Rapid communications

INTERIM ANALYSIS OF PANDEMIC INFLUENZA (H1N1) 2009 IN AUSTRALIA: SURVEILLANCE TRENDS, AGE OF INFECTION AND EFFECTIVENESS OF SEASONAL VACCINATION

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Between May and September each year, influenza sentinel surveillance is conducted in general practices in Melbourne and the state of Victoria in southern Australia. We describe the first 11 weeks of sentinel surveillance in 2009 (weeks 18-28), during which time pandemic influenza (H1N1) 2009 virus became established, and investigate the protective effect of seasonal influenza vaccine against laboratory-confirmed infection caused by the pandemic virus. At the time of reporting, the peak ILI activity in 2009 had been reached and was similar to the peak recorded in 2007 but below the peak of 2003. The proportion of cases positive for any influenza virus increased from 6% in the first week of surveillance (week 18) to 59% by week 28, during which time the proportion of influenza viruses detected as pandemic influenza increased from zero to 95%, with at least 91% of all influenza viruses confirmed as pandemic influenza by the eighth week of surveillance (week 25). The median age of all 223 patients with pandemic influenza for whom age was known was 21 years (range 2-63 years) compared with the median age of 53 patients with seasonal H1N1 influenza in 2007 or 2008 of 23 years (range 1-75 years). There was no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group.

Introduction

Australia reported its first case of pandemic influenza (H1N1) 2009 on 8 May 2009 in a traveller returned from the United States [1]. Ten days later the state of Victoria in southern Australia reported its first three cases, in three brothers from one family, also recently returned from the United States [2]. Victoria has used an existing sentinel general practice network, established with laboratory support in 1998 [3], to monitor the pandemic. Sentinel monitoring is designed to overcome the potential testing biases that arise from monitoring all diagnosed cases, including those identified from outbreaks and contact tracing. During the current pandemic, sentinel surveillance general practitioners have been encouraged to test those patients who satisfied the case definition of fever (reported or observed), cough and fatigue/malaise [4], as they have done in previous years [5-10].

We have previously demonstrated the feasibility of estimating influenza vaccine effectiveness (VE) using a case control study of patients tested for influenza as a component of sentinel surveillance [11]. We now aim to describe the first 11 weeks, from 27 April to 12 July (weeks 18–28), of sentinel surveillance in Victoria in 2009, during which time pandemic influenza (H1N1) 2009 virus became established. We compare influenza-like illness (ILI) in 2009 with previous seasons and compare our surveillance system with ILI surveillance using the novel Google Flu Trends. We investigate the protective effect of seasonal influenza vaccine against medically attended ILI due to laboratory-confirmed infection caused by the pandemic virus in this period.

Methods

The Victorian sentinel general practice network

Victoria is a southern Australian state with a temperate climate. The influenza season occurs in winter and often extends into the early months of spring. Between May and September each year, sentinel surveillance is conducted in general practices scattered throughout Melbourne and regional Victoria. Victoria's population is more than 5 million, with 3.9 million people living in the state capital, Melbourne. For each season, participating general practitioners (GPs) report weekly on the total number of consultations and any patients presenting with ILI, defined as fever (reported or observed), cough and fatigue/malaise [4].

Laboratory-confirmed influenza has been a gazetted notifiable disease in Victoria since 2001. Because of the legal requirement

FIGURE 1

Influenza-like illness (ILI) from GP sentinel surveillance and the Melbourne Medical Deputising Service, Victoria, Australia, 27 April-19 July 2009
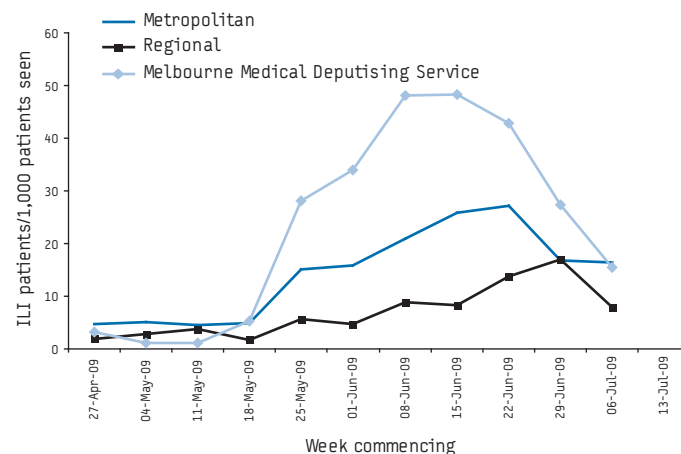
for the laboratory to notify positive cases, formal ethics approval is not required for the surveillance program. However written consent is obtained from sentinel patients, indicating that aggregate anonymous data will be used for surveillance purposes and influenza positive results will be notified to the state government Department of Human Services, Victoria. After consent is obtained GPs collect data on the age, sex, symptoms and vaccination status (recording the date of administering the vaccine) of the sentinel patients. GPs collect a combined nose and throat swab from consenting patients. The swab is couriered to the Victorian Infectious Diseases Reference Laboratory (VIDRL), a WHO National Influenza Centre, for laboratory testing. In 2009 sentinel surveillance commenced on 27 April (week 18), with a network of 87 sentinel GPs, 60 in Melbourne and 27 in regional Victoria. Optional on-line data entry was introduced and we continued to use surveillance data from the Melbourne Medical Deputising Service (MMDS) [12]. We compared publicly available ILI data from the Google website, (http://www.google.org/flutrends/intl/en_au/) expressed as the Google search ratio, with our surveillance data, expressed as ILI consultations per 1,000 consultations.

We used data from all surveillance sources to describe the first 11 weeks of the influenza season and compared features of the 2009 season with previous influenza seasons. Seasonal thresholds were based on the proportion of ILI cases per 1,000 consultations. Baseline activity, normal seasonal and higher than expected seasonal activity were defined as below 2.5, between 2.5 and <15, and between 15 and <35 per 1,000 consultations, respectively. According to these thresholds, 'epidemic influenza activity' was defined by proportions at or above 35 cases per 1,000 consultations [13].

Laboratory testing
Specimens were tested in the Viral Identification Laboratory at the Victorian Infectious Diseases Reference Laboratory (VIDRL). Viral RNA was extracted and tested for all influenza types and specific subtypes using a series of in-house polymerase chain reaction (PCR) assays directed at matrix gene sequences of influenza A and B. Any sample positive for influenza virus A was subtyped as influenza A(H1N1), influenza A(H3N2) or pandemic influenza A(H1N1) using specific PCR assays directed at hemagglutinin gene sequences. Any positive samples were referred to the World Health Organization Collaborating Centre for Influenza Reference and Research where an attempt to culture an isolate was made.

Estimating influenza vaccine effectiveness
Analysis was restricted to patients who presented for medical attention to any of the sentinel surveillance practices and who subsequently had a swab taken for the identification of influenza virus by real-time PCR. Patients whose PCR tests were inhibited were excluded from the analysis, as were patients whose vaccine

Influenza-like illness (ILI) from GP sentinel surveillance, 2003 to 2009, Victoria, Australia

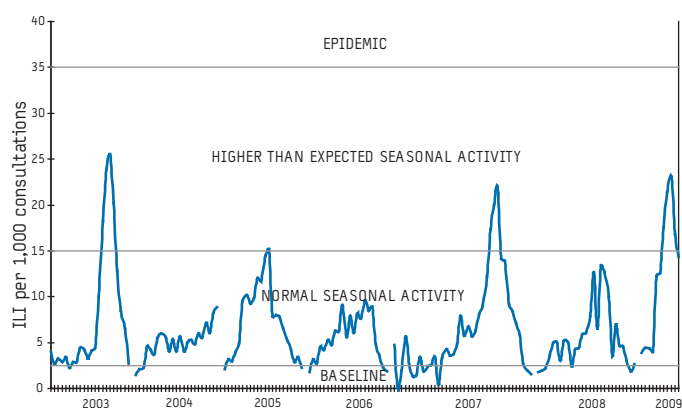**The proportion of influenza detections and the proportion of detections due to pandemic influenza H1N1 2009 from sentinel surveillance patients, Victoria, Australia, 2009**

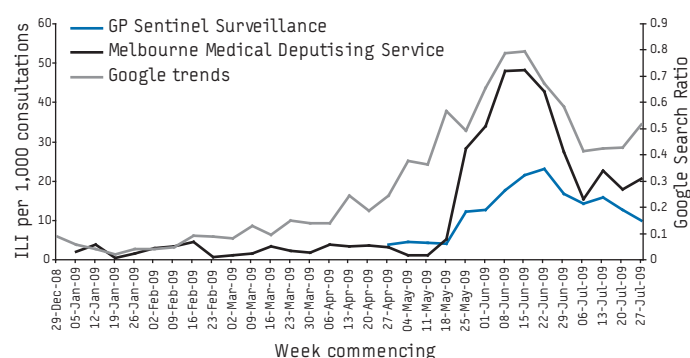| Week number	Date commencing	Patients tested	Number (%) of influenza detections	Patients with subtyping data available (% of patients with influenza)	Number (% of patients with influenza) of influenza detections due to pandemic (H1N1) 2009
18	27 April	16	1 (6%)	0	Not available
19	4 May	17	2 (12%)	2 (100%)	0
20	11 May	23	1 (4%)	1 (100%)	0
21	18 May	20	3 (15%)	3 (100%)	1 (33%)
22	25 May	69	11 (16%)	6 (55%)	6 (55%)
23	1 June	82	20 (24%)	5 (25%)	5 (25%)
24	8 June	73	32 (44%)	1 (3%)*	1 (3%)
25	15 June	105	55 (52%)	50 (91%)	50 (91%)
26	22 June	123	75 (61%)	70 (93%)	70 (93%)
27	29 June	84	56 (67%)	51 (91%)	51 (91%)
28	6 July	70	41 (59%)	39 (95%)	39 (95%)
18-28	27 April - 12 July	682	297 (44%)	228 (77%)	223 (75%)**

* Confirmed as pandemic (H1N1) 2009
** Per cent underestimated because subtyping is incomplete to date

status or age was unknown, and patients for whom subtyping data were not available. We used a case control design to estimate VE, where case and control status were not defined at the time of recruitment. Counting all patients from whose swabs pandemic (H1N1) 2009 influenza virus was detected as cases and all patients whose swabs were negative for influenza as controls, we estimated unadjusted VE (%) = (1-OR) x 100, where OR, the odds ratio,

was the odds of being a vaccinated case divided by the odds of being a vaccinated control. We performed age-stratified analyses and adjusted for age by logistic regression using the following age groups: 0-4 years, 5-19 years, 20-49 years, 50-64 years and 65 years and above. The southern hemisphere seasonal vaccine contained A/Brisbane/59/2007-like virus as the H1N1 component.

Results
The 2009 influenza season

The influenza season of 2009 appeared to be already established when surveillance commenced at the end of April, with ILI activity above the threshold designated as normal seasonal activity. ILI activity increased quickly, crossing the threshold designated as higher than normal activity in the week commencing 8 June. Activity appeared to peak in week 26, and decreased again almost to the threshold of normal seasonal activity by the end of week 27 (Figure 1).

At the time of reporting the peak ILI activity in 2009 was similar to the peak recorded in 2007 (in week 34) but below the peak of 2003, also recorded in week 34 (Figure 2).

The proportion of cases positive for any influenza virus increased from 6% in the first week of surveillance to 59% by week 28, by which time the first 223 cases of pandemic H1N1 influenza had been detected. During this same period the proportion of influenza viruses detected as pandemic influenza increased from zero to 95%, with at least 91% of all influenza viruses confirmed

FIGURE 3

Influenza-like illness (ILI) from GP sentinel surveillance, Melbourne Medical Deputising Service and Google Flu Trends, Victoria, Australia, 2009

TABLE 2

Proportion of detections of seasonal H1N1 influenza 2007 or 2008 and pandemic H1N1 influenza 2009 compared with population proportions by age group, Victoria, Australia, 2009

Age group (years)	Seasonal H1N1 influenza detected 2007 or 2008 N (%)	Pandemic H1N1 influenza detected 2009 N (%)	Per cent Victorian population 2008* N = 5,297,560
0-4	3 (6%)	7 (3%)	6%
5-19	14 (27%)	81 (37%)	19%
20-49	30 (57%)	118 (53%)	43%
50-64	5 (9%)	15 (7%)	18%
65+	1 (2%)	0	14%
All	53	221	100%

Australian Bureau of Statistics 32010D0001_200806. Population by Age and Sex, Australian States and Territories, June 2008.

TABLE 3

Vaccine effectiveness of seasonal influenza vaccine against pandemic influenza H1N1 2009 by age group, Victoria, Australia, 2009

Age group (years)	Patients tested (age and vaccine status known)	Number (%) positive for pandemic influenza (cases)	Number (%) negative for influenza (controls)	Number (%) vaccinated	Cases (%) vaccinated	Controls (%) vaccinated	Vaccine effectiveness (%)	95% confidence interval
0-4	35	7 (20%)	28 (80%)	7 (20%)	1 (14%)	6 (21%)	39%	-510 to 94
5-19	158	80 (51%)	78 (49%)	12 (8%)	6 (8%)	6 (8%)	3%	-216 to 70
20-49	311	111 (36%)	200 (64%)	57 (18%)	19 (17%)	38 (19%)	12%	-62 to 52
50-64	52	14 (27%)	38 (73%)	25 (48%)	8 (57%)	17 (45%)	-65%	-467 to 52
>=65	21	0 (0%)	21 (100%)	15 (71%)	0	15 (71%)	not defined	
All	577	212 (37%)	365 (63%)	116 (20%)	34 (15%)	82 (22%)	3%*	-56 to 40

*Adjusted for age-group as a discrete variable

as pandemic influenza by the eighth week of surveillance (week 25) (Table 1).

Comparison of ILI surveillance using sentinel practices and the MMDS with Google Flu Trends showed remarkable correlation between all three systems, with the comparison shown for surveillance extended to week 31, ending 2 August (Figure 3).

Although males comprised 56% of the sample of sentinel patients, pandemic influenza virus was detected in equal proportions of males and females (37.7% vs 36.8%). The median age of infection of all 221 patients with pandemic influenza for whom age was known was 21 years (range 2-63 years) compared with the median age of infection of 53 patients with seasonal H1N1 infection in 2007 or 2008 of 23 years (range 1-75 years). By contrast the median age of infection of patients with seasonal H3N2 was 28 years in 2007 (n=147) and 33 years in 2008 (n=43). Although the proportion of patients in whom pandemic H1N1 influenza was detected was higher in 2009 than the proportion in whom seasonal H1N1 influenza was detected in 2007 or 2008 (37% vs 6%, respectively), there was no significant difference by age group in the proportion of seasonal H1N1 infection detected in 2007 or 2008 compared with the proportion of pandemic H1N1 infection detected in 2009 (Table 2, Fisher's exact p=0.17). However the proportion of the 5-19 year old age group with seasonal or pandemic influenza H1N1 was higher than the proportion of this age group in the population (Table 2).

Vaccine effectiveness

By week 28, sentinel practitioners had seen 81,992 patients, had notified 982 (1.2%) of these patients with ILI and taken nose and throat swabs from 682 (69%) of them. Influenza virus was detected in 297/682 (44%) patients, and in 223/297 (75%) patients pandemic influenza (H1N1) 2009 was detected. After exclusion of patients for whom definitive subtyping is pending (n=69), patients for whom age was unknown (n=10), patients with unknown vaccination status (n=22) and patients with influenza due to a non-pandemic subtype (n=6), 577 patients were available for analysis, of whom 212 (37%) had pandemic influenza virus detected and the remainder had no virus detected. These patients were used for the estimates of VE.

Twenty per cent of patients were vaccinated against influenza but, as expected, the proportion of patients differed significantly by age group, with people aged at least 50 years more likely to have been vaccinated (p<0.001, Table 3). Pandemic influenza virus was detected in 37% of all patients, again with significant differences by age group (p<0.001, Table 3). People aged 5-19 years were most likely to have influenza virus detected (80/158, 51%), compared with none of 21 patients aged at least 65 years and 7/35 (20%) patients aged 0-4 years (Table 3).

There was no evidence of significant protection from seasonal vaccine against pandemic influenza virus infection in any age group, with point estimates ranging from 39% in persons aged less than 5 years to -65% (OR = 1.65) in persons aged 50-64 years (Table 3). Age adjusted VE was 3% (95% CI -56 to 40) for all patients, 10% (95% CI -54 to 48) in patients aged 5-49 years and 1% (95% CI -70 to 42) in patients aged 20-64. In patients younger than 50 years, VE was 12% (95% CI -48 to 48) and VE was -65% (95% CI -467 to 52) in patients aged 50 years or older. The latter estimate was based only on patients aged 50-64 years, as pandemic influenza was not detected in the group of patients

aged 65 years and older. The oldest patient in whom pandemic influenza was detected was aged 63 years.

We further restricted our analysis to weeks 25-28 inclusive, when pandemic influenza comprised at least 90% of all influenza detections, and the age groups 5-49 years, where most infections occurred. This period accounted for 352 patients with known age and vaccination status (61% of all comparable patients) and 201 cases (95% of all comparable cases). For all ages in this four-week period, age-adjusted VE was 24% (95% CI –37 to 58) and, for ages 5-49 years, VE was 20% (95% CI –52 to 48).

Discussion

The seasonal pattern of ILI in Victoria between 27 April and 12 July 2009 was similar comparing data from sentinel general practices and the Melbourne Medical Deputising Service (MMDS). Both surveillance systems peaked in the same week, although the peak from the MMDS was higher. We have shown these two surveillance systems can be used interchangeably to monitor ILI in the community but, as seen in the first 11 weeks of surveillance in 2009, the correlation between the two systems is better for lower ILI activity [14]. These two systems also showed remarkable concordance with Google Flu Trends. Google used historical data from the Victorian sentinel surveillance system from 2006-2008 to validate its Australian version of Flu Trends (http://blog.google.org/2009/06/google-flu-trends-for-australia-and-new.html) so that retrospective similarity of data is expected. The prospective similarity is interesting. Unfortunately there is no detailed published information on the approach used by Google for ILI surveillance in the southern hemisphere, preventing a more detailed comparison.

With complete subtyping, influenza in sentinel patients was shown to be exclusively due to pandemic influenza in weeks 30 and 31 (not included in Table 1, available from: http://www.vidrl.org.au/surveillance/flu%20reports/flu_idx.html). However, considering only patients for whom subtyping data were complete in previous weeks when these patients comprised at least 90% of all influenza detections, influenza in these sentinel patients was entirely due to pandemic influenza from week 25 (commencing 15 June, Table 1).

We have previously suggested the median age of patients infected with influenza A(H1N1) was similar for patients infected with seasonal and pandemic influenza H1N1 strains [15, 16] and the surveillance data presented here confirm these original observations. Infections with influenza A(H3N2) tend to occur in older people [15, 17] and comparisons of the age of infection with pandemic H1N1 influenza with the age of infection of all seasonal influenza may be misleading if previous seasons were dominated by influenza A(H3N2). A younger median age of infection with pandemic H1N1 influenza is likely to reflect the age of infection with influenza A(H1N1) viruses. We detected no sentinel patients with pandemic influenza over the age of 63 years, consistent with some protection afforded to older people as demonstrated by the detection of cross-reacting antibodies to the pandemic H1N1 virus in people aged 60 years and above [18].

We found no evidence of protection against medically attended laboratory-confirmed pandemic influenza from receipt of the seasonal vaccine in age-stratified or age-adjusted analyses. However, we do not collect data on co-morbidities and could not adjust for potential confounders, other than age. The ILI case control observational study design has limitations, some of which may bias the VE estimate towards the null. Sampling of patients

is not systematic and the sampling proportion increased to 69% in 2009 from 40% in the five influenza seasons from 2003 to 2007 [11]. Seasonal influenza infection may be asymptomatic or afebrile [19] and the same is no doubt true for infection with pandemic H1N1 influenza. Sentinel patients therefore represent the mid-range of the influenza morbidity spectrum, although this is likely to be true for both seasonal and pandemic infections. Given the high level of community concern, patients may have been more likely to attend their general practitioner with an ILI in 2009, compared with previous seasons, and GPs may have been more likely to swab patients. However the proportion of 44% of sentinel patients positive for influenza in the first 11 weeks of surveillance in 2009 is not significantly different to the proportion of 42% positive in the five influenza seasons between 2003 and 2007 [11].

Because of the high workload in the early weeks of the pandemic in Victoria, not all influenza positive specimens have been definitively subtyped. However, the distribution of vaccination status and pandemic influenza infection in the weeks where subtyping is incomplete would need to be remarkably different to the distribution in the weeks with almost complete data for this lack of data to bias our estimate of VE. Because of low case numbers in the early weeks, we did not adjust for week of presentation in the interim analysis, but performed an analysis restricted to the four weeks when subtyping data were almost complete and in which pandemic influenza comprised at least 90% of all influenza detections. There was no significant difference in VE estimates comparing these four weeks with the entire period. We did not adjust for time between symptom onset and date of specimen collection since GPs are instructed to collect a specimen only within four days of symptom onset.

While there are potential limitations with interim analyses of VE from observational studies using routinely collected data, the results reported here, showing no protection from seasonal vaccine against laboratory confirmed medically attended infection due to pandemic influenza (H1N) 2009, are not unexpected.

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