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SYNDROMIC SURVEILLANCE: THE NEXT PHASE OF PUBLIC HEALTH MONITORING DURING THE H1N1 INFLUENZA PANDEMIC?

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In this edition of *Eurosurveillance*, Coory and colleagues describe the use of a deputising medical service for influenza-like illness (ILI) surveillance in Australia [1]. They validate these novel surveillance data against a traditional general practitioner (GP) sentinel network. The use of sentinel GP surveillance networks is considered the gold standard of influenza surveillance in many European countries and formed the basis of the European Influenza Surveillance Scheme (EISS), which tracked seasonal influenza across 30 European countries from 1996 to 2008 [2]. Coory *et al.* demonstrate that the data collected from the deputising medical service were comparable with the sentinel GP data, thus illustrating the potential of these novel surveillance data to track influenza.

We are now in the midst of the first influenza pandemic the world has experienced for over 40 years. The pandemic influenza A(H1N1)v virus spread surprisingly quickly: the initial cases detected in North America and Mexico during the first few weeks of April 2009 [3,4] were quickly followed by detection in other countries, and by the end of April, the virus had spread to over 123 countries. To date (25 October 2009), it is estimated that there have been over 440,000 laboratory-confirmed cases [5]. Despite initial fears regarding the relatively high mortality rate in Mexico, the pandemic H1N1 influenza infection has so far generally presented with relatively mild acute respiratory symptoms. During the early stages of the pandemic the majority of deaths occurred in the Americas, with the only other recorded deaths in Australia, the Philippines, Spain, Thailand and the United Kingdom (UK) [6]. Currently (25 October 2009), the estimated number of deaths is at least 5,700; these deaths now are more widespread across the globe, however the main burden still lies in the Americas [5].

There are several ways of tracking the spread of influenza and estimating the burden of disease within the community. Monitoring confirmed laboratory reports, GP-diagnosed episodes of disease, emergency department (ED) attendances, hospital admissions and excess deaths are all methods employed by public health authorities. Laboratory-confirmed case reporting of influenza was used to track the initial pandemic H1N1 influenza cases during the first months of the outbreak. However, in some countries the number of cases then increased markedly, resulting in a change of policy from 'containment' to 'treatment'. In these situations, the large number of cases makes it impractical to use laboratory testing to confirm each case and therefore, the use of syndromic

surveillance takes precedence as the primary means of estimating the community burden of pandemic influenza infections.

The origins of the recent increase in the use of syndromic surveillance can be traced to the United States (US), where the use of data from secondary healthcare facilities for sentinel surveillance is relatively common (though few systems are national). The response to the threat from (bio)terrorist activities since the events on 11 September 2001 has increased the frequency of such systems which are now common in individual states [7-10]. One of the first syndromic surveillance systems to evolve from the anti-terrorist response started in New York City, where ED patient attendances with 'chief complaints' are monitored on a daily basis [11].

Although the US have been the main focus of syndromic surveillance (predominantly ED systems), other international groups have developed similar systems, now including the current paper by Coory *et al.* in this edition of *Eurosurveillance* [1]. A French syndromic surveillance system (Oscour®) was developed in response to the European heatwave in summer 2003 [12]. Amongst a range of infections, this system has been utilised to monitor influenza and norovirus activity, and has also been used to report on potential heatwave-related morbidity in France [13]. Although the main focus of these systems has concentrated on monitoring respiratory [13,14] and gastrointestinal infections [15-17], the systems have in some cases included linkages with mortality data [13].

In the UK, a combination of sentinel GP surveillance and data from telephone-health lines comprise the current national syndromic surveillance capability, although it is hoped that this will be expanded to use other sources such as ED attendances and GP out-of-hours provisions. Sentinel GP networks have been in operation for over 40 years in the UK: the Royal College of General Practitioners (RCGP) Weekly Returns Service (WRS) has provided continuous weekly reporting of GP-diagnosed ILI incidence rates in England and Wales since 1967 and monitored the 1968-1969 influenza pandemic which impacted on the UK during the winter 1969-1970 [18]. QSurveillance® is a UK-based GP system that, since 2005, operates on a larger scale (in terms of both geographic coverage and patient population) compared to the RCGP WRS [19]. NHS Direct is a nurse-led telephone helpline run by the National Health Service (NHS) in England

and designed to triage callers based on presentation of symptoms [20]. The syndromic surveillance system operated by NHS Direct and the Health Protection Agency (HPA) uses these symptom-based telephone call data to provide real-time daily monitoring of influenza, and other seasonally occurring communicable diseases such as norovirus infections [21,22]. The main advantage of these systems is the provision of data in real-time, i.e. daily reports, thus providing a much more responsive surveillance system which allows early warning of potential problems. All NHS Direct data can be aggregated into specific age bands and broken down by region (including postcode analysis), which enables recognition of potential regional hot spots that might not be detected using traditional methods [23].

In the UK, there are surveillance programmes that undertake the integration of microbiological investigation into syndromic surveillance systems. Since 1992, the RCGP WRS sentinel GP system has, in collaboration with the HPA, undertaken virological investigation of a sample of patients diagnosed with ILI [24]. Results from this scheme are vital in providing the earliest community-based influenza virus isolations during an influenza season, providing information on the circulating influenza virus types/subtypes, potential virus-vaccine mismatch, vaccine effectiveness and the emergence of antiviral resistance. In addition, community-based respiratory samples from this system have been used retrospectively to assess the impact of newly discovered pathogens, e.g. human metapneumovirus [25]. In recent years the NHS Direct/HPA syndromic surveillance system has also been used to obtain clinical samples from patients calling the helpline. The novel aspect of this system is the self-sampling protocol which involves sending swabbing kits to patients who then take nasal swabs themselves and return the samples to a central laboratory [26]. Results from this pilot study were encouraging, and this has now been rolled out in the current pandemic situation in England to assess the frequency of community-based pandemic H1N1 influenza infections [27].

A potential disadvantage of using syndromic surveillance systems is the lack of specificity of the data collected. Laboratory reporting of confirmed cases provides an accurate representation of how many cases are positive for the pathogen of interest. Syndromic surveillance monitors disease patterns using syndromic indicators, which are primarily based upon clinically diagnosed (but not confirmed) episodes or symptom presentation. However, previous work has shown that despite these limitations, syndromic data can be extremely sensitive to community-based infections and act as potential early warning of imminent problems. This 'broad brush' approach of using non-specific indicators may capture patients who do not specifically meet the case definition, e.g. ILI. Experience from using the NHS Direct/HPA syndromic surveillance system has demonstrated that calls for 'fever' in children aged between five and 14 years can be used as an early warning indicator of influenza activity [28]. Fever calls in this age group are sensitive to increasing community-based influenza activity, thus demonstrating that using an indicator that is not based upon a range of presenting symptoms associated with influenza can be reliably used to monitor influenza activity [28].

Another potential disadvantage of syndromic surveillance is the impact of media reporting. In situations such as the outbreak of severe acute respiratory syndrome (SARS) in 2003, and the current H1N1 influenza pandemic, the mass media reporting on these

events can cause anxiety amongst the population. This can prompt symptomatic patients, who would normally have self-treated their symptoms, to seek healthcare advice such as a GP consultation or a call to NHS Direct. It is therefore very difficult to disentangle the effects of media reporting from the true burden of infection in the community, and without laboratory reporting it is not possible to estimate the proportion of true positives.

Syndromic surveillance constitutes the use of data systems that do not rely on confirmatory laboratory testing of patient samples. In principle, the data used in syndromic surveillance are primarily collected for other purposes, e.g. clinical management of patients. The general advantage of these systems is the provision of data that are timelier than traditional laboratory reporting, i.e. 'real-time'. In most cases, fewer resources are required to maintain the systems. They also have the potential to cover a greater range of disease indicators and therefore can be used to monitor many different scenarios within public health protection. This also includes the surveillance of non-infectious public health issues such as bioterrorist threat, chemical incidents, natural phenomena such as heatwaves or flooding, and mass gathering events, for instance the Olympic Games.

In recent years, there have been moves to utilise the massive potential of the internet for surveillance purposes. The health information seeking behaviour of the population has now changed with the wealth of online help available: in response, Google.org has released *Google Flu Trends*, a system that monitors influenza-based search queries from the Google search engine. Analyses of data collected from the US were modelled using CDC sentinel GP surveillance data with remarkably high correlation between the two data series [29]. This work has now been transposed to a publicly accessible website that uses this system to monitor regional influenza activity in the US, and has more recently expanded to cover Australia, New Zealand, Mexico and Europe [30,31]. In this week's issue of *Eurosurveillance*, Wilson *et al.* present a rapid communication comparing results from *Google Flu Trends* with data from existing surveillance systems in New Zealand [32].

The continuing advancement of syndromic surveillance is providing further public health monitoring of infectious diseases, and in particular influenza. Novel systems such as internet-based search queries are providing a new aspect to the established systems and thus providing another piece of the syndromic surveillance jigsaw.

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Rapid communications

SURVEILLANCE OF THE FIRST 205 CONFIRMED HOSPITALISED CASES OF PANDEMIC H1N1 INFLUENZA IN IRELAND, 28 APRIL – 3 OCTOBER 2009

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From 28 April 2009 to 3 October 2009, 205 cases of confirmed pandemic H1N1 influenza were hospitalised in Ireland. Detailed case-based epidemiological information was gathered on all hospitalised cases. Age-specific hospitalisation rates were highest in the age group of 15 to 19 year-olds and lowest in those aged 65 years and over. Nineteen hospitalised cases (9%) were admitted to intensive care units (ICU) where the median length of stay was 24 days. Four hospitalised cases (2%) died. Fifty-one percent of hospitalised cases and 42% of ICU cases were not in a recognised risk group. Asthma was the most common risk factor among cases; however, people with haemoglobinopathies and immunosuppression were the most over-represented groups.

Introduction

In late April 2009, a novel influenza virus led to human infection in Mexico and the United States (US) and subsequently spread worldwide. On 11 June, 2009, the World Health Organization (WHO) declared a phase 6 pandemic of moderate severity [1].

The first case of pandemic influenza in Ireland was diagnosed on 28 April 2009. Existing surveillance systems were augmented and enhanced case-based surveillance of pandemic H1N1 influenza was commenced. Until mid-July, all cases of influenza were actively followed up; most cases were imported, mainly from the US, the majority were in young adults and there were few hospitalisations [2]. On 16 July Ireland moved to mitigation, and detailed case-based surveillance was confined to hospitalised cases. Influenza-like illness (ILI) presentations to sentinel general practices remained below the seasonal threshold (17.8/100,000) between April and mid-July [3]. By late July, the ILI rate reached 35 per 100,000 population and fluctuated around this level until mid-September. Since then ILI rates have risen, reaching 87.3 per 100,000 population in the week ending 3 October [3].

The WHO has recommended that countries undertake case-based surveillance on the first 200 hospitalised cases, as it is important to identify those most at risk of adverse outcomes, hospitalisation and death due to pandemic H1N1 influenza. To date, there is

limited research on risk factors associated with adverse outcomes in Europe [4-11] and therefore, we report on the enhanced case-based surveillance of the first 205 hospitalised cases of confirmed pandemic H1N1 influenza in Ireland.

Methods

Enhanced surveillance was undertaken on all cases of confirmed pandemic H1N1 influenza deemed to require admission to hospital for management of their illness by the treating clinician. Regional Departments of Public Health or the treating hospital clinician completed the enhanced surveillance form. Data collected included demographic details, premorbid medical conditions and pregnancy, antiviral therapy, and complications associated with influenza. Data on asthma and chronic respiratory disease were collected separately, based on findings from elsewhere which indicated that asthma was a significant risk factor [8,10]. These data were checked by the Departments of Public Health for completeness and cases identified with missing or inconsistent data were followed up and the information corrected. Surveillance and laboratory data were collected on the Irish computerised infectious diseases reporting system (CIDR). The Health Protection Surveillance Centre (HPSC) analysed the data. Analysis of variance (ANOVA) was used to test the effect of age on length of stay.

The prevalence of diseases/risk factors in the population was collected using a variety of methods. Data from the Cystic Fibrosis Registry [12], National Cancer Registry [13] and Infectious Disease Registry [14] were extracted to quantify numbers of people in the population with cystic fibrosis, certain malignancies and acquired immunodeficiency syndrome (AIDS). Hospital In-Patient Enquiry (HIPE) data over four years was used to estimate the prevalence of liver, renal disease and asplenia [15]. The prevalence of haemoglobinopathies was based on personal communication from the clinician with national responsibility for this disease group [16]. The number of pregnant women was extrapolated from the number of births in 2008 [17].

Other estimates were calculated by applying disease prevalence estimates from Irish or international data to the Irish population

recorded by the Central Statistics Office (CSO) [17]. Prevalence of asthma and diabetes was estimated extrapolating from prescription data in the Primary Care Re-imbursement Service (PCRS) system (the national scheme providing free medical services to those unable to afford these services without undue hardship; approximately 25% of the population are eligible [18]). Irish and international prevalence studies were used for chronic heart disease [19], respiratory disease [20], obesity [21,22] and neurological disease [23].

Length of stay was calculated as the time from date of admission to date of discharge, or if still in hospital, from date of admission to the date of data extraction from CIDR for analysis (13 October).

Results

During the period from 28 April to 3 October 2009, 205 confirmed cases of pandemic H1N1 influenza were hospitalised, of whom 19 (9.3%) were admitted to ICU.

Of the 205 confirmed hospitalised cases, 106 were female (51.7%). The median age of cases was 21 years (mean age: 25 years; range: five months to 78 years). Seventy-five percent of cases were in persons under 35 years of age (Figure 1).

From mid-July there was an increase in the numbers of people hospitalised and admitted to ICU with pandemic H1N1 influenza (Figure 2).

Age-specific hospitalisation rates have been shifting to younger age groups over time, with the highest age-specific rate initially in teenagers and currently in children under five years (age-specific hospitalisation rate <5 years: 3.4/100,000; age-specific hospitalisation rate total population: 1/100,000) (Figure 3).

Information on medical risk factor and pregnancy were available for 180 (88%) of the 205 hospitalised cases including all those

admitted to ICU. Ninety-one cases (51%), including eight ICU cases (42%) were not in a recognised risk group.

Eighty-nine cases (49%), including 11 (58%) admitted to ICU, were in a risk group (medical risk factor or pregnancy). Sixty-seven (37%) had only one risk factor, 14 (7%) had two risk factors, seven (4%) had three risk factors and one case had four risk factors.

Twelve pregnant women with pandemic H1N1 influenza were hospitalised, eleven of whom were admitted due to pandemic H1N1 influenza infection, and one was admitted for a pregnancy-related indication. Period of gestation was available for nine women admitted due to influenza; one was in the first trimester, two in the second trimester and six in the third trimester. Three women had risk factors other than pregnancy, including asthma, obesity, liver disease and immunosuppression.

Being on medication for asthma was the most common risk factor for hospitalisation due to pandemic H1N1 influenza. Chronic respiratory disease and immunosuppression were the next most common risk factors. Chronic respiratory disease was the most common risk factor in ICU admissions, followed by chronic neurological disease, asthma and severe obesity (Table 1).

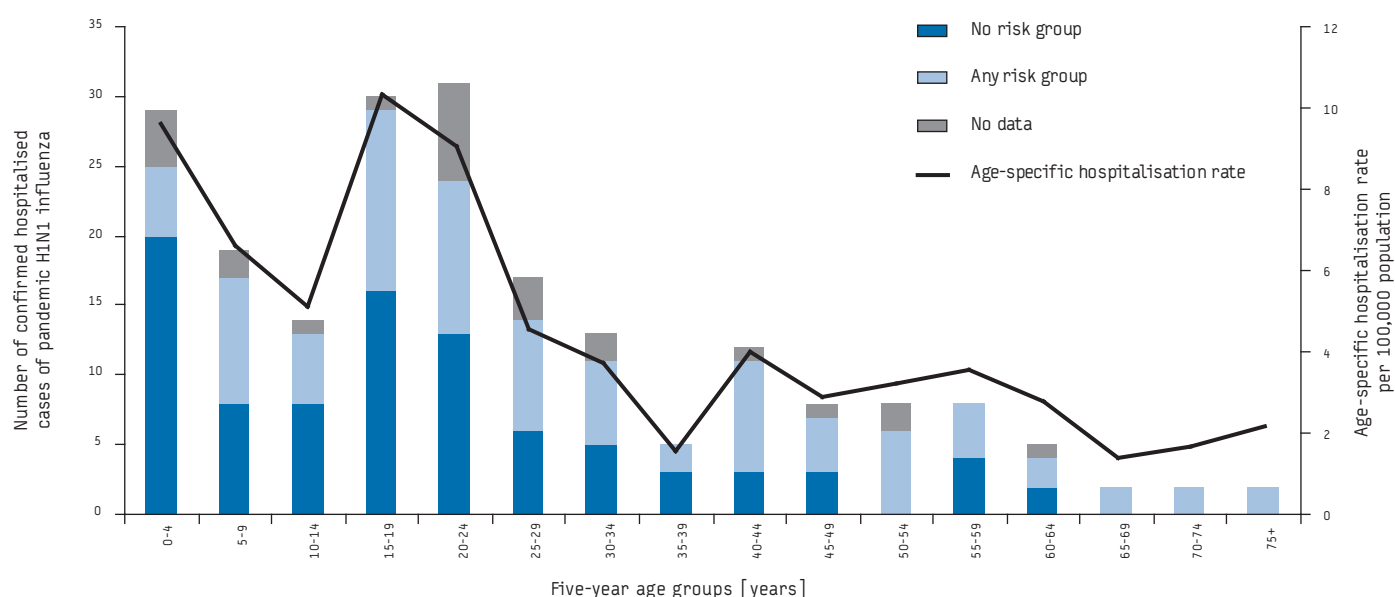
Data on antiviral treatment were available for 196 (96%) of the cases. One hundred and fifty-eight people (79%) received antiviral therapy either prior to admission or in hospital. Oseltamivir was used in 155 people (98%).

Onset date was recorded for 176 (85%) of confirmed cases. Table 2 shows the mean, median and range of the time between date of onset of symptoms and date of diagnosis, date of admission to hospital and date of admission to ICU.

Dates of admission to and discharge from hospital and/or length of stay were recorded for 198 (97%) of cases, including all ICU cases (Table 2). The median length of stay in hospital was two days

FIGURE 1

Cumulative number and age-specific hospitalisation rate for confirmed hospitalised cases, by presence or absence of risk factors, by five-year age groups, Ireland, 28 April-3 October 2009 (n=205)



for cases under the age of 24 years. While there was a large range of length of stay, there was a significant trend of increasing length of stay for those in the age groups of 25-44 year-olds and 45-64 year-olds, increasing to seven days in adults over 65 years (ANOVA: $F=3.16$, $P<0.001$) (Table 3).

Those with chronic neurological disease had the highest mean length of stay, followed by those with severe obesity and then chronic respiratory disease. Asthma, the most frequent risk factor associated with hospitalisation, was associated with a mean length of stay of six days (median: three days). Most risk-groups were associated with a wide range of length of stay (Table 4).

Data on complications were available for 177 (86%) of hospitalised cases. Forty cases (23%) developed pneumonia, 17 (43%) of whom were in a risk group. Ten people (6%) developed adult respiratory distress syndrome (ARDS), of whom six (60%)

were in a risk group. Fifteen patients (8%) were ventilated. Fourteen were ventilated in ICU and one received non-invasive ventilation on a general ward.

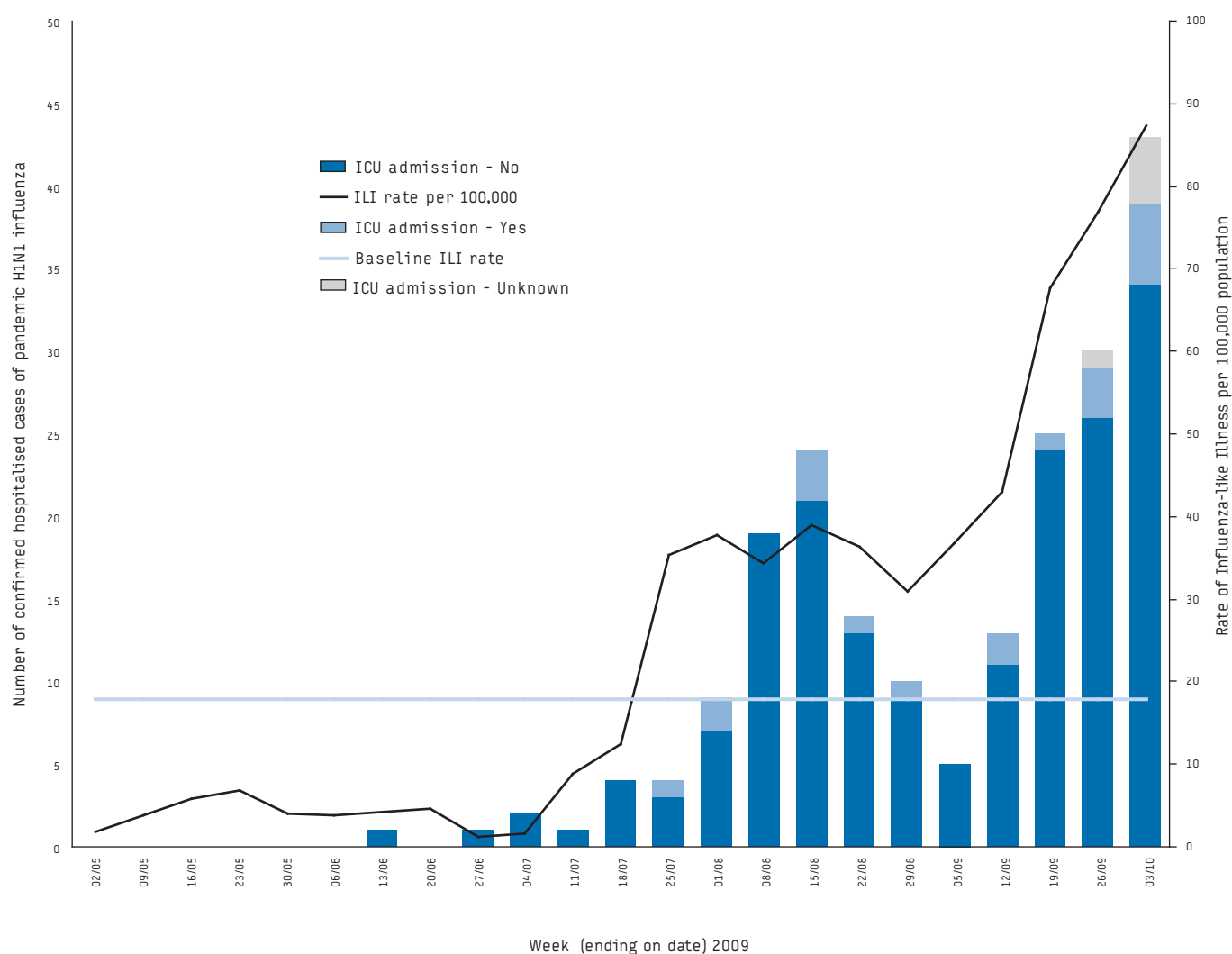
There were four deaths (2% of hospitalised cases) due to pandemic H1N1 influenza, three females and one male. Two were in the 15-24 year age-group, and two in the 50-59 year age-group. Three fatal cases (75%) had underlying risk factors.

Discussion

The epidemiology of hospitalised cases in the first months of the pandemic was similar in Ireland to other countries [24-28]. While younger age groups were more likely to be hospitalised they had shorter lengths of stay than older age groups. The age specific hospitalisation rate for children in Ireland was lower than that reported elsewhere [27,29,30]. Haemoglobinopathies and immunosuppression were the most over-represented risk factors in hospitalised cases. Pregnancy was associated with an increased

FIGURE 2

Confirmed hospitalised cases (ICU and non-ICU) of pandemic H1N1 influenza and ILI rate per 100,000 population by week, Ireland, 28 April - 3 October 2009 (n=205)*



ICU: intensive care unit; ILI: influenza-like illness.

risk of hospitalisation with the risk highest in the third trimester. Stay in ICU (median: 22 days; range: 0-72 days) was found to be much longer than reported in other countries [11,27].

The under-representation of children under the age of five years among hospitalised cases when compared with other countries

[27,29,30] may be a reflection of the stage of the pandemic wave that Ireland is currently in. It is known that the majority of cases before mid-July were imported [2] and therefore more likely to be in young adults who travel. July and August are school holidays in Ireland and this may have further limited spread among children and thus hospitalisations in children. In this time period the majority of

FIGURE 3

Age-specific hospitalisation rates (per 100,000) of pandemic H1N1 influenza, by week, Ireland, 28 April -3 October 2009 (n=205)

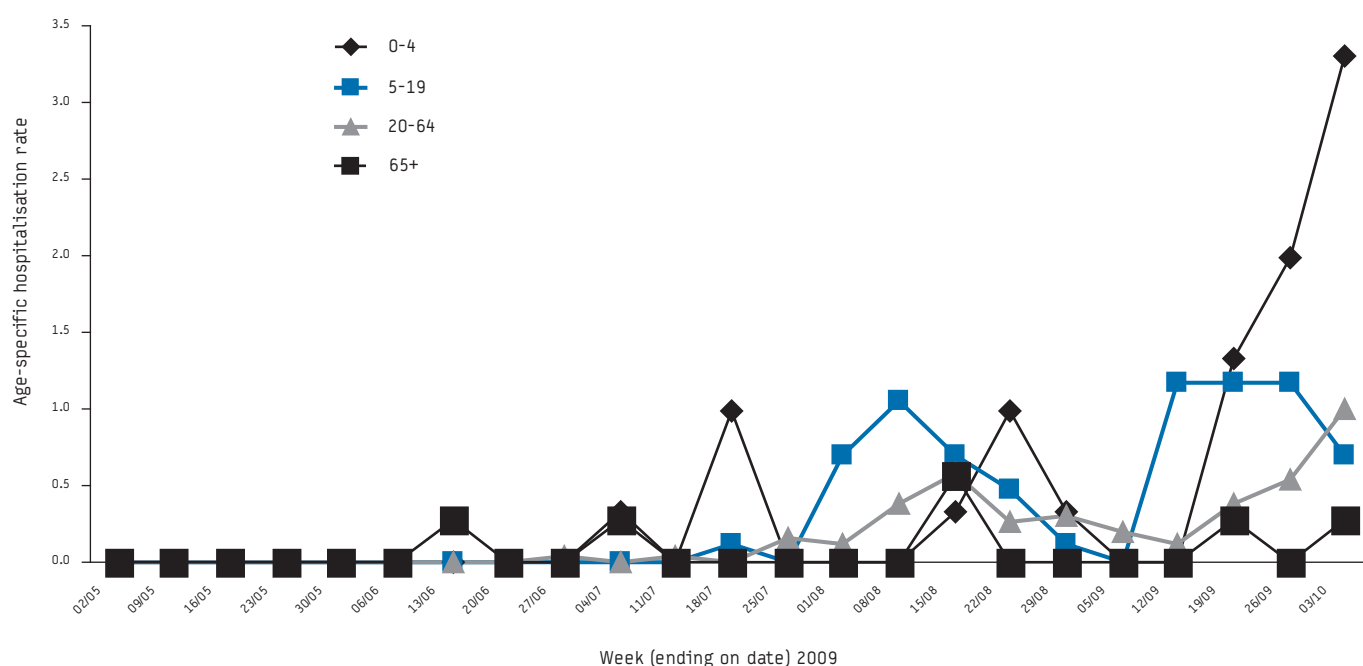


TABLE 1

Number and percentage of cases of confirmed pandemic H1N1 influenza in risk groups and in the Irish population, Ireland, 28 April – 3 October 2009 (n=180)

Risk Group	N hospitalised cases in risk group*	Risk group as a % of total hospitalised cases n=180** †	N ICU cases in risk group*	Risk group as a % of total ICU cases n=19**	Risk group as a % of total Irish population
No listed risk group	91	50.6	8	42.1	n/a
Chronic respiratory disease	18	10.0	5	26.3	6.00
Chronic neurological disease	9	5.0	2	10.5	8.89
Severely obese (BMI ≥ 40)	4	2.2	2	10.5	1.20
People on medication for asthma	32	17.8	2	10.5	11.50
Chronic liver disease	3	1.7	1	5.3	0.30
Chronic heart disease	9	5.0	0	0.0	7.60
Chronic renal disease	4	2.2	0	0.0	0.30
Immunosuppression	17	9.4	0	0.0	0.08
Haemoglobinopathies	5	2.8	0	0.0	0.01
Pregnancy	12	6.7	0	0.0	1.40
Diabetes mellitus	8	4.4	0	0.0	5.00
Post partum ≤ 6 weeks	0	0.0	0	0.0	0.20

BMI: body mass index; ICU: intensive care unit.

** A case may belong to more than one risk group and so may be counted in more than one row of this table.

** Number of cases with data on risk groups.

† ICU cases are included in the hospitalised case count.

cases in children were associated with residential summer camps [3], suggesting that it is educational settings that are most likely to result in spread in the age groups under 16-year-olds.

The ILI rates exceeded the threshold of seasonal influenza in July, but then reached a plateau in late July and August, and it was only in September (following reopening of schools) that rates started to rise again [3]. International evidence suggests that as the

TABLE 2

Time from onset of symptoms to admission to hospital, to laboratory confirmation, to admission to ICU, and length of stay associated with pandemic H1N1 influenza, Ireland, 28 April - 3 October 2009

Time period	N Cases	Mean (days)	Median (days)	Min (days)	Max (days)
Onset of symptoms to admission to hospital	176	3	1	0	20
Onset of symptoms to laboratory confirmation†	174	5	4	0	26
Length of stay in hospital* **	198	6	3	0	79
Onset of symptoms to admission to ICU	16	6	5.5	1	20
Length of stay in ICU - all patients	19	25	22	0	72
Patients discharged from ICU	8	21	8	0	72
Patients in ICU on 13 October 2009**	11	28	25	13	62

ICU: intensive care unit.

* ICU and non-ICU cases combined.

** Data extracted on 13 October 2009; only cases confirmed by 3 October 2009 are included.

† Time to laboratory confirmation is longer than time to admission reflecting time taken for laboratory confirmation.

TABLE 3

Length of hospital stay of pandemic H1N1 influenza cases, by age group, Ireland, 28 April - 3 October 2009 (n=198)

Age group [years]	Mean (days)	Median (days)	Min (days)	Max (days)
0-4	5	2	1	30
5-14	3	2	1	12
15-24	4	2	0	37
25-44	8	3	0	65
45-64	11	5	1	60
65+	8	7	6	11

TABLE 4

Length of hospital stay by risk group, Ireland, 28 April-3 October 2009 (n=180)

Risk Group	Length of Stay*				
	N Cases**	Mean (days)	Median (days)	Min (days)	Max (days)
Chronic neurological disease	9	15	8	2	62
Severely obese (BMI ≥ 40)	4	13	10	2	28
Chronic respiratory disease	17	12	6	1	60
Chronic liver disease	3	11	11	2	19
Chronic heart disease	9	7	7	1	12
Chronic renal disease	4	6	6	1	12
Immunosuppression	17	6	4	1	22
People on medication for asthma	32	6	3	0	37
No listed risk group	86	5	2	0	79
Haemoglobinopathies	5	5	3	2	11
Pregnancy	12	4	3	1	11
Diabetes mellitus	8	4	3	1	7
Post partum ≤ 6 weeks	0	-	-	-	-

BMI: body mass index.

*Length of stay based on date of analysis for those still in hospital

** A case may belong to more than one risk group and so may be counted in more than one row of this table. Only cases where length of stay is available are included

overall number of cases of pandemic H1N1 influenza increases, the age-specific incidence of hospitalisations will shift to younger age groups [10,31]; the same shift is being seen in cases in Ireland. However, in other countries, highest hospitalisation rates were seen in the children under the age of five years at all stages of the pandemic wave, although the magnitude of this difference varied over time [27,31,32].

The under-representation of young children may reflect an ascertainment bias, as children may not present with typical ILI symptoms, and the diagnosis might not have been considered. This has been reported for seasonal influenza [33].

Some patients have an extremely protracted ICU stay, with a number of current patients in ICU in excess of 60 days. There were limited numbers of patients in ICU initially and hence it is difficult to draw conclusions. However, long stays may reflect the availability of suitable step-down facilities, with for instance some smaller acute hospitals having no high dependency units (HDU) to move patients who no longer require full ICU care to. This will impact on ICU and HDU resources as the pandemic progresses.

Length of stay increased with age. One third of children under the age of 15 years had a length of stay of less than two days compared to 25% of the age group of 15-24 year-olds, 17% in the group of 25-64 year-olds and none of the over 65 year-olds. Short lengths of stay in children have been noted elsewhere [8].

Time from onset of symptoms to admission to hospital was shorter than seen in the US [10]. This may be accounted for by the stage of the pandemic in Ireland. Early in the pandemic there was a high level of uncertainty in relation to clinical presentation and likely progression of the disease, which may have led to a lower threshold for early admission to hospital. As clinicians became more experienced in treating pandemic influenza they may have been more confident in advising homecare.

Data gathered in this paper were for surveillance purposes and provide epidemiological information on the early hospitalised cases of pandemic H1N1 influenza. They also provide information on clinical details but it must be borne in mind that the data were not collected primarily for this purpose and so there are a number of limitations. Enhanced surveillance forms were completed at an early stage of hospitalisation and were updated where possible later during the stay and at discharge. A retrospective chart review was not carried out. This may impact on data validity, particularly recording of influenza complications and on time of onset of symptoms. Data on risk factors were gathered from the treating clinician and may have been subject to bias such as misclassification bias. The proportion of hospitalised cases with risk factors was lower than that reported in studies elsewhere. This may be due to the fact that a detailed case review of each patient's notes was not carried out, as was done elsewhere [10,11]. However, efforts were made to ensure that data collected from clinicians was complete, and incomplete data was rechecked at a later stage, with over 90% of data completed. Also, as data were collected on all hospitalised cases in Ireland, there was less potential for bias than would have occurred if the cases were a sample presenting at one or a few sites.

The prevalence of risk groups in the general population were derived by a number of different methods based on data of varying quality. Information on pregnancy and diseases for which registries are available can be considered reliable. Other data are of varying quality and should be interpreted with caution. Nevertheless, they

provide some indication of the representation of different risk groups among hospitalised cases compared with their distribution within the general population as well as some indication as to whether they are over- or underrepresented.

Surveillance data continue to be very important in understanding the pandemic in Ireland. However, information needs have changed. It is now important to identify those at highest risk of complications and to understand what those complications are in order to plan both prevention strategies and hospital surge capacity. Hospital surveillance will continue to be important. In addition, enhanced surveillance of ICU cases has been implemented in Ireland and will provide more information on complications in these patients, particularly severe complications

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*Erratum: The x-axis in Figure 2 indicated the wrong dates and this was corrected on 6 November 2009.

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MEASURES AGAINST TRANSMISSION OF PANDEMIC H1N1 INFLUENZA IN JAPAN IN 2009: SIMULATION MODEL

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The first outbreak of pandemic H1N1 influenza in Japan was contained in the Kansai region in May 2009 by social distancing measures. Modelling methods are needed to estimate the validity of these measures before their implementation on a large scale. We estimated the transmission coefficient from outbreaks of pandemic H1N1 influenza among school children in Japan in summer 2009; using this transmission coefficient, we simulated the spread of pandemic H1N1 influenza in a virtual community called the virtual Chuo Line which models an area to the west of metropolitan Tokyo. Measures evaluated in our simulation included: isolation at home, school closure, post-exposure prophylaxis and mass vaccinations of school children. We showed that post-exposure prophylaxis combined with isolation at home and school closure significantly decreases the total number of cases in the community and can mitigate the spread of pandemic H1N1 influenza, even when there is a delay in the availability of vaccine.

Introduction

Cases of pandemic H1N1 influenza were first reported in Mexico in April 2009 [1]. Subsequently, the virus spread rapidly across the United States and Canada, and then became a global concern [2]. Initial countermeasures, including rigorous fever screening at ports of entry, were introduced by the Japanese government in response to the elevated pandemic alert level of the World Health Organization [3].

In May 2009, an outbreak of pandemic H1N1 influenza occurred in the Kansai region of Japan in Hyogo and Osaka prefectures and was contained by the end of the month [4]. After early July, the virus emerged again and spread throughout Japan [5].

Urgent implementation of measures against pandemic H1N1 influenza is required.

Vaccination against pandemic H1N1 influenza was started in Japan on 19 October 2009, targeting first the healthcare workers. As there may not be enough vaccines to cover all needs, and it is already November, the effectiveness of other measures, such as the use of antiviral drugs and social distancing, must also be considered.

To implement these measures effectively in order to contain the spread of the disease and decrease the associated costs to society, we must first estimate the impact of these measures.

Simulation is a useful method for this purpose. We have developed an individual-based Monte Carlo simulation code by constructing a virtual regional community called the virtual Chuo Line, based on the real Chuo Line area west of Tokyo [6].

In the present study, we use the virtual Chuo Line model for the simulation of pandemic H1N1 influenza and propose measures to be implemented. To estimate the impact of these measures in Japan, we decided to base the parameters on the simulation of Japanese pandemic H1N1 influenza cases.

Methods

Simulation of the spread of pandemic H1N1 influenza in virtual communities

We have developed a Monte Carlo simulation code using an individual-based model [6]. We constructed a virtual regional community called the virtual Chuo Line, based on statistical data of the real Chuo Line area west of Tokyo. In the virtual Chuo Line scenario, the total number of people involved was 8,800, including 2,000 in Hachioji City, 2,600 in Tachikawa City, 2,800 in the Kichijoji area of Musashino City next to Suginami ward in Tokyo metropolitan area, and the rest were in Shinjuku and Tokyo. In our model 8,800 people were sufficient for Monte Carlo simulation in the preliminary estimation. These people were connected to many different types of families: singles, couples, fathers, mothers, and children. We also constructed "compartments" consisting of 4,040 homes, 60 schools, 658 companies, and 117 shops. The size of the families ranged from single to eight persons. The proportion of different size families was determined by Japanese census data. For schools we modelled using local government statistics one class or two classes per school; the numbers of students were 30-40 or 70-100 per school. The size of workplace was from 3 to 30 persons and the various size workplaces were determined using local government statistics. We operated trains that moved between stations in the cities according to a virtual railroad timetable. Twelve percent of the people in the model commuted to Tokyo. We gave people event histories, consisting of movement from one compartment to another. Event histories were constructed using statistical data of the daily life of about 30,000 Japanese people. In these compartments, people contacted each other stochastically and were occasionally infected. When measures, such as school closure or prohibition of traffic, were implemented, students or commuters were assumed to stay in their households. The results

of simulations were obtained by an average of 100 runs. We showed other two numbers in parentheses, one is the sum of the lower values of 95% CI and the other is the sum of the upper values of 95% CI.

Real data in public health centres

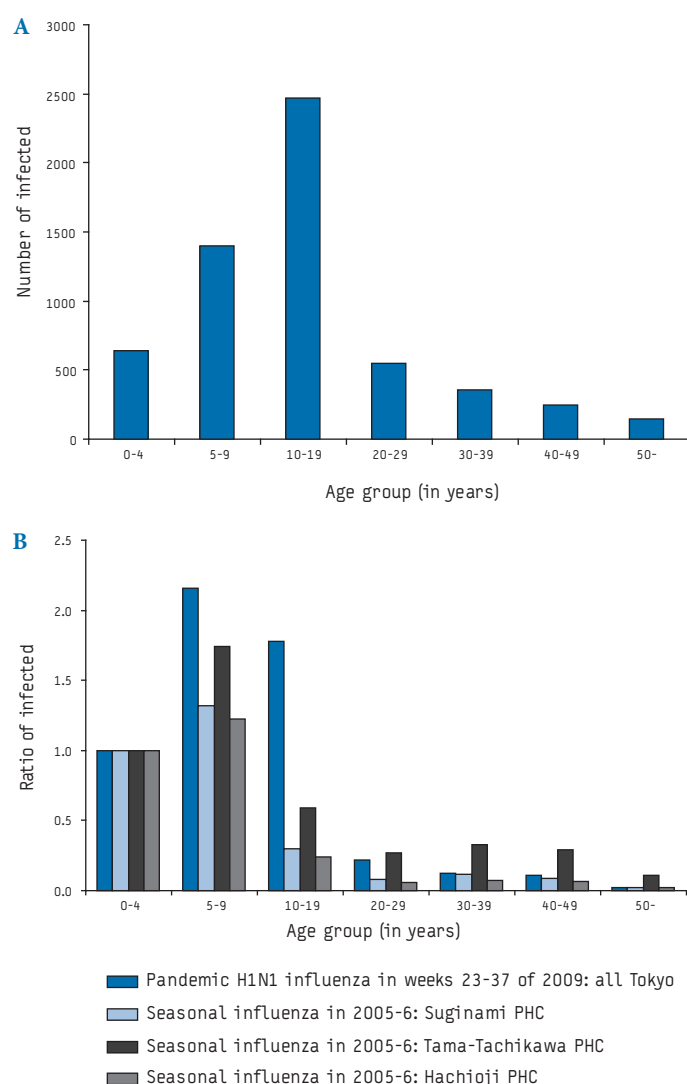
The spread of pandemic H1N1 influenza was reported to be prominent among young people. In order to confirm this, we compared the data on age distribution of cases of pandemic H1N1 influenza in Tokyo in the summer 2009 [7] with the data on cases of seasonal influenza in 2005-6 in three public health centres

FIGURE 1

Real data on reported numbers of cases of pandemic H1N1 influenza in Tokyo in 2009 and of seasonal influenza in three public health centres (PHCs) along a real railway, the JR Chuo Line in Tokyo in 2005-6:

A. Age distribution of reported cases of pandemic H1N1 influenza in greater Tokyo from week 28 to week 37 of 2009;

B. Ratio of persons infected by seasonal influenza per unit population normalised by the age group of zero to four, Tokyo and three PHCs along the Chuo Line, 2005-6.



(PHC): Hachioji, Tama-Tachikawa and Suginami which are in the Chuo Line area [6]. We used surveillance data of infectious diseases including influenza collected by the National Institute of Infectious Diseases (NIID) to which every PHC reports the number of newly infected persons every week. The data reported to PHCs come from 3,000 paediatricians and 2,000 general practitioners. With the permission of NIID, we analysed the number of notifications in the winter of 2005-6 from the Hachioji, Tama-Tachikawa and Suginami PHCs [6]. As for the data of summer 2009, the number and age of patients in the greater Tokyo was published weekly by the Tokyo Metropolitan Institute of Public Health through the notifications from PHCs in the greater Tokyo [7]. The influenza data reported after July 2009 were considered to be mostly the pandemic influenza data, because seasonal influenza is rare in summer in Japan. We also estimated the transmission coefficient of pandemic H1N1 influenza among school children using data on outbreaks among small groups of students during summer vacation 2009.

Results

Age distribution of cases of pandemic H1N1 influenza

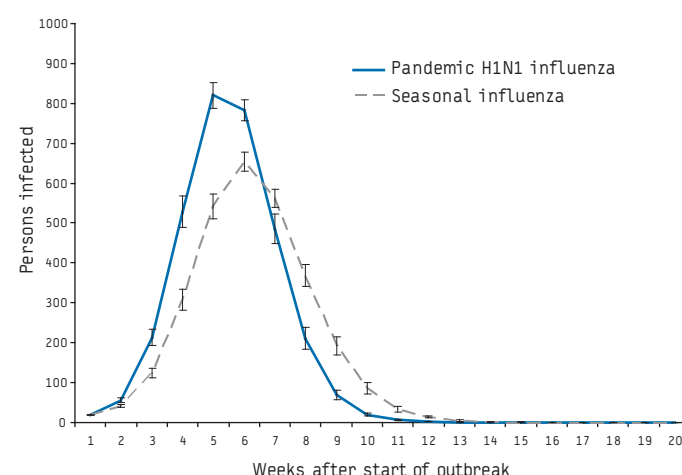
Data on age of persons infected with pandemic H1N1 influenza from week 28 to week 37 (6 July to 13 September) 2009 in Tokyo was obtained from the PHC reports [7] (Figure 1A). We calculated the ratio of the number of persons infected divided by the population of each age group in Tokyo from the Japanese census data and normalised it by age group from 0 to 4 years (Figure 1B). As shown in Figure 1B, the number of cases among school children, especially among teenagers, was significantly higher in comparison to seasonal influenza in the three PHCs in Tokyo: Kichioji PHC, Tama-Tachikawa PHC, and Hachioji PHC in the Chuo Line area during the 2005-6 season [6].

Transmission coefficient

We searched the national newspapers for information on outbreaks of influenza among children during the summer vacation 2009. During the summer holidays, outbreaks of seasonal influenza are rare in Japan therefore we assumed these outbreaks had been due to the pandemic. We analysed the cases if the size of the group was specified. After 24 July, the policy of the Japanese government

FIGURE 2

Simulation model results for the number of persons infected with pandemic H1N1 influenza and seasonal influenza



has changed from testing all suspected cases to sample testing by PCR. If H1N1 is confirmed by sampling, we assume all cases to be infected with H1N1. After 25 August, no laboratory testing by PCR has been required to confirm an outbreak of H1N1 in a school setting.

The following outbreaks were identified:

Outbreak 1: Health recovery camp for asthmatic children, 29-31 July 2009. Approximately 70 people attended the camp: 43 children and 27 staff members. Of these, 22 children and four staff members showed symptoms, and one child was confirmed to have H1N1.

Outbreak 2: A university tennis club, 30-31 July 2009. Approximately 100 persons attended. The university announced that 12 were infected with H1N1.

Outbreak 3: Residential high school training camp, 1-4 August 2009. Enrolment was 47 people: 38 students, two teachers and seven former students. Of these, 26 were shown by a simple test to be infected with influenza A, and one was confirmed with the pandemic H1N1 influenza.

Outbreak 4: Regional basketball camp on 6 August 2009. Approximately 150 attended, including elementary and junior high school students and coaches. Simple test indicated nine junior high school students were infected with influenza A, and three of them were confirmed with the pandemic H1N1 influenza by PCR.

We estimated the transmission coefficient β by $\beta = \ln(I(T))/(S_0 * T)$, $I(T)$: the number of persons infected; S_0 : the size of the group; T : the period of the event. To derive the formula, we integrated the following equation from time 0 to T , assuming the number of the initially infected children to be one:

$$\frac{dI(t)}{dt} = \beta S_0 I(t), I(0) = 1.$$

The pandemic H1N1 influenza did not prevail during summer vacation in Japan and seasonal influenza is rare in summer, therefore we could assume that susceptible children who attended the event were not exposed to other sources of infection except at the event. Then, $I(T)$ is the number of children infected during the event. The estimated values per day are 0.016, 0.011, 0.017 and 0.012. The settings where the above outbreaks occurred were different from schools. However, from the point of view of the behaviour of a group of children, there are many similarities regarding the contacts among children during class room or physical activities. It is therefore expected that the transmission coefficients calculated from the above outbreaks can be applied to school outbreaks as well.

For probability of infection by seasonal influenza, we used $P = 0.005$ per hour for homes, $P = 0.0016$ for schools, $P = 0.0125$ for trains, and $P = 0.00001$ for companies and shops. For the probability of becoming infected on the train, we assumed passengers are densely crowded, as during the rush hour peak. The probability of infection by pandemic H1N1 influenza is within the range of seasonal influenza, except for school children. We used the probabilities of seasonal influenza, except for schools. We estimated the probability of infection among school children to be $P = 0.0023$, assuming 5-8 hours of activity per day in these cases. The medical conditions of simulation were specified by scenario of infection. We specified the latent time to be two days and the period of infection five days.

Simulation in model cities along the virtual Chuo Line

The average number of infected people in 100 simulation runs is shown in Figure 2. No social distancing measures were implemented in the runs. The peak of pandemic H1N1 influenza was higher than that of seasonal influenza and occurred one week earlier. The total number of persons infected with pandemic H1N1 influenza was 3,211 (range: 3,001-3,421), whereas the total number of people with seasonal influenza was 2,945 (2,756-3,152).

Home isolation of school children (HIS)

When one in three adults and 70%, 80%, 90%, or 100% of children stayed home 48 hours after the appearance of symptoms, the total number of persons infected in the community was 2,729 (2,443-3,015), 2,561 (2,298-2,824), 2,425 (2,167-2,683) and 2,121 (1,853-2,389), respectively. When all of the children and 0%, 66% and 100% of adults stayed home 48 hours after the appearance of symptoms, the total number of persons infected was 2,288 (2,089-2,487), 2,001 (1,760-2,242) and 1,779 (1,514-2,044). Figure 3A (simulation with no SC) illustrates a situation where all of the children and one-third of the adults stayed home 48 hours after the appearance of symptoms

School closure (SC)

We implemented SC in a situation where all students/pupils and one-third of adults stayed home 48 hours after onset of symptoms. We simulated seven-day SC for one and two weeks after the outbreak (Figure 3A), and then compared the results with the option without SC. The total number of persons infected was 1,812 (1,532-2,092), 1,766 (1,461-2,071) and 2,121 (1,853-2,389), respectively. Next, we simulated SC for four, five and six days, one week after the outbreak (Figure 3B). The total number of persons infected was 2,136 (1,845-2,427), 1,997 (1,714-2,280) and 1,927 (1,662-2,192), respectively. The spread lasted approximately 20 weeks, averaging the results of 100 runs. However, in some cases, the spread ended before 10 weeks. Four of 100 runs in situations without SC ended before 10 weeks. Three, nine, 12 and 17 runs ended before 10 weeks in case of four-, five-, six- and seven-day SC.

Post-exposure prophylaxis with antiviral drugs (MED)

We assumed antiviral drugs were used only for household contacts of cases. When all children and one-third of adults stayed home 48 hours after symptoms appeared, we simulated the situations where all families used MED but the proportion of family members who were administered the antiviral drugs at any time within 48 hours after appearance of symptoms was 20%, 40%, 60%, 80%, and 100%. Then, the total number of persons infected was 1,903 (1,682-2,124), 1,654 (1,397-1,911), 1,412 (1,180-1,644), 1,082 (889-1,275) and 883 (666-1,000), respectively (Figure 3C). In these runs, we assumed the efficiency of antiviral drugs to be 80%, i.e. to prevent infection in eight out of ten contacts of the infected persons.

In the situation where 40% of families were administered the drug with an efficiency of drugs 60%, 70%, and 90%, the total number of persons infected was 1,815 (1,560-2,070), 1,761 (1,519-2,003), and 1,574 (1,336-1,812), respectively.

Mass vaccination of school children (VSC)

Children were assumed to be vaccinated and become immune before the influenza season. When the efficiency of vaccine is $X\%$, X persons in 100 were assumed to become immune. We also

FIGURE 3

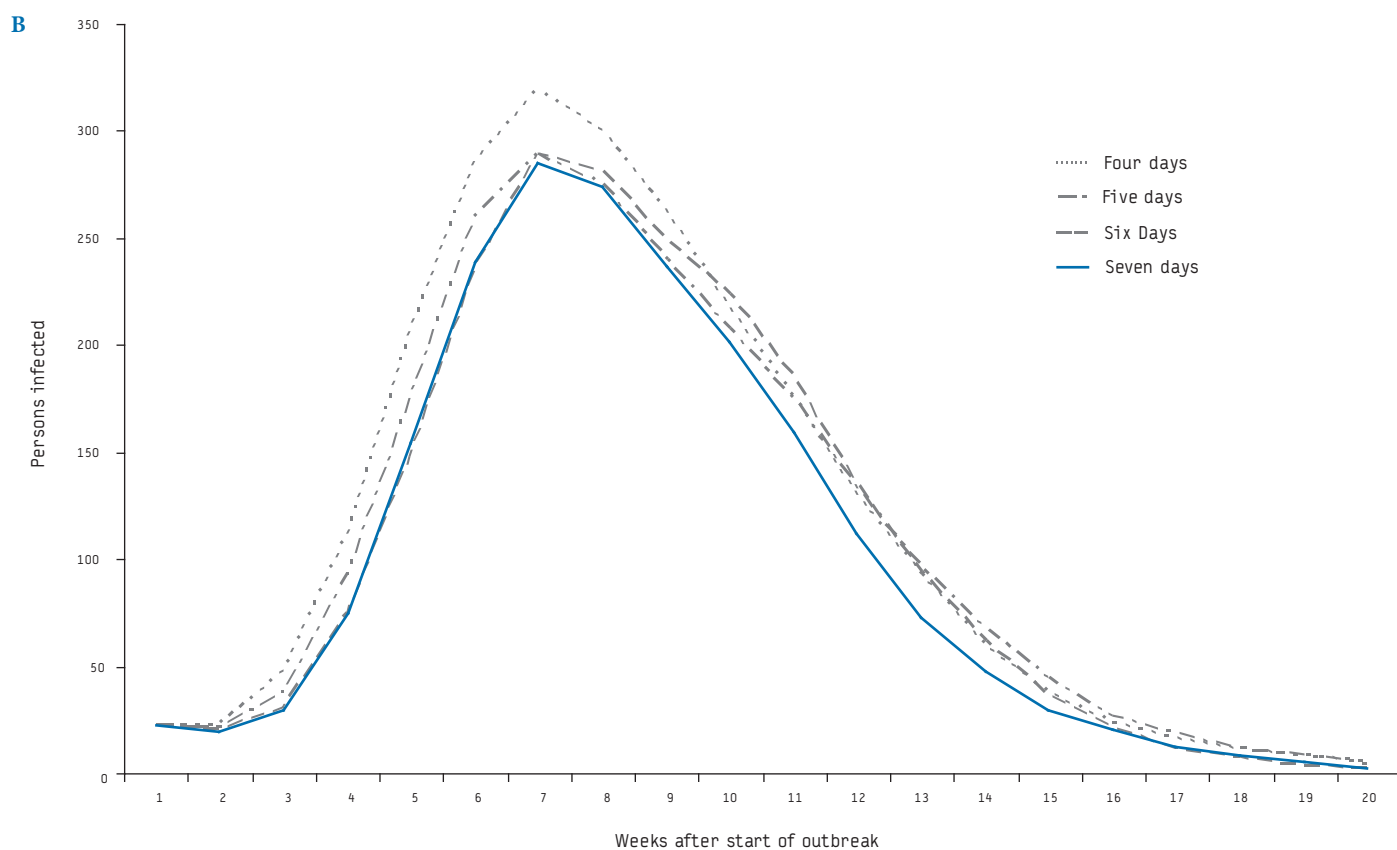
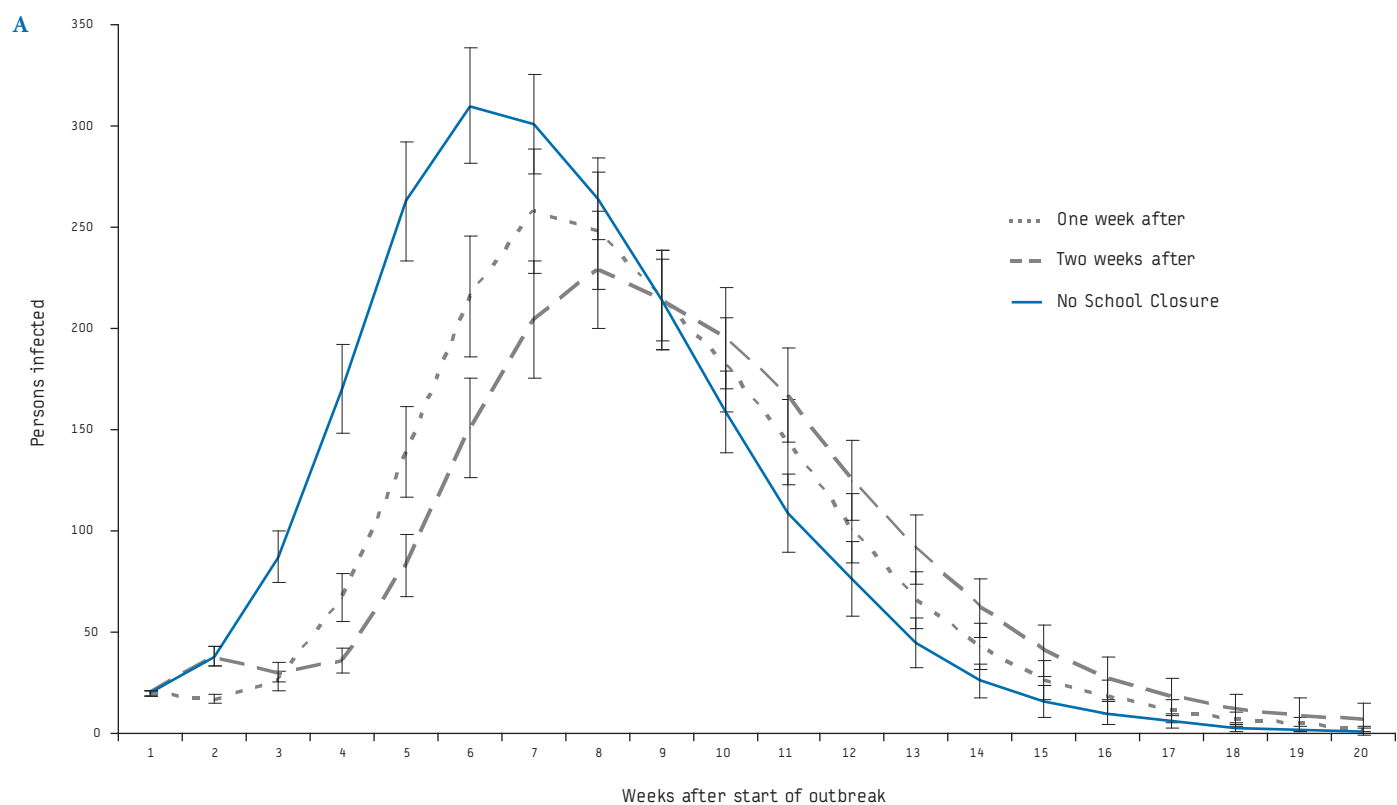
The number of persons infected with pandemic H1N1 influenza, simulation model results for different scenarios:

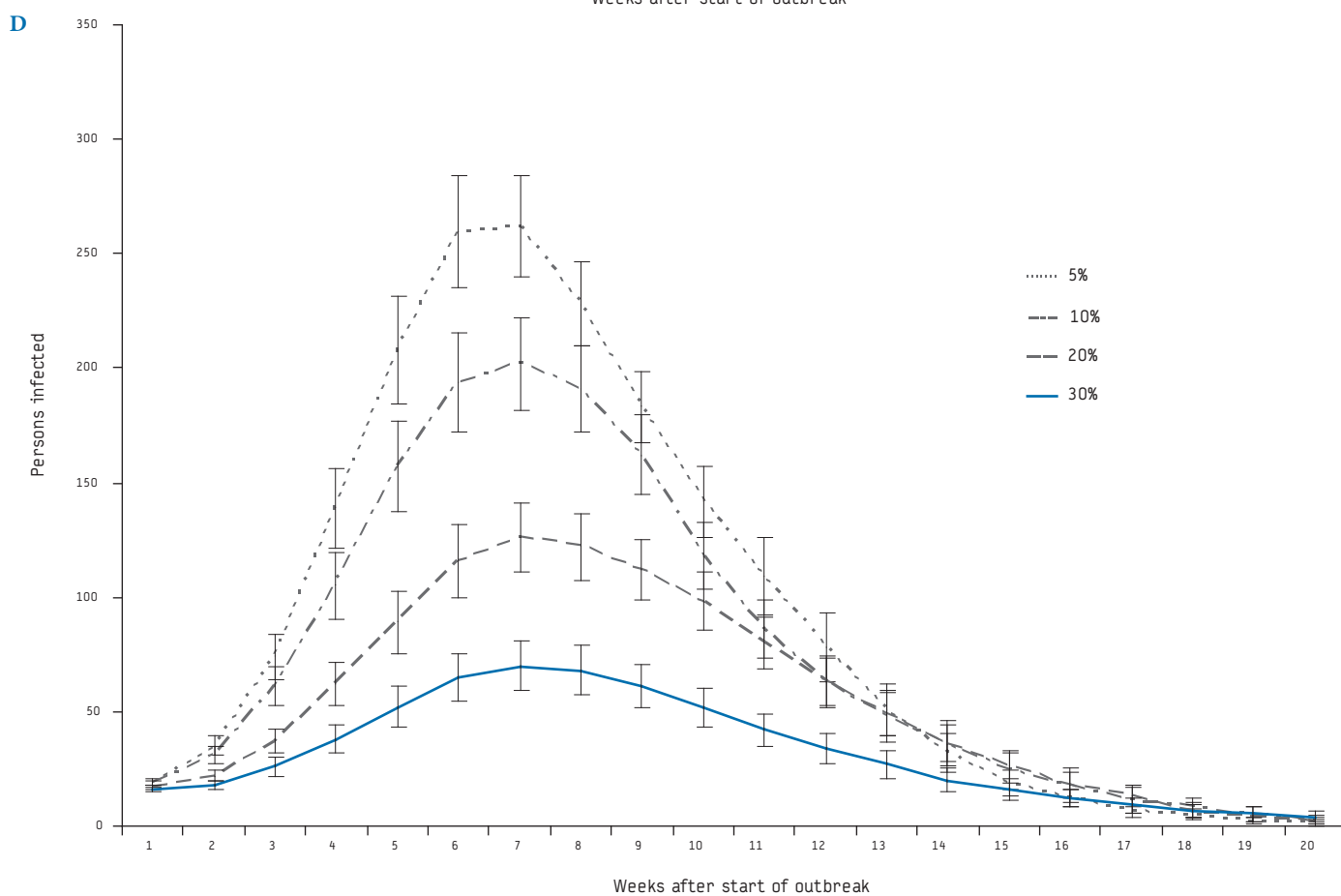
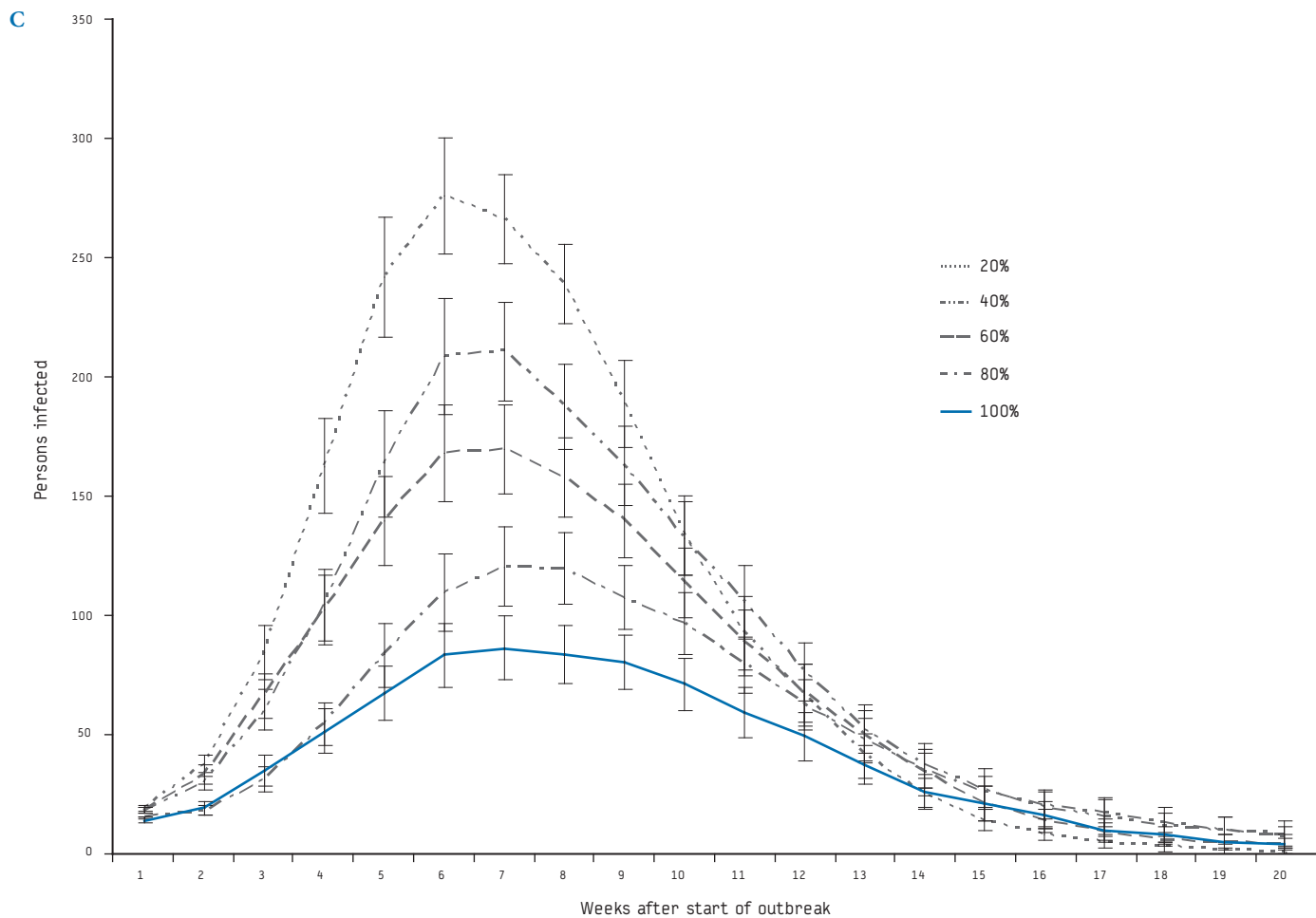
A. Seven-day school closure one or two weeks after the outbreak and no school closure;

B. School closure for four, five, six and seven days one week after the outbreak;

C. Post-exposure prophylaxis with antiviral drugs administered to 20%, 40%, 60%, 80%, and 100% of the family members;

D. Mass vaccination of school children, assuming the efficiency of vaccinating children was 5%, 10%, 20%, and 30%.





assumed all children and one-third of adults stayed home 48 hours after symptoms appeared. The total number of persons infected in the community was 1,879 (1,624-2,134), 1,546 (1,324-1,768), 1,094 (932-1,270) and 645 (528-780) when the efficiency of the vaccine to children was 5%, 10%, 20%, and 30%, respectively (Figure 3D). The number of infected children was 975 (838-1,112), 793 (676-910), 538 (451-625) and 291 (229-353), respectively. When the vaccine was delayed, children became immune 1, 2, or 3 weeks after the spread of pandemic H1N1 influenza, and the total number of persons infected was 762 (628-896), 881 (744-1,018) and 1,011 (872-1,150) in case of 30% efficiency.

Combination of measures

We performed a simulation of measures according to the following possible scenario: all children and one of three adults were isolated 48 hours after the appearance of symptoms. Four-day SC one week after the outbreak was implemented. Thirty percent of children became immune by vaccination only eight weeks after the outbreak. Forty percent of families of persons infected were administered the antiviral drugs with efficiency 80%. It is shown that the number of persons infected, indicating the major venues where they became infected, was 1027(860-1194) (Figure 4), strongly suggesting measures to mitigate the spread of pandemic H1N1 influenza even if the vaccine is delayed.

Discussion

In the present study, it was shown that the spread of pandemic H1N1 influenza in Japan is more severe among school children than seasonal influenza. Nishiura et al. [8] estimated the average number of secondary cases in children generated by a single primary child case in Japan to be 2.8. Meanwhile, transmission among other age groups is comparable to that of seasonal influenza. It was thus confirmed that children play an especially important role in the spread of pandemic H1N1 influenza [4].

Home isolation

School principals have the authority to suspend children infected by influenza according to Japanese school health laws. Our

simulation shows the total number of persons infected decreased to approximately two-thirds when all children and one-third of adults were isolated at home compared with the scenario of no measures taken. When all children and two-thirds of adults were isolated at home the additional decrease was not so significant, indicating that the impact of HIS is mainly through preventing infection in schools. Children in the household could infect their family members. However the family members were fewer than their classmates.

School closure

In May 2009, an outbreak of pandemic H1N1 influenza, the first in Japan, occurred in Hyogo and Osaka prefectures. In the beginning of the outbreak, primarily high school students were infected. After peaking on 17 May 2009, the outbreak decreased [4]. All junior high and high schools in Osaka prefecture were closed for 1-2 weeks after 16 May, and elementary schools and kindergartens in the cities where cases occurred were closed. Schools were also closed in Kobe city [4].

SC was implemented in our present simulation in addition to HIS, resulting in a lower peak and a decrease of the total number of infected persons in comparison to the scenario without SC. SC without HIS slows only the transmission of spread; peak becomes lower, but the decrease of the total number of persons infected is small [6]. SC mainly slows down the spread and HIS decreases the number of persons infected by pandemic H1N1 influenza in the present simulation.

For the scenario of SC implemented one week later, our simulation shows that SC for four days was not sufficient, although it did delay the peak. The total number of infected decreased with longer SC. However, infected children may be expected to recover at home during SC for four days due to its latency for two days. In large infected families (i.e. 5-8 members) children would be infected newly during SC.

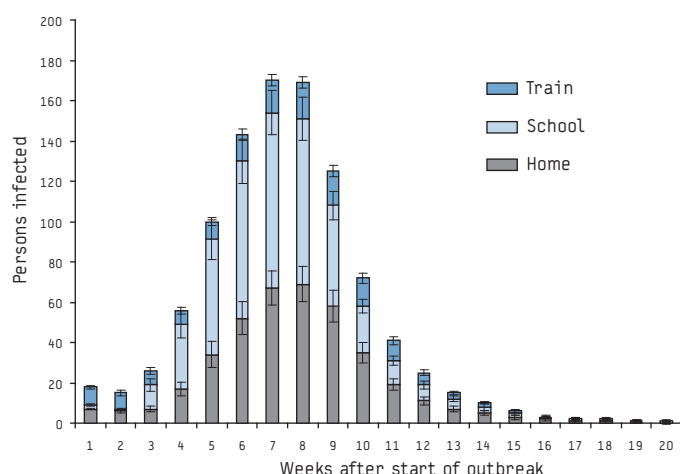
Our simulation shows it is not easy to affect outbreaks using SC in the commuter towns of Tokyo after an epidemic. Although in some cases the spread of disease in three cities ended soon after implementation of SC, in other cases, commuters mitigated the effect of SC. For example, in Hachioji and Tachikawa, the spread ended, but in Kichijoji, it persisted. Influenza was introduced into the cities and began to spread again by commuters in Hachioji and Tachikawa, who were infected in trains or businesses. If we prohibited traffic between cities in the case of seven-day SC, 83 of 100 runs ended before 10 weeks. Indeed, the first outbreak for a short period in Osaka spread among high school students, not adult commuters.

Post-exposure prophylaxis

Post-exposure prophylaxis by administration of antiviral drugs is not officially permitted in Japan. However, antiviral drugs, for example oseltamivir, are the first prescription of choice in cases of seasonal influenza. The use of neuraminidase inhibitors has been reported to decrease the incidence of influenza by 68-89% [9]. Our results show the total number of persons infected in the community decreased significantly when the number of families who received antiviral drugs increased. Hence MED is an effective method that blocks infections in households.

FIGURE 4

The number of persons infected with pandemic H1N1 influenza in a scenario with combination of measures: traffic prohibition, school closure, and isolation at home



Vaccination of school children

The supply of vaccine for pandemic H1N1 influenza in Japan is estimated to be insufficient and therefore priority of vaccination will have to be scheduled, but to date no decision has been taken as to whether children, except those in the lower grade of elementary school, would be included among the priority groups. Even if the vaccine is closely matched, we cannot expect high efficiency. However, simulations show that vaccines are highly effective in protecting communities; this also holds true for seasonal influenza [6].

We considered mass vaccination of school children, because systematic vaccination of adults seems difficult due to lifestyle differences. In Japan, children were mass-vaccinated by law against seasonal influenza from 1962 to 1987. In 1987, the law was relaxed and then repealed in 1994, but the effectiveness of VSC against seasonal influenza is still under discussion. A study on deaths from pneumonia and influenza from the 1950s to the 1990s demonstrated mortality of the elderly decreased when school children were vaccinated [10].

When children were mass-vaccinated against seasonal influenza, not only did the number of infected children decrease, but also that of infected adults [6]. Mass vaccination of children is therefore effective in protecting the whole community. However, our simulations showed that when children did not become immune due to the delay of vaccine the number of persons infected increased. Our simulation strongly suggests vaccination is effective; however, delay of distribution of vaccine mitigates the effectiveness. After the end of October 2009, the effectiveness of vaccine in preventing the spread of disease is questionable.

Combination of measures

In the present study, the spread of influenza is decreased, even when the delivery of the vaccine is delayed. The mechanism of spread also shows that infected commuters introduce influenza into cities, then infections occur in the homes, children spread influenza in the schools and, in turn, infected children infect their families in the households, similar to seasonal influenza [6].

Conclusions

Home isolation of infected children greatly decreases the number of persons infected. In Osaka in May 2009, SC slowed down the outbreak. However, our simulation shows it is not easy for the commuter towns of Tokyo to slow down outbreaks after the beginning of an epidemic, even if long SC with HIS is implemented. Post-exposure prophylaxis combined with HIS greatly decreases the total number of infected people in the community. Also mass vaccination of school children combined with HIS greatly decreases the total number of persons infected, even if the efficiency is low. However, the delay of VSC decreases the efficiency. Our simulation shows that a combination of measures can mitigate the spread of pandemic H1N1 influenza, even when vaccines are delayed.

Acknowledgements

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INTERPRETING “GOOGLE FLU TRENDS” DATA FOR PANDEMIC H1N1 INFLUENZA: THE NEW ZEALAND EXPERIENCE

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For the period of the spread of pandemic H1N1 influenza in New Zealand during 2009, we compared results from *Google Flu Trends* with data from existing surveillance systems. The patterns from *Google Flu Trends* were closely aligned with (peaking a week before and a week after) two independent national surveillance systems for influenza-like illness (ILI) cases. It was much less congruent with (delayed by three weeks) data from ILI-related calls to a national free-phone Healthline and with media coverage of pandemic influenza. Some patterns were unique to *Google Flu Trends* and may not have reflected the actual ILI burden in the community. Overall, *Google Flu Trends* appears to provide a useful free surveillance system but it should probably be seen as supplementary rather than as an alternative.

The website *Google Flu Trends*, developed by Google.org, uses aggregated Google search data on influenza-like illness (ILI) symptoms to estimate influenza activity “up to two weeks faster than traditional systems” [1]. As of mid-October 2009, the site graphically presents data for Australia, New Zealand, Mexico (selected regions only), the United States (US) and 14 European countries [2]. An analysis of this surveillance system for seasonal influenza data in the US indicated that it was able to “accurately estimate the current level of weekly influenza activity in each region of the United States, with a reporting lag of about one day” [3]. For the Australian state of Victoria, the data from *Google Flu Trends* showed a “remarkable correlation” with ILI surveillance data from sentinel practices and the Melbourne Medical Deputising Service [4]. This was for data from May and June 2009 – the time of the spread of new pandemic H1N1 influenza in that state. In fact, the Google data showed an increase in ILI activity five to six weeks prior to the actual increase in reported ILI cases.

As New Zealand has a number of different influenza surveillance systems in operation [5-7], we aimed to further explore the possible utility of *Google Flu Trends* in the setting of an influenza pandemic.

Methods

We downloaded the freely available data for New Zealand in 2009 from the *Google Flu Trends* website [1] from the week beginning 29 March (week 14) to the week beginning 4 October 2009. Data were for the ‘Google search ratio’, a metric developed by Google and based on Google searches for ILI symptoms that were calibrated against past seasonal influenza data reported through the specific surveillance system(s) in a given country. These data were

then compared graphically with ILI data from a national network of sentinel general practices (Sentinel GP system) and another much larger national network of computerised general practices (HealthStat). A comparison was also made with ILI data from a national free-phone Healthline. These systems have all previously been described in *Eurosurveillance* [5]. Of note is that in the graphs the ‘weeks’ are shifted by one day against those used for *Google Flu Trends*: the reporting week in *Google Flu Trends* starts on Sunday, while the HealthStat week starts on the day before (Saturday) and the reporting weeks in the Sentinel GP system and Healthline start on the day after (Monday).

In addition we obtained a weekly tally of media reports relating to the H1N1 influenza pandemic in New Zealand in 2009 by searching the news archive of ‘Google news (New Zealand)’ [8]. The search used all the following terms together: ‘swine’ AND ‘flu’ AND ‘Zealand’ AND (the phrase) ‘Ministry of Health’. Less specific search strategies (e.g. without the phrase ‘Ministry of Health’) did not return results that were sufficiently specific for local news media reports from New Zealand because there was extensive international media reporting of some early events relating to New Zealand, such as the arrival of a group of symptomatic students in Auckland on a flight from Mexico in late April 2009.

Results

The initial increase in the weekly rate of ILI cases reported from the Sentinel GP system and the increase in the Google search ratio (representing internet searches for ILI symptoms) were very similar and were noted between week 19 (starting 3 May) and week 24, 2009 (Figure 1). However, the Google search ratio peaked a week earlier, in week 28 (starting 5 July) versus week 29.

The comparison with computerised general practice (HealthStat) ILI data gave some indication that the Google search ratio increased initially before the increase in the ILI data (Figure 2). After that, it seemed to lag behind and peaked a week later, in week 28 versus week 27 for HealthStat data.

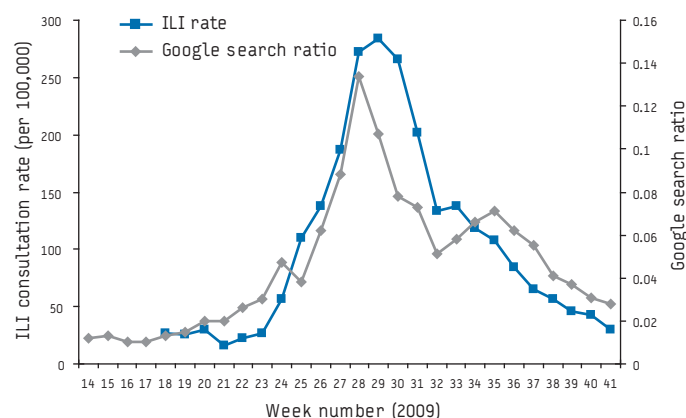
When compared to the ILI calls to the Healthline, there was a similar pattern initially and then a growing gap with the Google search ratio following behind (Figure 3). Indeed, the latter peaked 3 weeks after the peak in ILI Healthline calls (which peaked in week 25 [starting 14 June]).

The comparison with news item media coverage is shown in Figure 4. There appears to be little congruence, especially around the massive peak in media coverage associated with week 18 (starting 26 April) when a group of symptomatic school students returned to New Zealand on a plane from Mexico, the first confirmed cases in New Zealand. There was some similarity in the pattern of increase in week 24 when official reports were of cases first exceeding a total of 1000. But there was no similarity after that point except where both levels declined from week 29 onward.

While a second, smaller peak appears in the Google search ratio in week 35 (starting 23 August), no such peak was seen in the Sentinel GP and HealthStat systems, in the Healthline calls data, or in media items (Figures 1–4).

FIGURE 1

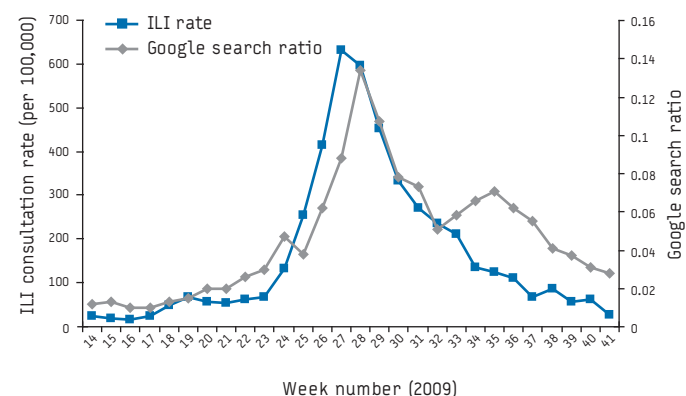
Weekly rate of ILI per 100,000 registered population from the national Sentinel General Practice Surveillance System, compared to the Google search ratio, New Zealand, 29 March – 4 October 2009



ILI: influenza-like illness.

FIGURE 2

Weekly rate of ILI per 100,000 registered population from the national computerised general practice (HealthStat) surveillance system, compared to the Google search ratio, New Zealand, 29 March – 4 October 2009



ILI: influenza-like illness.

Discussion

Key findings and interpretation

These results suggest that the patterns from the *Google Flu Trends* system are fairly congruent with actual surveillance systems for ILI cases in New Zealand. For 2009, these ILI cases were representative of mainly pandemic H1N1 influenza activity, albeit with some minor contribution of seasonal influenza [5]. Furthermore, the week in which the Google search ratio peaked (week 28, starting 5 July) was also the peak week for hospitalisations and admissions for pandemic H1N1 influenza to intensive care units in New Zealand (as detailed elsewhere [5]). Nevertheless, *Google Flu Trends* would not have provided any advance warning of ILI cases compared to the weekly reporting of HealthStat data (neither of the major increase nor the timing of the peak).

The overall similar results with primary care data on ILI are not surprising in that *Google Flu Trends* for New Zealand was initially calibrated on the Sentinel GP surveillance data for seasonal influenza in previous years. But of course the congruence of the two systems with regards to pandemic influenza, has never before been examined for New Zealand.

The fact that *Google Flu Trends* data lagged behind the increase in Healthline ILI-related call levels may reflect the design of the former, being originally calibrated on Sentinel GP surveillance. Another contributing factor could be that symptomatic people used the Healthline before thinking of performing Google searches. This could reflect Ministry of Health promotion (e.g. in media statements) of this national free service as an alternative to people consulting their general practitioner. It might also reflect social patterning of disease spread: If lower-income New Zealanders were at increased risk of influenza early in the pandemic (e.g. household crowding and family size are influenced by socio-economic status), then this group may prefer using Healthline as they have better telephone access than internet access. Healthline callers may also represent individuals who were influenced more by media coverage, but in fact, the major increase in Healthline calls occurred several weeks before the week when the first death attributed to pandemic H1N1 influenza in New Zealand was officially announced (in week 27, starting 28 June) [9]. In the same week, the regular (at least daily) Ministry of Health media release first referred to hospitalised cases of pandemic H1N1 influenza.

Google Flu Trends data might also produce spurious minor patterns that are not mirrored by other systems e.g. the second peak identified in week 35, starting 23 August. This second peak was probably not due to the return to school, as this appears to have occurred earlier during the holiday period and was identified through increased HealthStat consultation rates for school age groups (5–14 years) in weeks 30–32 (the weeks starting 19 June to 2 August) [5].

Implications for surveillance and research

A major benefit of *Google Flu Trends* is that it is free and that it is likely to provide some indication of when the incidence of ILI has started to increase in the community and is likely to have peaked. This system also provides daily graphical data and weekly total data that are immediately available to download at the end of each reporting week. This contrasts with an average delay of four days for the GP Sentinel system and four days for HealthStat data (the time for national health authorities to report these data to the rest of the health sector at the end of the data collection week).

Google Flu Trends could be particularly useful for countries where other influenza surveillance systems are poorly developed, though it would probably be less reliable if it had not been calibrated with a robust existing surveillance system for the country in question. Countries with well-established surveillance systems can also potentially profit from *Google Flu Trends* as a supplementary and partial backup surveillance system. In particular, it could assume an important role if the normal systems were disrupted (e.g. in a particularly severe pandemic where health systems are

overburdened), or when people with mild illness are discouraged from visiting doctors. *Google Flu Trends* should therefore continue to be closely studied. One question to be addressed is, for example: Does the area under the *Google Flu Trends* epidemic curve reflect the total disease burden in the community (as validated by sero-surveys) better than other surveillance systems?

Acknowledgements

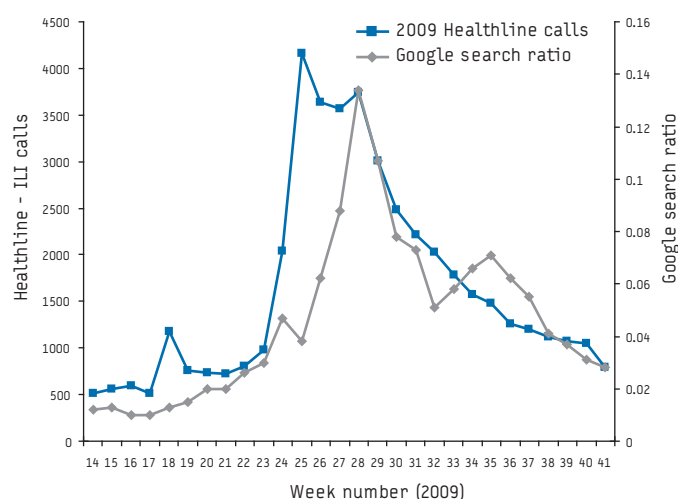
We thank the many health workers in New Zealand who collect ILI data via the different surveillance systems referred to in this study.

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FIGURE 3

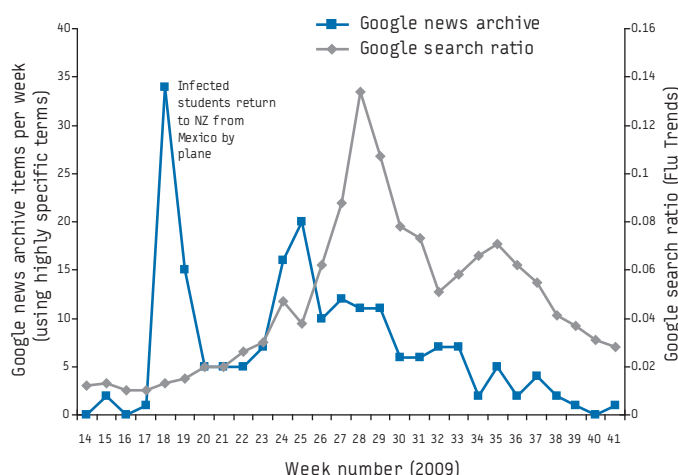
Weekly ILI-related calls to the national Healthline, compared to the Google search ratio, New Zealand, 29 March – 4 October 2009



ILI: influenza-like illness.

FIGURE 4

Weekly news items from the Google news archive related to pandemic H1N1 influenza in New Zealand*, compared to the Google search ratio, New Zealand, 29 March – 4 October 2009



* Retrieved in a search for 'swine AND flu AND Zealand AND "Ministry of Health" '.

Rapid communications

TRICHINELLOSIS ACQUIRED IN NUNAVUT, CANADA IN SEPTEMBER 2009: MEAT FROM GRIZZLY BEAR SUSPECTED

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Five cases of trichinellosis with onset of symptoms in September 2009, were reported in France, and were probably linked to the consumption of meat from a grizzly bear in Cambridge Bay in Nunavut, Canada. Travellers should be aware of the risks of eating raw or rare meat products in arctic regions, particularly game meat such as bear or walrus meat.

Case detection and description

On 5 October 2009, the French National Reference Centre (NRC) for *Trichinella* was informed about a possible case of trichinellosis in an individual returning from Nunavut, Canada. This very asthenic patient had high eosinophil counts and elevated plasma levels for muscle enzymes. Specific antibodies were detected by ELISA and Western-blot (Diasorin & LDBio, France). The patient belonged to a group of five marine navigators who had travelled from the Aleutian Islands to Greenland and crossed the North-West Passage in northern Canada. The NRC started an investigation and identified four more cases among these travellers. Case 2 presented primary symptoms of shivers and fever without diarrhoea on 7 September. At the time she had been diagnosed with influenza but symptomatic treatment did not improve her condition. As high fever (40.4° C), intense muscular and joint pain, extreme asthenia and bilateral inferior limbs oedema persisted, the patient was hospitalised on 22 September. She also had elevated levels of eosinophils and muscle enzymes and was serologically positive on 30 September for trichinellosis (ELISA and Western-blot). The third and fourth crew members also had asthenia, high levels of eosinophils and muscle enzymes; one had a lasting diarrhoeal disease at the end of August; these two cases were tested positive by ELISA and Western-blot by the NRC and Biomnis lab in late October. The fifth traveller, living in Brussels, was also investigated and found to have been initially diagnosed with influenza but subsequently revised as trichinellosis (particularly when the link was made with the other cases) with manifestations of fever, myalgia, increased eosinophils and muscular enzymes levels and positive serology. Serological assays were not performed on one of the two patients with mild symptoms. No cardiac or neurological complications were observed. Only case 2 was hospitalised, discharge occurring 11 days later. All patients were treated with albendazole (7.5 mg/kg twice a day for 10 days) and corticosteroids were used in the first case and in the hospitalised patient (case 2).

Outbreak investigation

During the travel expedition many stopovers were made in Inuit's villages, and, on these occasions, the crew consumed meat of various wild animals: caribou, walrus, seal, polar bear and grizzly bear. Considering the occurrence, onset and duration of signs and symptoms, the source of infection were probably grizzly (*Ursus arctos*) steaks which were consumed in the Cambridge Bay area (Iqaluktuuttiaq), Victoria Island, Nunavut, Canada between the 19 and 22 August 2009. Information obtained from residents of Cambridge Bay indicated the grizzly bear was shot at Elu Inlet Lodge, at the beginning of August, transported fresh to Cambridge Bay where it was frozen for about a week. A leg was thawed, cut into pieces and given to the travellers. The pieces were frozen again for two days. After departure, the meat was stored for two additional days in the boat. All five members of the crew consumed this meat, barbecued or pan-fried, on several occurrences after the 19 August. All the remaining meat from the bear was consumed locally in Cambridge Bay, but well cooked and no suspected cases were reported. The Centre for Food-borne & Animal Parasitology, Canadian Food Inspection Agency, in Saskatoon, Canada was contacted on 6 October 2009 and informed of the outbreak. In the course of the investigations, it was established that, for some time, the boat of the five travellers sailed together with another one with four persons on board and members of both crews ate at the same places. The second boat was on the way for Halifax, Canada in mid-October when the crew was contacted by email and alerted of the possibility of trichinellosis infection and of specific preventive and treatment measures that might be necessary. According to their blog, one of the crew members had been affected by a persistent flu during the same period as the travellers on the first boat. But no additional information could be obtained from this second crew.

Discussion

This report illustrates well the fact that trichinellosis can be misdiagnosed for influenza, which is particularly important in the context of the pandemic H1N1 influenza outbreak when health professionals and the general public are more inclined to suspect influenza. Misdiagnosis of trichinellosis for influenza is not unusual because the initial clinical symptoms of these diseases occurring at the acute stage of infection are not pathognomonic. In another occurrence, Laurichesse *et al.* [1] emphasized that "general

practitioners could have misdiagnosed cases of trichinellosis because they did not routinely order serological tests". The presence of specific clinical and biological signs (facial oedema, elevated levels of eosinophils and muscle enzymes, and specific antibodies) can readily confirm the diagnosis of trichinellosis.

Trichinellosis is a widespread helminthic zoonosis endemic in northern Canada where the incidence rate among the indigenous population was estimated at 11 cases per 100,000 [2], which is 200 times the national Canadian rate [3]. Walrus (*Odobenus rosmarus*) meat is the most frequent source of trichinellosis infection in humans; polar bear (*Ursus maritimus*) seems to be less important. *Trichinella nativa* and the genotype T6 are widespread in northern Canada [4,5]. The precise genotype responsible for this small outbreak could not be determined, as the infected meat was not conserved and no muscular biopsies were performed. In an extensive survey recently performed on wildlife across northern Canada, Gajadhar and Forbes found that 29.4 % of grizzly bears examined harboured *Trichinella* larvae [5]. The prevalence was 65.9% among polar bears, 40.6% in walrus and 7.3 % in black bears (*Ursus americanus*). There are no other recent survey reports for *Trichinella* in wild fauna in Nunavut, except for a survey of wolverines (*Gulo gulo*) which found 87.8 % of these animals positive [6]. Outbreaks of trichinellosis among Inuit population have been described earlier in Nunavut on Baffin Island [7] and Repulse Bay [8]. They occurred in the local residents after consumption of walrus meat. Apparently, Inuit populations consume bear meat thoroughly cooked whereas walrus meat is eaten frozen, fermented or air-dried [9]. An earlier study has shown that traditional northern foods used by Inuit can harbour infective *Trichinella* larvae [10]. Other outbreaks, linked mainly to walrus meat consumption have been described in neighbouring Nunavik (from Inukjuak on south Hudson Bay and as far north as Salluit) leading to the development and implementation of a prevention program for trichinellosis in Inuit communities [8,9]. We also described, in 2005, an outbreak of trichinellosis among French hunters and their families in France after consumption of black-bear meat obtained from northern Quebec [11,12]. Apparently, French tourists, especially hunters, are particularly fond of bear meat. Including the present report, a total of 25 cases linked to bear meat consumption have been reported to the NRC since 1995 [12]. The present outbreak appears to be associated with the most northern geographic area described to date in Canada with grizzly bear meat as source. As shown in this report, the arctic species of *Trichinella* (*T. nativa* and T6) are resistant to freezing and are killed by sufficient cooking at 67°C. Travel in endemic regions is a classical driver for acquiring trichinellosis, and travellers should be aware of the risks of eating raw or rare meat products, particularly game meat such as bear or walrus meat [13].

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Rapid communications

GENOME SEQUENCE ANALYSIS OF THE FIRST HUMAN WEST NILE VIRUS ISOLATED IN ITALY IN 2009

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In 2009, six new human cases of West Nile neuroinvasive disease (WNND) were identified in Veneto region, following the six cases already reported in 2008. A human West Nile virus (WNV) isolate was obtained for the first time from an asymptomatic blood donor. Whole genome sequence of the human WNV isolate showed close phylogenetic relatedness to the Italy-1998-WNV strain and to other

WNV strains recently isolated in Europe, with the new acquisition of the NS3-Thr249Pro mutation, a trait associated with avian virulence, increased virus transmission, and the occurrence of outbreaks in humans.

FIGURE 1

Sites where human cases of symptomatic West Nile neuroinvasive disease occurred in Veneto region, Italy, in 2008 and 2009



Dark grey dots: cases in 2008
Light grey dots: cases in 2009

Introduction

In Italy, the first outbreak of West Nile virus (WNV) infection was reported in 1998 among horses residing in Tuscany region [1]. The virus re-emerged in Italy in 2008, when equine and human cases of West Nile neuroinvasive disease (WNND) were notified in Veneto and Emilia Romagna regions [2,3]. In Veneto region, six clinical cases of WNV infection were identified with disease onset in August-September 2008 and all were from Rovigo province [4]. Three further human cases of WNND were notified in Emilia Romagna region in September-October 2008 [5]. Moreover, the veterinary and entomological surveillance documented that WNV infection was widespread in the same areas in north-eastern Italy [2]. In 2008, WNV strains were isolated from one horse in Rovigo province, Veneto region, and from one donkey, one pigeon and three magpies in Ferrara province, Emilia-Romagna region. Sequencing of 255 bp of the WNV *E* gene showed the virus had 100% amino acid identity with the equine strain isolated in Tuscany in 1998 [6]. The complete genome sequences of two WNV strains isolated from magpies in Italy in 2008 were also deposited in the Genbank database (Accession No. FJ483548 and FJ483549).

In 2009, further 16 human cases of WNND were notified in northern Italy, including six from Veneto region, eight from Emilia-Romagna region and two from Lombardia region, as recently reported in a detailed description of the epidemiological situation in Italy [7].

Here we report the results of genome sequencing of the first human WNV isolate reported in Italy, which provide evidence of the emergence of a strain more virulent than the WNV strain isolated in Italy in 1998. Moreover, we report further clinical and epidemiological details on human cases of symptomatic WNV infection detected in 2009 in Veneto region.

Samples and methods

Human cases of West Nile neuroinvasive disease in Veneto region, 2009

A surveillance programme for possible human cases of WNND has been implemented in Veneto region since September 2008, as reported previously [4]. According to this programme, all possible cases of WNV infection are referred to our Regional Reference Laboratory which performs the following diagnostic tests [4]: detection of WNV RNA in plasma and cerebrospinal fluid (CSF) samples by real-time RT-PCR and detection of IgM and IgG antibodies against WNV in serum and CSF samples by ELISA testing (Focus Diagnostics, Cypress, CA). ELISA-positive samples are further tested by plaque-reduction neutralisation test (PRNT) for confirming specificity of antibody response, while WNV RNA-positive samples are inoculated onto confluent monolayers of Vero E6 cells for virus isolation. Moreover, nucleic acid test (NAT) screening for WNV RNA has been applied to all blood, tissue and organ donations collected from 1 August to 30 October 2009 in the province of Rovigo.

In August-September 2009, six new cases of WNND were identified in Veneto region, following the six cases reported in 2008 [4]. Five of the patients in 2009 were resident in Rovigo province and one in a village in the south of Venice province, not far from Rovigo province (Figure 1).

To date, no cases of West Nile fever have been notified in 2009. Detailed clinical and laboratory data of cases are summarised in Table 1.

Genome sequence analysis of the first human West Nile virus isolate reported in Italy

At the end of August 2009, a WNV strain was isolated in Vero E6 cells from a NAT-positive blood donation of an asymptomatic individual resident in Rovigo province. At the time of blood donation, the donor was WNV IgM- and IgG-negative but after

TABLE 1

Clinical and laboratory data on cases of West Nile neuroinvasive disease notified in Veneto region, Italy, 2009

Referral date	Sex/age (years)	Symptoms	Laboratory data	Outcome*	Province
31 Aug	M/76	Fever, severe meningoencephalitis	IgM+/IgG+ in serum and CSF, PRNT confirmed, WNV RNA-negative.	Amelioration of symptoms, discharged from hospital on 13 October	Rovigo
8 Sep	F/78	Fever, severe meningoencephalitis	IgM+/IgG+ in serum and CSF, PRNT confirmed, WNV RNA-positive in plasma.	Still hospitalised, amelioration of symptoms	Venice
10 Sep	M/82	Fever, headache, severe meningoencephalitis	IgM+/IgG+ in serum and CSF, PRNT confirmed, WNV RNA-negative.	Death on 17 September	Rovigo
11 Sep	M/62	Fever, headache, severe meningoencephalitis	IgM+/IgG- in serum and CSF, PRNT confirmed, WNV RNA-negative.	Amelioration of symptoms, discharged from hospital on 25 September	Rovigo
24 Sep	M/78	Guillain-Barré syndrome	IgM+/IgG+ in serum and CSF, PRNT confirmed, WNV RNA-positive in plasma.	Still hospitalised with severe disease	Rovigo
28 Sept	F/84	Fever, arthritis, severe meningoencephalitis	IgM+/IgG- in serum and CSF, PRNT confirmed, WNV RNA-negative.	Still hospitalised with symptoms	Rovigo

WNV: West Nile virus; CSF: cerebrospinal fluid; PRNT: plaque-reduction neutralisation test.

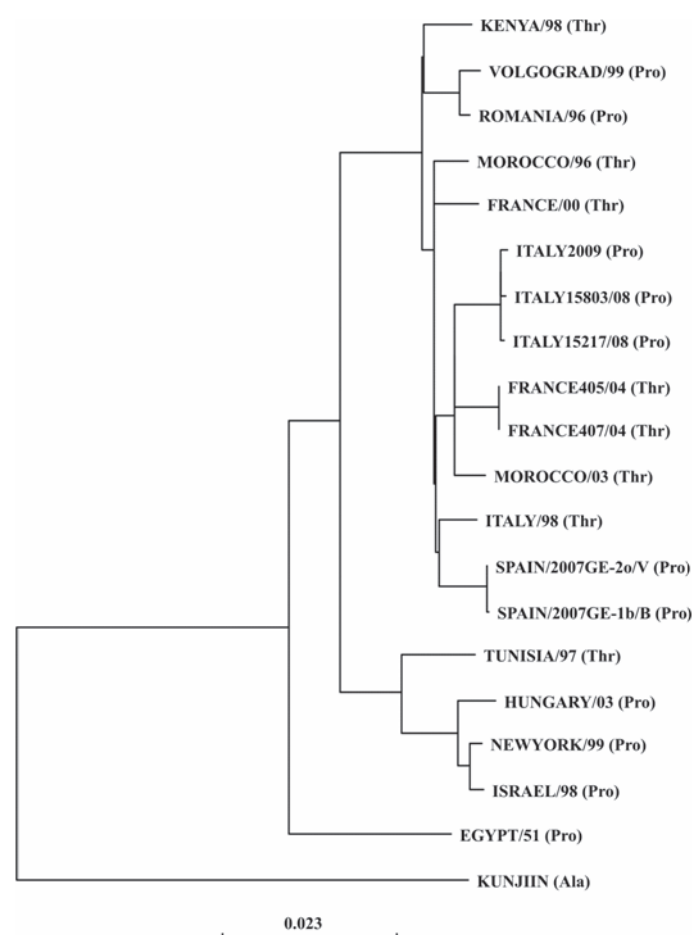
*As of 5 November 2009 (date of publication).

a few days showed seroconversion and remained asymptomatic. WNV growth in cell cultures was demonstrated by the presence of cytopathic effect in the monolayer and detection of WNV-RNA at real-time RT-PCR testing.

For WNV genome sequencing, the supernatant of infected Vero E6 cells at the first passage was collected for RNA and PCR amplification with a set of 21 primer pairs targeting overlapping sequences of ~600 nucleotides in WNV genome. Primer sequences are available upon request. Amplicons underwent bi-directional sequencing by using the BigDye® Terminator Sequencing Kit on

FIGURE 2

Maximum likelihood phylogenetic tree of aligned complete genome sequences of 20 West Nile virus strains, including the strain isolated from a blood donation in the province of Rovigo, Veneto region, in 2009, and two strains isolated from magpies in Italy, in 2008



ITALY2009: human, from blood donation in Rovigo province, Italy, 2009 (Genbank Accession No. GU011992)
 ITALY15217/08 and ITALY15803/08: magpies, Italy, 2008
 The amino acid at each NS3-249 site is indicated between brackets. Branch lengths are drawn to scale to indicate the number of nucleotide changes (genetic distances). Scale bar shows the number of base substitution per site. All WNV strains belong to lineage 1, clade 1a, with the exception of Kunjin virus (outgroup) which belongs to clade 1b.

a 3100 Genetic Analyzer (Applied Biosystems, Foster City, CA). After alignment and assembling with the SeqScape v2.5 software (Applied Biosystems), the consensus sequence (Genbank Accession No. GU011992) was aligned using ClustalW and Blastp with genome sequences of the following WNV strains: Kunjin 1973 (MRM61C; Westaway; Accession No. D00246), Egypt 1951 (Eg101; Accession No. AF260968), Romania 1996-mosquito (R097-50, *Culex pipiens*, Bucharest, Romania; Accession No. AF260969), Italy 1998-equine (PaAn981, Tuscany, Italy; Accession No. AF404757), Volgograd 1999-human (Accession No. AF317203), NY 1999-human (Accession No. AF202541), Spain 2007 GE-1b/B and GE-2o/V (golden eagle *Aquila chrysaetos*; Accession No. FJ766331 and FJ766332, respectively), France 407/2004 and 405/2004 (house sparrow *Passer domesticus* and common magpie *Pica pica*; Accession No. DQ786573 and DQ786572, respectively), Morocco 2003-equine (Accession No. AY701413), France 2000-equine (PaAn001, Accession No. AY268132), Morocco 1996-equine (Accession No. AY701412), Kenya 1998-mosquito (KN3829; Accession No. AY262283), Tunisia 1997-human (PaH001; Accession No. AY268133), Hungary 2003-goose (*Anser anser domesticus*; Accession No. DQ118127), Israel 1998-goose (*Anser anser domesticus*; Accession No. AF481864). Two WNV strains, 15217 and 15803, isolated from magpies in Italy in 2008 (Genbank Accession No. FJ483548 and FJ483549, respectively) were also included in the analysis. The aligned nucleic acid sequences were used to construct a phylogenetic tree using the maximum likelihood algorithm within Phylo_Win v2.0 software with bootstrap resampling analysis (500 iterations) (Figure 2).

Results

Phylogenetic tree analysis of the complete genome sequence of 20 WNV strains shows that the human WNV strain isolated in Italy in 2009 belongs to lineage 1, clade 1a, and is closely related to the two WNV strains isolated from magpies in Italy in 2008 (average nucleotide and amino acid divergence of 0.14% and 0.07%, respectively) (Figure 2). Both the human 2009 WNV isolate and the WNV strains isolated from magpies in Italy in 2008 were phylogenetically related to strains isolated since 1996 in the western Mediterranean area, including the Italy 1998-equine WNV strain (Figure 2). In particular, nucleotide and amino acid divergence of the 2009-human WNV isolate from the Italy 1998-equine WNV strain was 1.62% and 0.25%, respectively. All amino acid changes among Italian WNV isolates are detailed in Table 2.

The 2008-2009 Italian WNV isolates had a higher degree of divergence from the eastern European strains isolated in Romania in 1996 and in Russia in 1999 and from the American/Israeli cluster (Figure 2). Our findings obtained with WNV complete genome sequences, which confirm the results of a recently reported detailed genetic analysis of Mediterranean WNV strains [8], provide a more detailed picture of WNV evolution in Italy and in the Mediterranean area than the phylogenetic analysis performed on a partial sequence of the WNV *E* gene obtained from veterinary samples in Italy in 2008 [6].

Based on these results, we believe that the WNV strain responsible for the recent outbreaks might have originated from the Italy 1998-equine strain, since the virus seems to have had

a continuous low level, endemic circulation in Italy from 1998 to 2008. The virus might have also evolved somewhere else in western Mediterranean area and then it might have been reintroduced in Italy, for instance by migratory birds. The rapid spread in the last two years in Italy, with the occurrence of human cases of WNND, might be due to the positive selection of amino acid mutations in viral proteins conferring increased virulence and transmission capacity. In this regard, it is interesting to note that, in comparison with the Italy 1998-equine strain and with other western Mediterranean strains, the recent Italian WNV isolates have acquired the Thr249Pro mutation in the helicase domain of the NS3 protein, a trait associated with avian virulence [9]. In fact, this mutation is predicted to confer higher stability to the NS3 protein at high temperature conditions, such as in avian hosts, where the mutated virus can efficiently replicate leading to high levels of viraemia in birds that may facilitate the infection of new mosquito vectors. In support of this hypothesis, high mortality rates were reported among birds in the United States (US) and Israel, whereas seroprevalence studies in Romania indicated significant infection of resident birds [9,10]. It is important to note that the NS3 Thr249Pro mutation has emerged on at least three independent occasions (i.e., in the 1951 Egyptian isolate, in the 1996 Romanian isolate and within the Israeli/North American clade) and, in each case, viruses carrying this substitution have been associated with human disease outbreaks [9]. The WNV strains isolated from golden eagles in Spain in 2007 also carry the NS3 Thr249Pro change [8]. Studies in mice showed that the Spanish isolates do not have increased pathogenicity as compared with other strains, but virulence in birds has not been investigated [8].

Conclusions

Since 2008, an outbreak of WNV infection is ongoing in north-eastern Italy, in areas surrounding the Po river delta. The Italian outbreak is characterised by the occurrence of cases of severe meningoencephalitis [3-5,7], as also described in the recent outbreaks in the US [11], Romania [12], Israel [13], and Russia [14]. The number of human cases of WNND identified in the province of Rovigo represents about 1% of all cases of WNV infection occurring in 2009 in Rovigo province as estimated from

the preliminary results of an ongoing seroepidemiological survey on blood donors.

Genome sequencing of WNV isolates is providing insight into the mechanism of re-emergence of this virus in Italy. In fact, the human WNV strain isolated this year and the strains isolated from magpies in 2008 are closely related to the Italy 1998-equine strain and to other western Mediterranean strains, with the acquisition of new amino acid mutations in non-structural proteins. These mutations include the Thr249Pro change in WNV-NS3 helicase, a trait associated with avian virulence and rapid geographic diffusion of WNV in North America [9]. In this regard, the veterinary and entomologic surveillance demonstrates that the virus is endemic in Italy and that it is rapidly spreading to other regions [15]. However, at variance with the WNV outbreaks in the US and Israel [16], the Italian outbreak does not seem to be associated with a particularly high mortality rate among birds [15]. The mechanisms of susceptibility of different bird species for WNV virulence is still unknown and might be related both to the genetic and immunological characteristics of the avian hosts and to the particular genetic backbone of each WNV strain [16].

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TABLE 2

Description of amino acid differences among Italian West Nile virus strains

AA position in WNV polyprotein	AA position in WNV proteins	Italy- 98 AF404757 (equine)	Italy-08 FJ483548 (magpie)	Italy-08 FJ483549 (magpie)	Italy-09 GU011992 (human)
851	NS1-60	Val	Val	Val	Ala
1228	NS2A-85	Ile	Val	Val	Val
1248	NS2A-105	Ile	Ile	Thr	Ile
1494	NS2B-120	Ile	Ile	Val	Val
1754	NS3-249	Thr	Pro	Pro	Pro
2209	NS4A-85	Val	Ile	Ile	Ile
2224	NS4A-100	Pro	Ser	Ser	Ser
2581	NS5-53	His	His	Tyr	His
2786	NS5-258	Val	Ala	Ala	Ala
2950	NS5-422	Arg	Lys	Lys	Lys

AA: amino acid; NS: non-structural protein.

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Research articles

“I-MOVE” TOWARDS MONITORING SEASONAL AND PANDEMIC INFLUENZA VACCINE EFFECTIVENESS: LESSONS LEARNT FROM A PILOT MULTI-CENTRIC CASE-CONTROL STUDY IN EUROPE, 2008-9

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Within I-MOVE (European programme to monitor seasonal and pandemic influenza vaccine effectiveness (IVE)) five countries conducted IVE pilot case-control studies in 2008-9. One hundred and sixty sentinel general practitioners (GP) swabbed all elderly consulting for influenza-like illness (ILI). Influenza confirmed cases were compared to influenza negative controls. We conducted a pooled analysis to obtain a summary IVE in the age group of ≥ 65 years. We measured IVE in each study and assessed heterogeneity between studies qualitatively and using the I² index. We used a one-stage pooled model with study as a fixed effect. We adjusted estimates for age-group, sex, chronic diseases, smoking, functional status, previous influenza vaccinations and previous hospitalisations. The pooled analysis included 138 cases and 189 test-negative controls. There was no statistical heterogeneity ($I^2=0$) between studies but ILI case definition, previous hospitalisations and functional status were slightly different. The adjusted IVE was 59.1% (95% CI: 15.3-80.3%). IVE was 65.4% (95% CI: 15.6-85.8%) in the 65-74, 59.6% (95% CI: -72.6 -90.6%) in the age group of ≥ 75 and 56.4% (95% CI: -0.2-81.3%) for A(H3). Pooled analysis is feasible among European studies. The variables definitions need further standardisation. Larger sample sizes are needed to achieve greater precision for subgroup analysis. For 2009-10, I-MOVE will extend the study to obtain early IVE estimates in groups targeted for pandemic H1N1 influenza vaccination.

Introduction

The influenza virus has a high genetic mutation rate that frequently determines antigenic drifts and occasionally antigenic shifts. To achieve a good match between circulating and vaccine viruses, the composition of the vaccine has to be reformulated each season based on the recommendations of the World Health Organization (WHO) Global Influenza Surveillance Network [1].

Therefore, influenza vaccine effectiveness (IVE) can vary from year to year according to the degree of match between the selected vaccine strains and those actually circulating. Hence, IVE should be measured and monitored every year. In a pandemic situation, strain specific vaccines become available only four to six months after beginning the development of the vaccine. Consequently, when the vaccines start to be administered, the virus is already circulating and IVE results are needed rapidly. In addition, vaccine availability is likely to increase over time according to the speed of vaccine production and the licensing of additional vaccines, meaning that IVE measurements need to be repeated over time during the pandemic.

Many factors affect IVE in observational studies. IVE estimates vary according to the specificity of the outcome, the influenza incidence, the population targeted for vaccination and the confounding factors taken into account. Many of the case-control studies reported in the literature measured IVE against clinical outcomes (i.e. hospitalisations for pneumonia or influenza, acute respiratory infections, influenza-like illness (ILI)). Clinical outcomes for influenza are non-specific and likely to underestimate the IVE [2]. To minimise bias, laboratory-confirmed influenza is now being used as outcome in case-control studies in Canada, Australia and the USA [3-5].

Confounding affects IVE observational studies. IVE is underestimated when individuals at higher risk of acquiring influenza are more likely to be vaccinated than individuals at lower risk (negative confounding by indication) [6,7]. IVE is overestimated if individuals more cautious about their health and at lower risk of acquiring influenza are more likely to be vaccinated (positive confounding due to healthy vaccinee effect) [7,8].

In general practitioners (GP) based case-control studies, individuals who use health services more often are more likely to be vaccinated and more likely to consult their GP with influenza symptoms. Vaccinated individuals with influenza symptoms will have a higher probability of being included in the study than vaccinated individuals with no influenza symptoms. This would underestimate the IVE. To control for health seeking behaviour, recent studies suggested comparing individuals who consult for ILI and are influenza positive to individuals consulting for ILI who test negative for influenza (test-negative controls) [3-5;9]. The assumption is that test-negative controls have the same vaccination coverage as the source population giving rise to the influenza cases detected at the GP practice.

I-MOVE started in 2007 with the aim to measure IVE against seasonal and pandemic influenza in the European Union (EU) and the European Economic Area (EEA). Two cohort and five case-control studies to measure IVE were piloted in the 2008-9 season. In order to develop a sustainable system, the studies were conducted in the framework of existing GP-based influenza sentinel surveillance systems. All the country teams conducting I-MOVE pilot studies are members of the European Influenza Surveillance Network (EISN) (the successor of the Commission-funded network, EISS). EISN collects and exchanges timely information on influenza activity in Europe [11]. National Reference Laboratories participating in EISN are evaluated periodically through external inter-laboratory quality control assessments. All the EU Member States recommend seasonal vaccine for the elderly either defined as 65 years old and older or as 60 years old and older [12].

In the pilot case-control studies, we measured IVE against laboratory-confirmed influenza and collected variables to control for positive and negative confounding in the analysis. We restricted the study population to community-dwelling elderly. To increase the precision of the estimates and to provide a summary IVE for the five studies, we explored the feasibility of conducting a pooled analysis. We present here the pooled results of the pilot case-control studies conducted in Denmark, Hungary, Portugal, Romania, and Spain. We assumed that if the pooled case-control design was feasible for seasonal vaccine, the study population could later be expanded to include the age groups targeted for the pandemic vaccine.

Methods

The study population consisted of community-dwelling elderly living in selected sentinel GP practice catchment areas in the five participating European countries. Age groups included were 60 year-olds and older in Hungary and 65 year-olds and older in the other four countries. Participating sentinel GPs swabbed all community-dwelling elderly individuals consulting for ILI during 2008-9 influenza season.

For the first time, in Denmark, Hungary, and Romania sentinel GPs used the EU ILI case definition [13]. In Spain, the ILI EU case definition was used with an additional stated criterion “without any other suspected diagnosis”. In Portugal, ILI was defined as in the routine sentinel surveillance, according to GPs’ criteria. Clinical symptoms were collected for all ILI cases.

ILI patients were not eligible for the study if they were institutionalised, had evidence of dementia, did not speak the local language or refused participation.

A case of influenza was defined as an ILI patient who was swabbed and tested positive for influenza using real-time polymerase chain reaction (RT-PCR) or culture. Test-negative controls included in the five studies were ILI patients who were swabbed and tested negative for influenza.

To check if vaccination coverage observed among ILI patients testing negative for influenza was different from that observed in other potential control groups, we measured vaccination coverage among systematic samples of patients from participating GPs who had not had ILI since the beginning of the influenza season (non-ILI controls; up to two controls selected around the time of occurrence of a case) (Hungary, Portugal, Spain), in the community (Denmark, Portugal) and in the participating GPs’ catchment area (Hungary, Romania, Spain).

A person was considered vaccinated if s/he had received the 2008-9 influenza vaccine more than 14 days before date of onset of ILI symptoms or of selection as a control.

The minimum set of common confounding variables for the five countries included age, sex, presence of chronic conditions and their respective severity measured in number of hospitalisations for the chronic diseases in the previous 12 months or any hospitalisation in the previous 12 months (Hungary and Portugal), smoking history (none, past, current smoker), functional status (help for bathing and/or help for walking), and influenza vaccination in the previous two seasons.

All ILI patients had a nasal or throat swab taken, which was tested for influenza at the respective countries’ National Influenza Reference Laboratory (in Spain, all laboratories integrated in the Spanish Influenza Sentinel Surveillance System) using RT-PCR techniques and/or culture. In each country, all or a subset of influenza isolates were antigenically characterised. Laboratory viral detection, typing, subtyping and variant analysis performed in each of the National Reference Laboratories are described elsewhere [14].

The sentinel GPs carried out face-to-face interviews with ILI patients and non-ILI control patients using country-specific standardised questionnaires. Trained interviewers conducted telephone interviews with community controls using a standardised questionnaire in Denmark and Portugal. Each country study team entered and validated data.

A previously agreed minimum dataset for pooling, including information on case or control status and exposure status and several covariates, was sent to EpiConcept, the I-MOVE coordination focal point. EpiConcept checked the data again for inconsistencies, outliers and logical errors and conducted the pooled analysis.

We created a common restricted dataset of ILI patients meeting the EU case definition, older than 64 years and with a delay between onset of symptoms and swabbing of less than eight days. For each of the country specific datasets, we excluded the controls identified before the week of the first case and after the week of the last case, in order to include only ILI cases within the influenza season.

IVE estimates were obtained using the formula: 1- odds ratio, with 95% exact confidence intervals (CI) [10,15].

We computed study specific crude IVE and adjusted for the pre-defined set of confounders (including age, sex, chronic disease, smoking, previous influenza vaccination and functional status) where possible, using logistic regression. We evaluated heterogeneity between studies qualitatively by assessing the standardisation of the case and covariate definitions. We evaluated statistical heterogeneity using the Q-test and the I² index [16,17]. To estimate a pooled IVE, we used a one-stage method with study

as fixed effect in the model. Results were stratified according to influenza strain and two age groups: 65-74 and >74 years.

According to country specific requirements for ethical approval, all participants provided oral or written consent.

FIGURE 1

Influenza-like illness (ILI) incidence (cases per 100,000 population) reported by the national influenza sentinel surveillance systems in Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9*

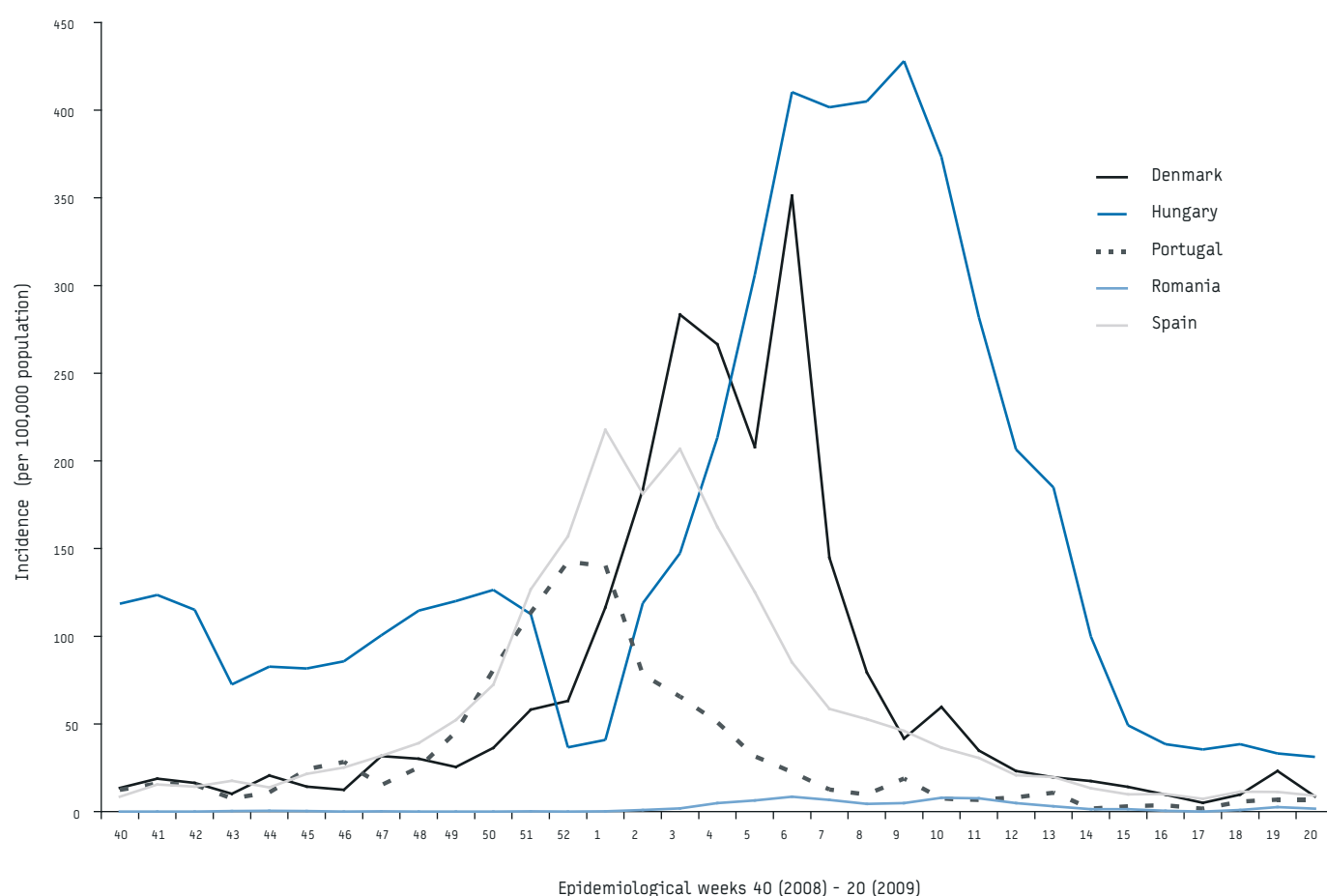


TABLE 1

General practitioner (GP) participation and influenza-like illness (ILI) cases recruitment by study, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

Study	Number of GPs accepting to participate	Number of GPs recruiting at least one ILI patient (%)	Number of ILI patients recruited by GPs	Number of ILI patients positive to influenza (%)	Number of non-ILI GP patients	Number of community controls
Denmark	40	29 (73)	63	25 (40)	N/A	80
Hungary	50	27 (54)	144	45 (32)	89	N/A
Portugal	42	9 (21)	42	15 (36)	40	136
Romania	47	28 (60)	103	30 (29)	N/A	N/A
Spain	164	67 (40)	103	44 (43)	88	N/A
Total	343	160 (47)	455	159 (35)	217	216

FIGURE 2

Diagramme with study exclusion criteria, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

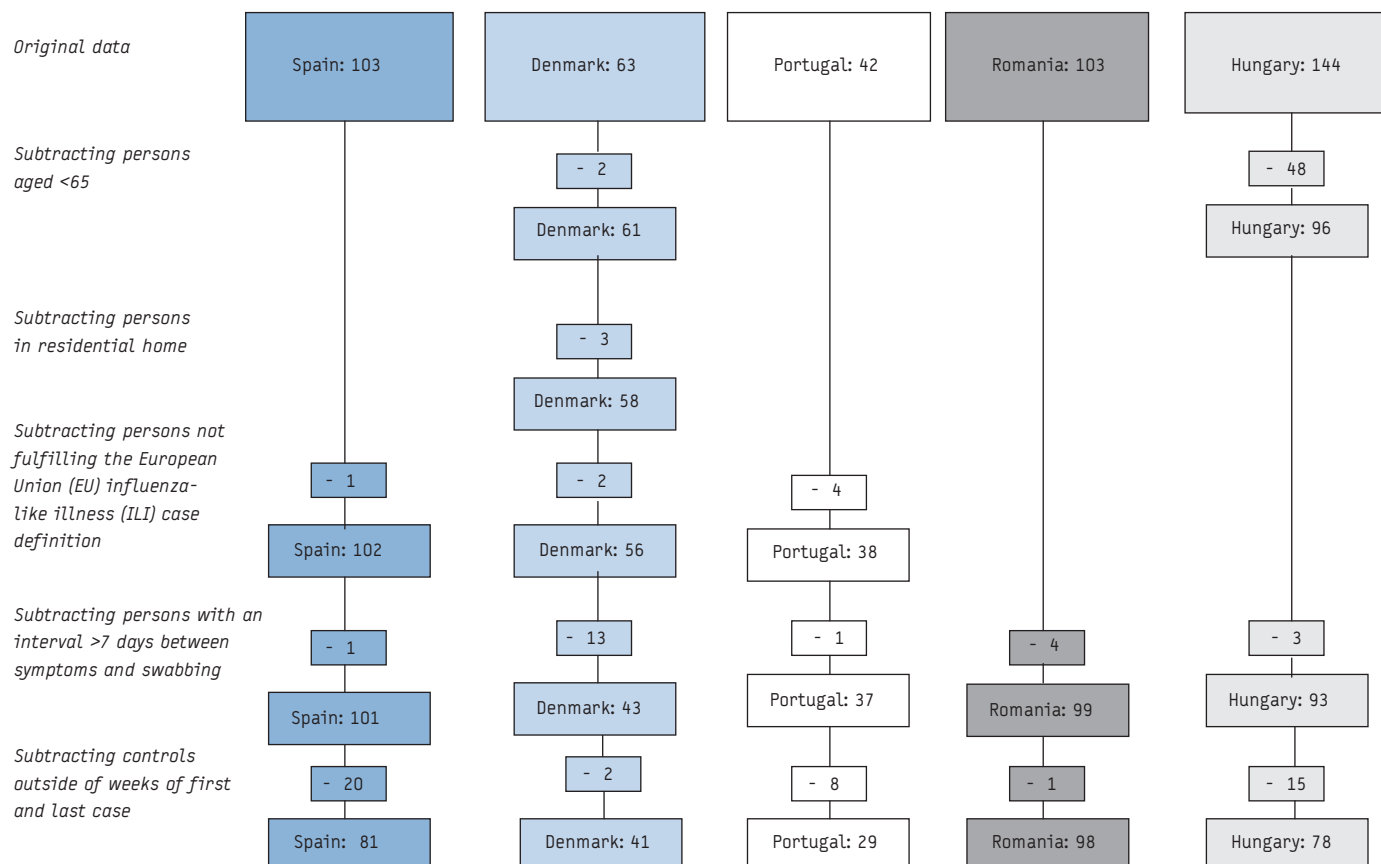


TABLE 2

Influenza cases and test-negative controls by study and characteristic, Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

Characteristics	Country	ILI patients		p
		Influenza cases	Test-negative controls	
Interval from symptom onset to swab sample collection (mean in days)	Denmark	3.05	4.25	0.001*
	Hungary	2.1	3.08	0.036*
	Portugal	1.5	2.33	0.030*
Mean age	Portugal	70	75	0.040*
		Number with characteristic / total	Number with characteristic / total	
Any influenza vaccination in past 2 seasons	Portugal	4/14	10/14	0.023**
	Spain	28/43	33/36	0.005**
Fever	Denmark	19/20	14/21	0.022**
	Romania	30/30	57/68	0.019**
Cough	Denmark	20/20	16/21	0.020**
Chronic pulmonary disease	Romania	1/30	13/68	0.040**

*Mann-Whitney U test, **Chi square

Results

In the participating pilot countries, the 2008-9 seasonal influenza epidemic started in Portugal at the end of 2008 (epidemiological week 49) and spread to the east of Europe (Hungary) in spring 2009 (week 4) (Figure 1).

The duration of the epidemic period ranged from seven weeks in Denmark to 13 weeks in Romania. The influenza peaks were reached between week 52 in 2008 (Portugal) and week 10 in 2009 (Romania).

In the five participating countries, the population was vaccinated with a trivalent inactivated influenza vaccine. In the 2008-9 influenza season, different vaccine brands were used in each of the countries. The number of GPs enrolled in each of the studies ranged from 40 in Denmark to 164 in Spain. Overall, 160 GPs recruited at least one patient ranging from 21% in Portugal to 73%

in Denmark (Table 1). GPs swabbed and interviewed a total of 455 ILI patients. Among them, 159 (35%) were positive for influenza (from 29% in Romania to 43% in Spain). The completeness of the variables in the returned questionnaires varied from 85% to 100%.

Among 147 isolates typed before the restriction criteria were applied, 131 (89%) were influenza A and 16 (11%) B. Ninety-five of the A isolates were H3N2. All H3N2 strains genetically characterised were A/Brisbane/10/07 similar to the H3N2 vaccine component of the 2008-9 northern hemisphere vaccine. The B strain included in the 2008-9 vaccine did not match the circulating strain. Eight out of the 16 type B isolates were from cases enrolled in Hungary.

After applying the study restriction criteria we included 138 cases and 189 test-negative controls in the analysis (Figure 2).

TABLE 3

Vaccination coverage for the seasonal 2008-9 influenza vaccine by control group and country study, Denmark, Hungary, Portugal, Romania, and Spain, 2008-9

Study	Vaccine coverage (%) in ILI positive cases	Vaccine coverage (%) in test-negative controls	Vaccine coverage (%) in non-ILI GP patients	Vaccine coverage in community controls	Vaccine coverage in participating GPs catchment area
Denmark	55	71.4	N/A	53.6**	N/A
Hungary***	41.9	48.7	42.7	N/A	38.5
Portugal	42.9	53.3	70	54.4*	N/A
Romania	46.7	67.6	N/A	N/A	86.9
Spain	61.4	89.2	80.7	N/A	65.3

N/A : not applicable

*Community controls sample selected for national telephone survey (Lisboa: Instituto Nacional de Saúde Dr. Ricardo Jorge, Observatório Nacional de Saúde)

** Community controls randomly selected from the Danish population register

*** Results apply to ages 65 years and above, apart from Hungary where the study was carried out for 60 year-olds and older

TABLE 4

Country specific and pooled crude and adjusted vaccine effectiveness (VE), Denmark, Hungary, Portugal, Romania, and Spain, influenza season 2008-9

		Crude analysis			Adjusted analysis			Variables used for adjustment
		N	VE	95% CI	N	VE	95% CI	
Country specific estimates	Spain	81	80.8	36.0 - 94.2	76	82.9	30.6 - 95.8	age, sex, chronic disease, smoking, functional status
	Portugal	29	34.4	-184.3 - 84.9	28	82.3	-70.5 - 98.2	age, sex, chronic disease, smoking
	Denmark	41	51.1	-78.2 - 86.6	34	90.9	-43 - 99.4	age, sex, chronic disease, smoking, previous influenza vaccination
	Romania	98	58.2	-0.8 - 82.6	92	86.8	38.0 - 97.2	age, sex, chronic disease, smoking, previous influenza vaccination
	Hungary	78	28.6	-78.6 - 71.5	72	43.6	-119.8 - 85.6	age, sex, chronic disease, smoking, previous influenza vaccination
Pooled estimates	65+	327	55.1	27.8 - 72.1	292	59.1	15.3 - 80.3	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	65-74 years				196	65.4	15.6 - 85.8	study, sex, chronic disease, smoking, previous influenza flu vaccination, functional status, previous hospitalisation
	75+ years				96	59.6	-72.6 - 90.6	study, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation
	A(H3) strain				259	56.4	-0.2 - 81.0	study, age, sex, chronic disease, smoking, previous influenza vaccination, functional status, previous hospitalisation

In Romania and Denmark, the proportion of ILI patients presenting with fever was higher among cases than among test-negative controls (Table 2). In Denmark, all of the cases and three quarters of the controls had a cough ($p=0.02$). In Romania, the proportion of ILI patients with pulmonary chronic disease was lower among cases than among controls (3% vs. 19%).

The mean delay between onset of symptoms and swab collection was shorter for cases than for test-negative controls in Portugal, Denmark and Romania (Table 2). In Spain and Portugal, the proportion of people having received influenza vaccines in at least one of the two previous seasons was lower among cases than among test-negative controls.

Vaccination coverage among controls varied according to country and control group; no specific pattern was identified (Table 3).

The country specific adjusted VE estimates ranged from 43.6% (95% CI: -119.8 - 85.6) in Hungary to 90.9% (95% CI: -42.6 - 99.4) in Denmark (Table 4).

In terms of heterogeneity between studies, two out of the five studies used a different ILI definition. Three variables (number of hospitalisations, presence of chronic diseases and functional status) were collected differently in the five studies. The Q test for heterogeneity was 2.87 ($p = 0.579$) and the I² index was 0%.

In the pooled analysis the crude IVE was 55.1% (95% CI: 27.8-72.1%). The IVE adjusted for study, age, sex, presence of chronic conditions, previous hospitalisations, smoking history, functional status, and previous influenza vaccination was 59.1% (95% CI: 15.3-80.3%) (Table 4).

The adjusted IVE was 65.4% (95% CI: 15.6-85.8%) in the 65-74 year-olds and 59.6% (95% CI: -72.6 -90.6%) in the age-group of ≥ 75 years. The adjusted IVE against the A(H3) strain was 56.4% (95% CI: -0.2-81.0%).

Discussion

We estimated influenza VE against laboratory-confirmed medically attended influenza using test-negative controls, within existing sentinel GP networks in five EU countries. The country specific and the pooled IVE estimates suggest a protective effect of the 2008-9 seasonal vaccine in the elderly population in a year with a good match between the seasonal vaccine and the A(H3) strain predominantly circulating in Europe [18]. However, the estimates have wide confidence intervals.

The case-control design using test-negative controls was performed easily in the framework of the established GP sentinel surveillance networks. Participating GPs had previous experience in collecting swabs and in completing a form for each patient swabbed. Among the GPs who accepted to participate in the study, less than half interviewed and swabbed ILI patients. This may be explained by the overall low incidence of ILI in the elderly in 2008-9 [18] rather than a low acceptability of GPs, as swabbing and interviewing ILI patients is a simple way of recruiting cases and test-negative controls. The questionnaires used for data collection were short leading to a high completeness of all variables. At the end of the season, the study coordinators in Denmark, Romania, and Spain interviewed GPs who participated in the 2008-9 study. Most of them (95% in Spain, 78% in Romania, 74% in Denmark) would be willing to participate in the study in 2009-10 (data not shown). In 2006 in Denmark (one of the current study sites),

Mazick *et al.* showed similar acceptability results following an influenza VE case-control study based on the sentinel GP network [19].

The recruitment procedure minimised selection bias as all ILI cases were swabbed. Furthermore, GPs did not know the case or control status when recruiting ILI patients. This was the first season in which the EU ILI case definition was introduced into the sentinel GP networks. For most ILI patients recruited, the case definition was correctly used: of 455 ILI patients reported, only 17 were excluded because they did not match the EU ILI case definition. However, we cannot rule out that some GPs did not include all patients corresponding to the EU case definition. If the sensitivity of GPs' ILI case definition were dependent on the vaccination status, IVE might have been over- or underestimated.

Various studies suggest that ILI test-negative controls represent the source population of influenza cases seen at GPs offices and that the study design adjusts for propensity to seek care. This would mean that the propensity to seek care is equal between ILI patients who test positive and those testing negative for influenza. Our results indicate that in three out of the five studies, the delay between onset of symptoms and swabbing was shorter for cases than for test-negative controls. Similar results were found in the Wisconsin study [3]. This may indicate a different health-seeking behaviour or a different severity of ILI in cases and in controls. Health-seeking behaviour of ILI cases and ILI test-negative controls should be further studied and compared.

To further assess the representativity of test-negative controls, we measured the vaccine coverage in other potential control groups. The vaccine coverage differed by control group (test-negative controls, non-ILI GP controls, community controls) and between countries with no specific pattern. This could suggest that the source population of influenza cases consulting a GP may be country specific. In general, the vaccine coverage in the community or in the GPs catchment area was lower than the vaccine coverage of GP clients indicating that community controls do not represent a good control group for medically-attended ILI influenza cases. In a recent study in Wisconsin, VE for laboratory confirmed medically attended-ILI was estimated for three seasons using two control groups: test-negative controls and controls randomly selected from individuals in the source population who did not have a clinical encounter for acute respiratory illness prior to the week of recruitment [3]. In the three seasons, the vaccination coverage of the test-negative controls was higher than among the other controls.

We took into account the main confounding factors identified in the literature. Most of them were based on patients' report for which validity is unknown. The pooled crude and adjusted IVE were similar suggesting a low distortion of effect due to confounding. In our study, a small proportion of ILI patients had indicators of frailty (4.3% had poor functional status and 6.4% were hospitalised in the previous year). Elderly ILI patients consulting GPs at their office may have a better health status than those not consulting. Therefore, functional status and severity may not be relevant confounding factors within this study population and study design. Our results may also reflect that using specific outcomes decrease the amount of confounding observed [5,7]. In Canada, using the same study design, IVE did not change when adjusting for chronic diseases [20].

The excellent collaboration between the study teams made the pooling of data from the five studies possible. Pooling increased the precision of the estimates. Given the small samples sizes of the individual studies, we used a one-stage pooling model that assumes that the effect of the exposure (the seasonal vaccine) and the effect of the covariates are the same in all the studies. We do not know if the difference in virus circulation in the various countries and a potential different health-seeking behaviour may violate this assumption. The pooled estimates of the pilot phase have to be interpreted with caution as heterogeneity between studies may exist. Furthermore, different vaccine brands were used. However, the aim of I-MOVE is not to guide the Member States in deciding which seasonal vaccine to purchase. In order to assess VE for the various vaccine brands, the sample size would have to be increased significantly. The definitions of some covariates were not exactly the same in the different studies. Tests for interaction between study and covariates did not suggest the presence of heterogeneity. However, the small sample size may have led to an insufficient power to detect heterogeneity.

Conclusions

In 2008-9 the match between the seasonal influenza vaccine and the predominant circulating strains was good and the IVE in the elderly relatively high. Our results suggest that GP based case-control studies using test-negative controls to estimate seasonal IVE against laboratory-confirmed medically-attended influenza, are feasible in Europe. The use of a laboratory confirmed outcome may reduce the magnitude of confounding. If other studies confirm this, the number of confounders documented may be reduced, thus simplifying the data collection. The representativity of test-negative controls should be further evaluated.

Pooling of country specific data is needed to have early seasonal or pandemic VE estimates and to increase the precision of the estimates for subgroup analysis. In 2009-10 we will increase the sample size, by increasing the number of countries participating in the study and including more GPs per country. The larger sample size will allow the use of a two-stage model that better takes into account the potential heterogeneity between studies [18,21]. The studies will use common definitions for all variables to minimise heterogeneity between studies. During H1N1 influenza pandemic, interim analyses will be conducted in different periods according to the available sample size. The timing for conducting each of the interim analyses will depend on the time necessary to reach the appropriate sample size. This will depend mainly on the ILI incidence, the influenza incidence and the vaccination coverage.

The suitability of the case-control studies based on sentinel GPs to measure pandemic IVE will depend on the vaccination and control strategy. If pandemic cases are seen by the sentinel GPs and GPs have the possibility to ascertain patient vaccination status, then the case-control design piloted in 2008-9 would be adequate to estimate pandemic VE. All age and risk groups targeted by the vaccine should be included in the study. The design will be adapted to reduce the GPs' workload by simplifying the questionnaire and revising the procedure to select patients to swab.

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- All participating GPs in Denmark, Hungary, Portugal, Romania, and Spain.

*Erratum: The x-axis in Figure 1 indicated the wrong weeks and this was corrected on 6 November 2009.

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Surveillance and outbreak reports

INFLUENZA-LIKE ILLNESS SURVEILLANCE USING A DEPUTISING MEDICAL SERVICE CORRESPONDS TO SURVEILLANCE FROM SENTINEL GENERAL PRACTICES

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Standard sources of data for influenza surveillance include notifications of laboratory-confirmed cases and notifications from sentinel general practices. These data are not always available in a timely fashion, leading to proposals to use more immediate data sources such as over-the-counter drug sales, ambulance call-outs and web searches to monitor influenza-like illness (ILI). We aimed to assess data from a deputising medical service as another source of data for timely syndromic influenza surveillance. We measured the extent of agreement between the weekly percentage of patients with ILI reported from sentinel general practices and the corresponding weekly percentage reported from a deputising medical service in Victoria, Australia over ten years, from 1999 to 2008. There was good agreement between the two data sources, with suitably narrow limits of agreement. The deputising medical service did not use a standardised definition of ILI and is not supplemented by laboratory confirmation of suspected cases. Nevertheless, the results of this study show that such data can provide low cost and timely ILI surveillance.

Introduction

In temperate southern Australia, the influenza season occurs between May (late autumn) and October (early spring). Sentinel general-practitioner (GP) surveillance, operational in Victoria during the influenza season, reports weekly on the number of patients fulfilling the Australian nationally agreed case definition of influenza-like illness (ILI): cough, fever and fatigue. Respiratory specimens taken from a proportion of cases permit diagnosis of laboratory-confirmed influenza [1]. Not all ILI cases are confirmed as influenza. In Victoria, Australia, the proportion of confirmed cases between 2003-2007 varied from 18-47%, annually [2].

Besides notifications from sentinel GPs, another standard method of influenza surveillance is to count the number of laboratory-confirmed cases notified to a public health authority [1]. Both these standard data sources, which involve laboratory testing, are associated with a reporting lag due to the time taken for specimen testing and reporting. For instance, the median interval between symptom onset and registration for a laboratory test was three days for a patient recruited through sentinel GPs in Victoria in 2007 and 2008.

To overcome the problem of delay, surveillance using more immediate data sources without laboratory confirmation, referred to as syndromic surveillance, have been implemented. These include over-the-counter drug sales [3], telephone calls to health information lines such as nurse on call [4], ambulance call-outs [5], school or workforce absenteeism [6,7], and web searches [8-10].

One surveillance source, previously described by Turner and Kelly [11] but not formally assessed, is a deputising medical service, that is, an out-of-hours service for GP consultations. Many deputising services record the reason for the call-out and the final diagnosis in an electronic database, such as the GP house call surveillance system in Bordeaux, France [12]. The aim of this study was to measure the extent of agreement between ILI surveillance data from the deputising service and data from the sentinel GP system in Melbourne, Australia, in order to assess whether the former could be used for routine influenza surveillance.

Methods

The Melbourne Medical Deputising Service (MMDS) is a deputising, out-of-hours general practice service. Deputising doctors attend patients in their homes within a 45 km radius of the Melbourne Central Business District. Demographic (e.g. age, sex) and clinical data (e.g. diagnosis) are entered by the deputising doctor into a customised database, usually within 24 hours of the consultation. Access to the data is available on a password-protected page of the MMDS website. The data are available for use in a surveillance system as soon as they are entered, i.e. within 24 hours of the consultation.

We routinely obtain the proportion of ILI call-outs from the MMDS once a week, although they could be obtained daily with a 24-hour lag. The weekly data extraction uses a validated search algorithm that identifies the number of call-outs for ILI. This is divided by the total number of call-outs for that week and expressed as a percentage per 100 call-outs. MMDS data are available throughout the year. The search algorithm has been validated by manual confirmation of the diagnosis of all patients identified by the search algorithm for week 34 in the years 2002 to 2007, a week of high activity for all years in that period. The search algorithm successfully identified ILI call-outs searching for the terms 'flu' and 'infl' and excluding terms such as 'reflux'

and 'fluid' that included the letters 'flu'. New exclusion terms, 'fluvax', 'at risk' and 'immunisation', were added to the algorithm in 2009 to exclude pandemic H1N1 influenza contacts who received prophylactic antiviral treatment.

For the sentinel GP system, we used the number of consultations that met the nationally agreed definition of ILI expressed as a percentage of total visits as the comparator. We then assessed the degree of consensus between this measure and that from the MMDS, using a standard statistical method developed by Bland and Altman [13,14]. This method is based on reporting the difference between the two measures, and the 95% limits of agreement, which provide an interval in which 95% of the differences between the two measurements are expected to lie. If the limits of agreement describe differences that are not of material importance, the data sources can be used interchangeably.

As described by Bland and Altman [14], it is not unusual for the difference between two measures and the standard deviation to increase with increasing values of the two measures being assessed, and this should be accounted for in the statistical analysis, otherwise the limits of agreement will be too wide for low values of weekly ILI proportions and too narrow for high

values. Accordingly, we regressed the difference of the weekly ILI percentages on their average, using absolute residuals to estimate the standard deviation.

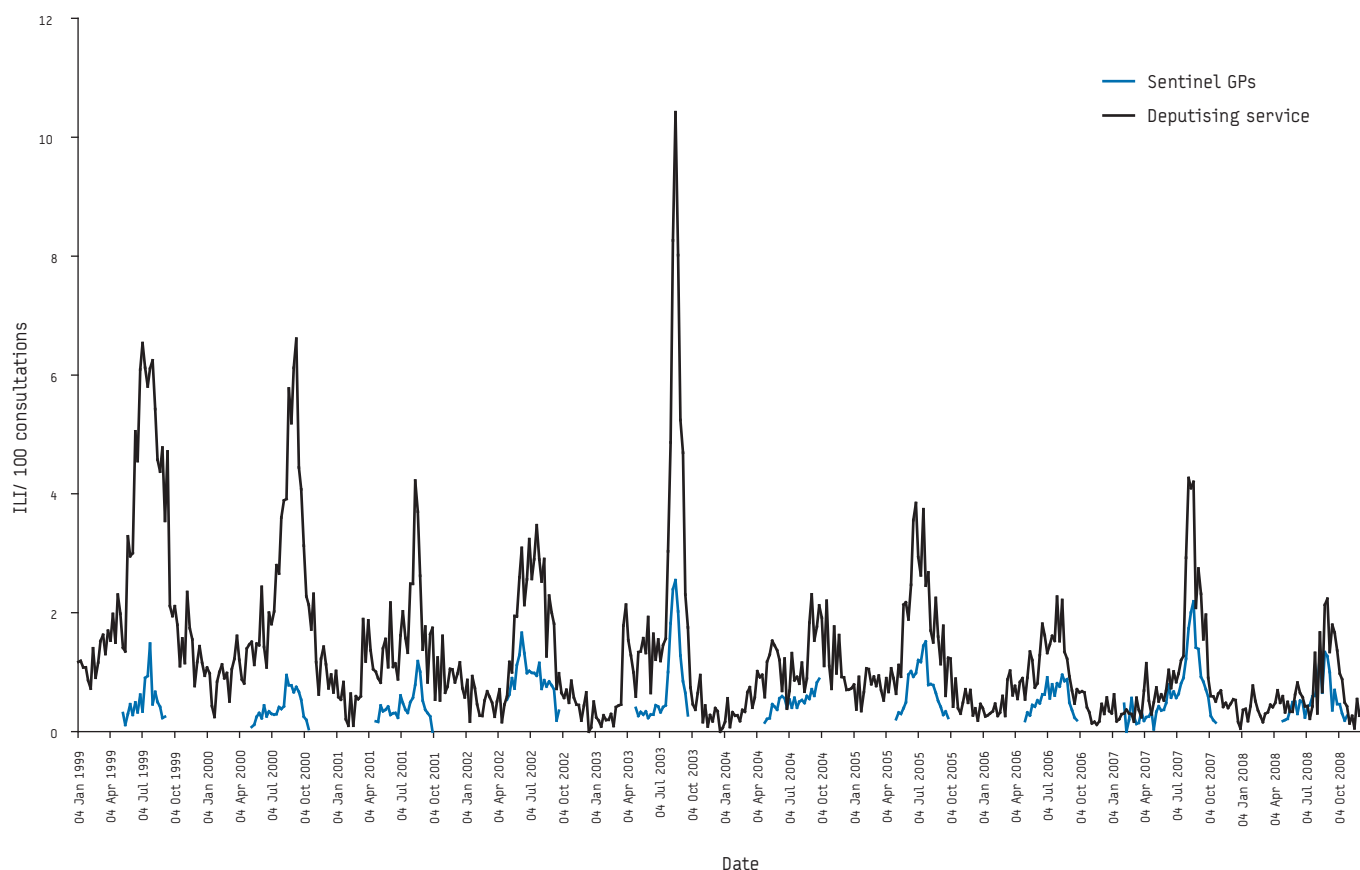
To further assess the comparability of the two surveillance systems, we calculated the area under the receiver operator characteristic (ROC) curve for the 10 years of data from the deputising service against the weeks with *higher than expected* seasonal activity as currently defined by a sentinel GP weekly ILI percentage of 1.5%, described by Watts *et al.* [15]. In the context of this study, as described by Bland and Altman [16], an area under the ROC curve of 0.5 would mean that the deputising service was no better than chance in detecting the influenza season, while a value of 1.0 would mean that it was a perfect measure. Confidence intervals for the area under the ROC curve were obtained using the algorithm of DeLong *et al.* [17].

Results

From 1999 to 2008, the weekly percentages of ILI reported through the deputising service were similar to the percentages seen in the sentinel GP system during periods of low seasonal activity, but were larger in periods of higher activity, although this was less evident in later years (Figure 1). The difference between the two

FIGURE 1

Weekly percentage of ILI reported through the deputising service versus the sentinel GP system, Melbourne, Australia, 1999-2008



GP: general practitioner; ILI: influenza-like illness

ILI data sources was small, but increased during the peak of the season, with data from the deputising service recording higher values than data from the sentinel GPs (Table).

The 95% limits of agreement increased with increasing ILI activity, the importance of which, as noted by Bland and Altman [13], is a matter of judgement, rather than a statistical issue. Our judgement is that the limits of agreement are appropriately small

TABLE

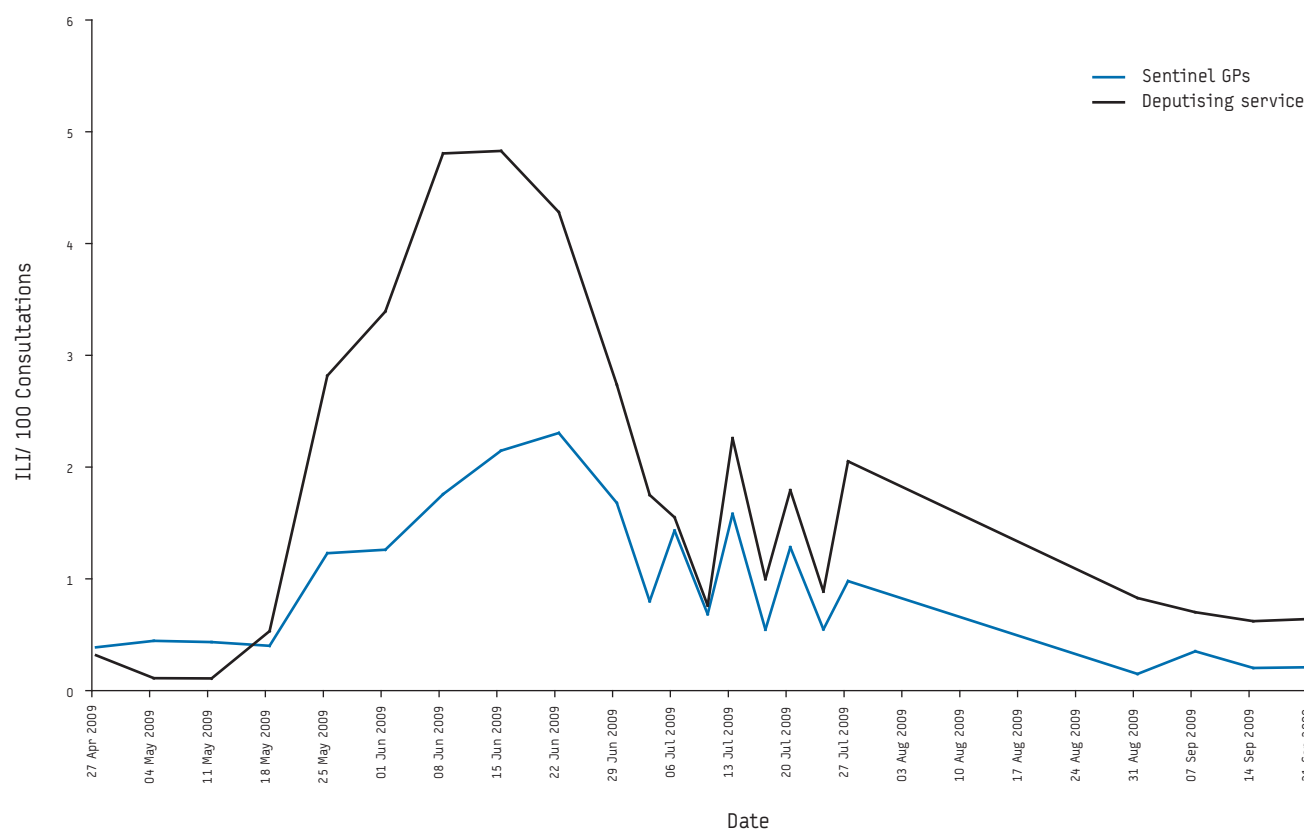
95% limits of agreement for deciles of the average* of deputising service and sentinel general practitioner data

(Cumulative percentage of observations) Average of ILI from deputising service and sentinel GP per 100 consultations	Difference between deputising service and sentinel GP ILI per 100 consultations	95% Limits of agreement
(10%) 0.42%	0.0%	-0.6%, 0.3%
(20%) 0.58%	0.2%	-0.4%, 0.8%
(30%) 0.72%	0.4%	-0.3%, 1.1%
(40%) 0.86%	0.6%	-0.2%, 1.4%
(50%) 1.00%	0.8%	-0.0%, 1.6%
(60%) 1.19%	1.0%	0.1%, 1.9%
(70%) 1.45%	1.3%	0.2%, 2.3%
(80%) 1.87%	1.6%	0.5%, 2.8%
(90%) 2.53%	3.1%	0.8%, 3.6%

* Assessing 95% limits of agreement against the average is the preferred method of assessing whether one set of measurements can substitute for (is equivalent to) another [19].
GP: general practitioner; ILI: influenza-like illness.

FIGURE 2

Weekly percentage of influenza-like illness reported through the deputising service versus the sentinel general practitioner system, Melbourne, Australia, Victoria, Australia, influenza season 2009



GP: general practitioner; ILI: influenza-like illness

during periods of normal seasonal ILI activity as well as at the start and end of the season, and that the wider limits at the peak of the season, or in seasons of higher activity, are of no material importance.

The area under the ROC curve was 0.91 (95% confidence interval (CI) 0.83, 0.98), confirming very close agreement between the systems when dichotomised around ILI activity describing normal and *higher than expected* seasonal activity.

Having both surveillance systems in place has been very useful in the H1N1 influenza pandemic of 2009 as the two surveillance systems provided complementary and confirmatory surveillance data when influenza A(H1N1)v was the dominant circulating strain [20]. As with previous years, however, ILI proportions from the two surveillance systems were more similar for lower values (Figure 2).

Discussion

There was good agreement between the weekly percentages of ILI in the deputising service and sentinel GP system, although the agreement for high ILI values was not as close as for lower values. This is probably because the deputising service is an out-of-hours service, which is likely to have a higher percentage of call-outs for acute illnesses, such as influenza. The deputising service is also less likely to see non-acute illnesses, effectively increasing the ILI percentage relative to sentinel GPs who would continue to see patients for chronic diseases during the peak of the influenza season. Moreover all ILI consultations are captured by the deputising service database, whereas GP data are recorded on paper forms which makes complete capture of all ILI patients is unlikely. This would reduce the reported ILI percentage from sentinel GPs compared with the deputising service.

We did not use the correlation coefficient to assess whether the deputising service data were equivalent to the sentinel GP data as some authors have done [8], because this approach has been questioned in a series of much cited papers by Bland and Altman [13,14,18,19]. There are two reasons for not using the correlation coefficient to assess equivalence of two data sources: First, if the values of the data vary across a wide range, as is the case for ILI data from both deputising service and sentinel GPs, the correlation coefficient will be close to 1.0 even if one measure is not a good substitute for the other. Second, correlation ignores any systematic bias between the two measures. To overcome these problems, Bland and Altman recommended reporting the difference, or bias, between the two measures and the 95% limits of agreement and we have followed their advice in this study.

We did not examine agreement for different age groups. However, for the most recent five-year period included in the analysis (2004–2008), the percentage of ILI cases under the age of 15 years was similar in the two systems (19.5% in the deputising service versus 18.8% in the sentinel GP system), while the ILI cases from the deputising service were slightly older than those from sentinel general practice (mean 40.7 years versus 39.9 years) and showed more variation (standard deviation 25.6 versus 20.3). This was because of the growing number of out-of-hours consultations by the deputising medical service at care facilities for the elderly in the latter years of surveillance; 8.6% of ILI cases identified by the deputising service were 80 years or older while the corresponding percentage for sentinel general practice was only 2.2%.

Deputising medical service surveillance does not use a standardised definition of ILI and is not supplemented by laboratory confirmation of suspected influenza cases. Nevertheless we have shown that data from a deputising medical service can provide low cost and timely ILI surveillance throughout the year, equivalent to ILI surveillance provided by sentinel GPs. Further confirming its utility, surveillance data from the deputising service confirmed the onset and peak of ILI activity during the 2009 pandemic in Victoria.

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Letters

RHINOVIRUSES, A(H1N1)v, RSV: THE RACE FOR HIVERNAL PANDEMICS, FRANCE 2009-2010

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To the editor: The A(H1N1)v circulation in France, like in other European countries (Sweden), is still reported as sporadic. The incidence of A(H1N1)v infections monitored in the community by the French National Influenza Centre has remained stable for 6 weeks from week 37 to week 42 (159 cases per 100,000 inhabitants). This is right above the epidemic cut-off of 114 cases per 100,000 inhabitants two months after the start of the new school year. This delay in the A(H1N1)v outbreak expansion is puzzling. At the same time, we report a high rhinovirus activity (34.5 % of samples positive for rhinovirus) in the community and in the hospital (unpublished data).

It has been postulated by A. Linde *et al.* [1] that the viral interaction between the A(H1N1)v and the rhinoviruses may explain partly this delay. This is an interesting hypothesis, indeed it is well known [2,3] that during winter, rhinovirus, respiratory syncytial virus (RSV) and influenza viruses epidemic peaks happen one after the other and occasionally overlap. The seasonal epidemiology of influenza is surely dependent on weather conditions such as low relative humidity and cold temperature [4]. These features were observed in our laboratory last winter.

Indeed, during the 2008-2009 winter, our laboratory analysed samples from the paediatric hospital of Lyon. The laboratory diagnosis was based on cellular culture for RSV and influenza

viruses detection and on specific RT-PCR technique for the influenza and the rhinoviruses detection. Between week 31 of 2008 and week 9 of 2009, 6516 respiratory samples (nasal swabs or nasopharyngeal aspirates) were analysed (culture and PCR) in our laboratory. The number of confirmed rhinoviruses, RSV and Influenza A viruses is reported week by week in the Figure.

This year, rhinovirus detection started on week 37, peaked on week 40 and decreased on week 43. At that moment, we can report the first detection of RSV and an increasing activity of A(H1N1)v. Regarding what was observed during last winter on the circulation of rhinovirus, RSV and A(H3N2) virus, it will be of much interest to follow the impact of the A(H1N1)v pandemic on the coming RSV peak. In other words, which respiratory virus between RSV or A(H1N1)v, will win the race for second place?

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FIGURE

Number of laboratory confirmed cases of rhinovirus, RSV and influenza A during autumn and winter 2008-2009, Lyon

