Influenza epidemiology, vaccine coverage and vaccine effectiveness in sentinel Australian hospitals in 2013: the Influenza Complications Alert Network

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Abstract

The National Influenza Program aims to reduce serious morbidity and mortality from influenza by providing public funding for vaccination to at-risk groups. The Influenza Complications Alert Network (FluCAN) is a sentinel hospital-based surveillance program that operates at 14 sites in all states and territories in Australia. This report summarises the epidemiology of hospitalisations with confirmed influenza, estimates vaccine coverage and influenza vaccine protection against hospitalisation with influenza during the 2013 influenza season. In this observational study, cases were defined as patients admitted to one of the sentinel hospitals, with influenza confirmed by nucleic acid testing. Controls were patients who had acute respiratory illnesses who were test-negative for influenza. Vaccine effectiveness was estimated as 1 minus the odds ratio of vaccination in case patients compared with control patients, after adjusting for known confounders. During the period 5 April to 31 October 2013, 631 patients were admitted with confirmed influenza at the 14 FluCAN sentinel hospitals. Of these, 31% were more than 65 years of age, 9.5% were Indigenous Australians, 4.3% were pregnant and 77% had chronic co-morbidities. Influenza B was detected in 30% of patients. Vaccination coverage was estimated at 81% in patients more than 65 years of age but only 49% in patients aged less than 65 years with chronic comorbidities. Vaccination effectiveness against hospitalisation with influenza was estimated at 50% (95% confidence interval: 33%, 63%, $P<0.001$). We detected a significant number of hospital admissions with confirmed influenza in a national observational study. Vaccine coverage was incomplete in at-risk groups, particularly non-elderly patients with medical comorbidities. Our results suggest that the seasonal influenza vaccine was moderately protective against hospitalisation with influenza in the 2013 season. *Commun Dis Intell* 2014;38(2):E143–E149.

Keywords: influenza; vaccine effectiveness

Introduction

Influenza vaccination is recommended in Australia for high risk groups, including the elderly, patients with chronic comorbidities, pregnant women and Indigenous Australians.[1] The National Immunisation Program, which provides public funding for influenza and other vaccinations, aims to reduce serious morbidity and mortality from influenza. Clinical trials have shown that the influenza vaccine is moderately protective against influenza[2] but fewer studies have examined its effectiveness in reducing serious complications, as the proportion of cases requiring hospitalisation is low. However, because infection with influenza virus is relatively widespread and estimated to affect 5%–10% of the population, the incidence of hospitalisation from influenza is of public health significance.

The Influenza Complications Alert Network (FluCAN) was established in 2009 primarily to provide timely surveillance to public health authorities nationally on hospitalisations with confirmed influenza.[3] In this report, we describe the epidemiology of hospitalisation with confirmed influenza, estimate vaccine coverage in hospitalised patients with acute respiratory illnesses but without influenza, and estimate influenza vaccine protection against hospitalisation with influenza during the 2013 influenza season.

Methods

FluCAN is a national hospital-based sentinel surveillance system.[3] For the 2 most recent influenza seasons including 2013, the participating sites have been The Alfred Hospital (Vic.), Royal Melbourne Hospital (Vic.), Canberra Hospital (ACT), Monash Medical Centre (Vic.), Geelong Hospital (Vic.), Royal Perth Hospital (WA), Royal Adelaide Hospital (SA), Royal Hobart Hospital (Tas.), Mater Hospital (Qld), Princess Alexandra Hospital (Qld), Cairns Base Hospital (Qld), Alice Springs Hospital (NT), Westmead Hospital (NSW), and John Hunter Hospital (NSW). Ethical approval

has been obtained at all participating sites, at Monash University and the Australian National University.

Definitions

An influenza case was defined as a patient admitted to hospital with influenza confirmed by nucleic acid testing (NAT). Surveillance was conducted from 5 April to 31 October 2013. Test negative controls (one for each case where available) were the next tested patient with acute respiratory symptoms who was negative for influenza by NAT. Admission or transfer to intensive care unit (ICU) included patients managed in a high dependency unit. The onset date was defined as the date of admission except for patients where the date of the test was more than 7 days after admission, where the onset date was the date of the test. Admissions that are listed as influenza A include both untyped and seasonal strains, and may include infections involving the pandemic H1N1/09 strain if not specifically typed.

Estimation of vaccination coverage and effectiveness

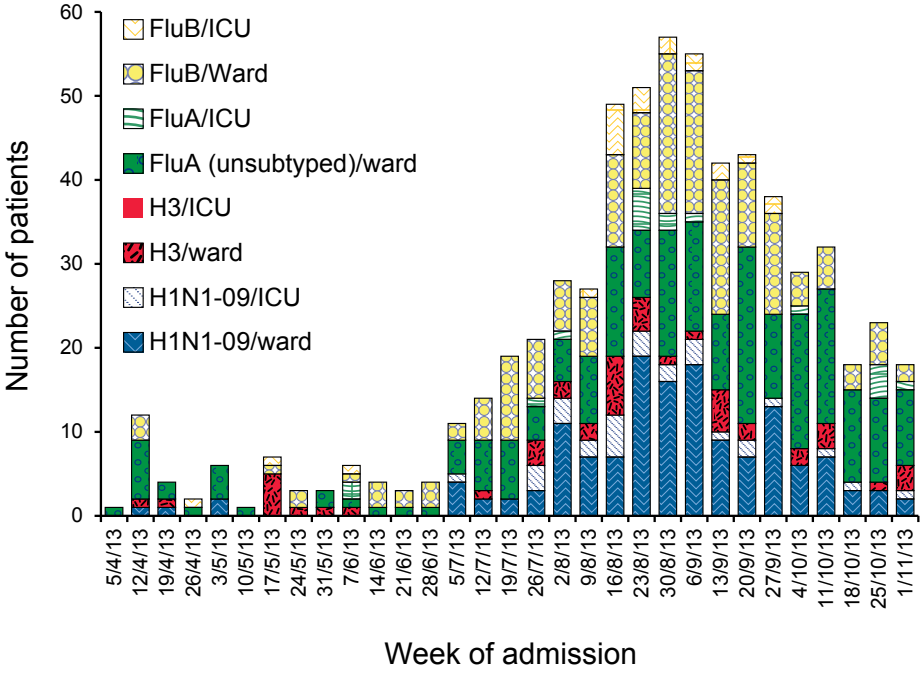
Vaccination coverage was estimated from patients admitted with influenza-like illness but who were negative for influenza by NAT. Patients were defined as being vaccinated if they reported receiving the 2013 trivalent seasonal vaccine more than 2 weeks prior to presentation (as documented in the medical record or from self-report). In Australia, only unadjuvanted vaccines are available under the National Immunisation Program although 1 adjuvanted vaccine is approved for use. Nasally administered live attenuated and quadrivalent influenza vaccines are not available in Australia.

We used an incidence density test negative design to estimate vaccine effectiveness, where controls are selected from patients without influenza contemporaneous to a case.[4–6] Vaccine effectiveness was estimated as 1 minus the odds ratio of vaccination in case patients compared with test negative control patients using methods previously described.[7,8] A multi-variable model was constructed from factors known to be associated with both vaccination and risk of illness, and therefore were regarded as potential confounders.

Results

During the period 5 April to 31 October 2013, 631 patients were admitted with confirmed influenza infection at the 14 FluCAN sentinel hospitals. In most jurisdictions, the peak number of hospitalised cases varied between late August and late October 2013 (Figure 1). The majority of cases were due to influenza A, but 30% were due to influenza B; however, the proportion due to influenza B varied from 2 of 50 cases (4%) at Alice Springs Hospital to 27 of 47 cases (57%) at Geelong Hospital.

Figure 1: Date of admission for patients hospitalised with confirmed influenza



Source: FluCAN sentinel hospitals

Of these 631 patients, 200 (32%) were more than 65 years of age, 60 (9.5%) were Indigenous Australians, 27 (4.3%) were pregnant and 488 (77%) had chronic co-morbidities (Table 1). Of the 514 patients (81%) of patients where influenza vaccination status was ascertained, 199 (31%) had been vaccinated. Factors associated with admission with confirmed influenza, compared with admission with non-influenza controls are detailed in Table 2. As there was no community-based control group, factors associated with hospital admission could not be quantified, but it was noted that 77%

Table 1: Demographics, risk factors and outcomes in hospitalised patients with confirmed influenza

	2012		2013	
	Number	Proportion	Number	Proportion
Demographics				
Number of patients	1,231		631	
Age group				
<18 years	148	12.0	32	5.1
18–<40 years	229	18.6	139	22.0
40–<65 years	281	22.8	260	41.2
65–<80 years	307	24.9	131	20.8
≥80 years	266	21.6	69	10.9
Male	614	49.9	314	49.8
Indigenous	99	8.0	60	9.5
State or territory				
ACT	105	8.5	35	5.5
NSW	84	6.8	125	19.8
NT	83	6.7	50	7.9
Qld	167	13.6	29	4.6
SA	200	16.3	109	17.3
Tas.	99	8.0	30	4.8
Vic.	390	31.7	202	32.0
WA	103	8.4	51	8.1
Influenza strain				
H1N1/09	12	1.0	167	26.5
Flu A (unknown/seasonal)	1,006	81.7	277	43.9
Flu B	213	17.3	187	29.6
Risk factors				
Pregnant	39	3.2	27	4.3
Nursing home resident	68	5.5	18	2.8
Medical co-morbidities	944	76.7	488	77.3
Chronic respiratory disease	446	36.2	226	35.7
Diabetes	260	21.1	136	21.6
Chronic liver disease	38	3.1	38	6.0
Immunosuppressed	217	17.6	155	24.6
Chronic cardiac disease	353	28.7	183	29.0
Chronic neurological disease	175	14.2	94	14.8
Chronic renal disease	116	9.4	76	12.0
Severity and outcome				
Initial admitting ward				
General ward	1,123	91.2	561	88.6
High dependency or intensive care unit	108	8.8	69	10.9
In-hospital mortality	40/1,157	3.5	20/621	3.2

Table 2: Estimated vaccine coverage in influenza cases and test negative controls

	Confirmed influenza		Test negative acute respiratory illness	
	n/N	%	n/N	%
All patients	199/514	38.7	283/450	62.9
Age >65 years	100/157	63.7	178/221	80.5
Medical comorbidities	95/143	66.4	172/214	80.4
No medical comorbidities	5/14	35.7	6/7	85.7
Age <65 years	99/357	27.7	105/229	45.9
Medical comorbidities	86/252	34.1	92/187	49.2
No medical comorbidities	13/105	12.4	13/42	31.0

of patients had medical comorbidities. The most commonly reported co-morbidities were respiratory disease, cardiac disease, immunosuppression and diabetes.

Clinical course, severity and outcome

In 609 patients with confirmed influenza where the duration of symptoms was known, the median duration of symptoms prior to admission was 3 days (interquartile range (IQR) 2, 5 days). In patients with confirmed influenza, 347 (54%) received oseltamivir. Of these, 142 patients received oseltamivir within 48 hours of symptom onset. The duration of hospital stay was similar for patients that did not receive antivirals (median 4 days, IQR 2, 8 days), received antivirals within 48 hours of symptom onset (4 days, IQR 2, 8 days) and who received antivirals more than 48 hours after symptom onset (5 days, IQR 3, 10 days).

Of all cases, 69 (11%) were initially admitted to ICU and a further 33 patients were subsequently transferred to ICU after initial admission to a general ward. In a multivariate model stratified by hospital site, more than 65 years of age and pregnancy were negatively associated with ICU admission in hospitalised patients with confirmed influenza, while the presence of medical comorbidities was positively associated with ICU admission (Table 3). Indigenous patients were more likely to be admitted to ICU, but this difference was not statistically significant. In patients where influenza vaccination status was ascertained, influenza vaccination was negatively associated with ICU admission (odds ratio 0.61, 95% CI: 0.24, 1.12, n=490) but this difference was not statistically significant.

Of the 621 patients where hospital mortality status was documented, 20 patients died, of which 10 patients died in intensive care. Ten (50%) of these patients were more than 65 years of age, 19 (95%) had medical comorbidities and 3 (15%) were Indigenous Australians. Significant medical comorbidities in patients who died following admission with confirmed influenza were recorded as chronic cardiac disease (n=10), chronic respiratory disease (n=9), immunosuppression (n=8), diabetes (n=4) and renal disease (n=3).

Table 3: Factors associated with admission to intensive care in patients hospitalised with confirmed influenza

Variable	Odds ratio (95% CI)	*P* value
Age >65 years	0.49 (0.29, 0.84)	0.01
Medical comorbidities	1.89 (1.02, 3.50)	0.042
Pregnancy	0.20 (0.04, 0.89)	0.034
Indigenous Australian	2.05 (0.68, 6.19)	0.206
Influenza type		
Influenza A	1 (referent)	–
Influenza B	1.08 (0.66, 1.77)	0.747

Vaccine coverage and vaccine effectiveness

During this same period, 594 control patients were enrolled; vaccination status was ascertained in 450 (76%) control patients. In test negative controls during the season, vaccination coverage was estimated at 81% (178/221) and 66% (264/401) in the elderly and those with medical co-morbidities respectively (Table 2).

The effectiveness of the 2013 trivalent seasonal influenza vaccine in reducing the risk of hospitalisation with influenza was estimated at 50% (95% CI: 33%, 63%, $P<0.001$) in the 2013 influenza season (Table 4). Vaccine effectiveness was estimated to be lower in elderly patients and in those with medical co-morbidities (Figure 2).

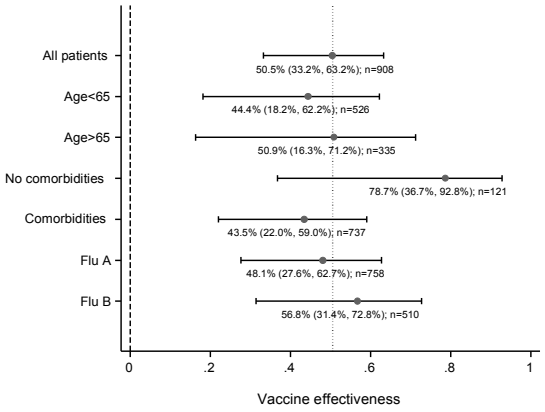
Discussion

In 2013, we recorded more than 600 admissions to the 14 participating hospitals, representing half those detected in 2012. Virological surveillance of circulating strains suggested that all 3 lineages

Table 4: Factors associated with hospitalisation with influenza compared with admission associated with non-influenza acute respiratory illnesses

Variable	Crude odds ratio	P	Adjusted odds ratio	P
Age ≥ 65 years	0.49 (0.38, 0.62)	<0.001	0.62 (0.45, 0.86)	0.003
Medical comorbidities	0.49 (0.36, 0.68)	<0.001	0.69 (0.46, 1.04)	0.076
Influenza vaccination	0.39 (0.30, 0.51)	<0.001	0.50 (0.37, 0.67)	<0.001
Pregnancy	3.02 (1.39, 6.58)	0.005	3.36 (1.09, 10.34)	0.035
Indigenous	1.08 (0.61, 1.90)	0.80	1.08 (0.50, 2.32)	0.84

Figure 2: Estimated vaccine effectiveness against hospitalisation for all patients, in specified subgroups and against infection with influenza subtypes



Numbers under bars represent point estimate (with 95% CI) and number of patients in analysis.

(A/H1N1/09, A/H3N2 and B/Yamagata-lineage) were detected in varying proportions in different states and territories, but vaccine match to circulating strains was good.[9] As the hospitals represented in this network represent approximately 12% of the national hospital bed capacity, the cases detected here are likely to represent approximately 5,400 admissions nationally. Compared with 2012, the 2013 season was later (peaking in September in 2013, compared with July in 2012), younger age groups were represented in a higher proportion of patients (<65 years: 68% vs 53%), and a higher proportion were due to influenza B (30% vs 17%). There was a similar number of patients in the 40–65 year age group but a decrease in all other age groups. It should be noted that the relative number of cases between jurisdictions does not reflect true influenza activity, due to differences in the number and size of sentinel hospitals in each jurisdiction.

The World Health Organization recommends surveillance for severe acute respiratory illness. Hospital-based surveillance programs similar to FluCAN are operating in many countries.[10–15] By providing information on influenza severity, hospital-based surveillance complements community– and primary care-based surveillance systems, which provide information on the extent of spread.

Influenza vaccine coverage has been estimated infrequently in hospitalised patients in Australia.[16] In 2012, we estimated vaccine coverage in 2 separate groups of patients: patients with pneumonia prior to the influenza season, and patients during the influenza season who had tested negative for influenza. The results in these groups were consistent with each other, and are similar to the vaccine coverage estimated in 2013. Self-reported vaccination status has been shown to slightly overestimate true influenza vaccination status.[16–18] Community-based estimates of influenza vaccine coverage, last reported in 2009, have shown similar results that have been consistent over time since 2002.[19]

The test negative study design to estimate vaccine effectiveness is becoming increasingly accepted and is ideally suited to being incorporated into surveillance systems. Two recent papers have examined the validity of this design. Foppa et al found that the estimates would be robust to most assumptions, but bias may be introduced by differences in health care-seeking behaviour amongst cases and non-cases by vaccine status, strong viral interference, or modification of the probability of symptomatic illness by vaccine status.[20] De Serres et al compared estimates from per protocol analyses of 4 randomised controlled trials of live attenuated influenza vaccine, with estimates based on the test negative design, and found minimal bias.[21] However, these studies have primarily considered vaccine effectiveness in the primary care setting.

Several studies, many of them embedded in surveillance systems, are able to provide regular estimates of vaccine effectiveness against hospitalisation. We previously reported vaccine effectiveness of 37%–48% in the 2010 and 2011 seasons, and of 41% in the 2012 season.[7,8] Estimates from other hospital-based studies have ranged widely from 30% to 71%, in part reflecting smaller sample

sizes than in community-based studies.[22–25] These results reinforce previous findings that vaccination coverage in non-elderly patients with comorbidities is relatively low. Further work is required to explore reasons for poor vaccination uptake, whether related to poor awareness in patients or healthcare providers.

There are several limitations to this study. Incomplete case ascertainment is likely due to the lack of use of influenza laboratory tests, despite the diagnosis of influenza having implications for infection control and antiviral use in hospitals. Delayed presentations or secondary bacterial pneumonia may be associated with false negative influenza tests as the influenza infection may be cleared at the time of presentation. There may also be unmeasured confounding of the association between vaccination and admission with influenza, a bias that has plagued studies of influenza mortality.[26] Although previous studies have suggested that self-reported influenza vaccination status only slightly overestimates vaccination coverage, we have not validated this in our population.[16–18]

In summary, we detected a smaller number of hospital admissions with confirmed influenza in a national observational study in 2013 compared with 2012. Vaccine coverage was incomplete in at-risk groups, particularly non-elderly patients with medical comorbidities. Our results suggest that the 2013 seasonal influenza vaccine was moderately protective against hospitalisation with influenza.

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