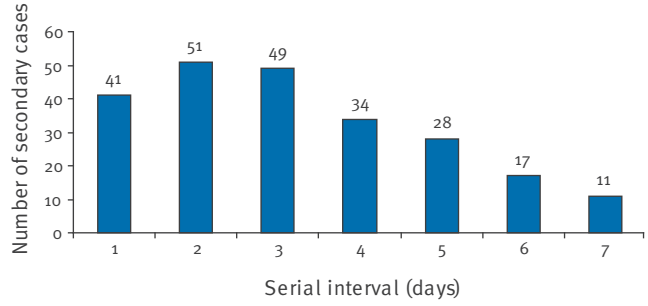


Figure 3

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)



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.

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 symp-

tomatic 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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WHO publishes report on health and health inequalities based on data from the Eurostat Labour Force Survey

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The World Health Organization (WHO) has recently published a report based on data from Eurostat, the statistical office of the European Union (EU). The report, "What does Eurostat's Labour Force Survey say about health and health inequalities in the European Union", is only available online [1].

The publication analyses data made available recently from the Eurostat Labour Force Survey [2] and seeks to measure health and socioeconomic inequalities in health. It includes data from 25 European countries and covers the period 1983-2004.

The report concludes that 'the Labour Force Survey may add a useful and hitherto unexploited resource for measuring socioeconomic inequalities in health across European countries and over time. Future research should use the Labour Force Survey data to try to identify and measure the drivers of health inequalities in the region'.

The main limitations of the report as stated by the authors are that while they consider the potential of the Labour Force Survey dataset to be of importance, it has limitations from a health perspective because its health information is exclusively related to various dimensions of absence from the workplace due to illness, or to being employed.

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