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Allen C Cheng, Mark Holmes, Dominic E Dwyer, Sanjaya Senanayake,
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Communicable Diseases Intelligence is produced by:
Health Protection Policy Branch
Office of Health Protection
Australian Government
Department of Health
GPO Box 9848, (MDP 6)
CANBERRA ACT 2601

Email:

cdi.editor@health.gov.au

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Abstract

The Influenza Complications Alert Network (FluCAN) is a sentinel-hospital-based surveillance program that operates at sites in all jurisdictions in Australia. This report summarises the epidemiology of hospitalisations with laboratory-confirmed influenza during the 2017 influenza season.

In this observational surveillance system, cases were defined as patients admitted to any of the 17 sentinel hospitals with influenza confirmed by nucleic acid detection. Data are also collected on a frequency-matched control group of influenza-negative patients admitted with acute respiratory infection.

During the period 3 April to 31 October 2017 (the 2017 influenza season), 4,359 patients were admitted with confirmed influenza to one of 17 FluCAN sentinel hospitals. Of these, 52% were elderly (≥ 65 years), 14% were children (< 16 years), 6.5% were Aboriginal and Torres Strait Islander peoples, 1.6% were pregnant and 78% had chronic comorbidities. A significant proportion were due to influenza B (31%). Estimated vaccine coverage was 72% in the elderly (≥ 65 years), 50% in non-elderly adults with medical comorbidities and 24% in children (< 16 years) with medical comorbidities. The estimated vaccine effectiveness (VE) in the target population was 23% (95% CI: 7%, 36%).

There were a large number of hospital admissions detected with confirmed influenza in this national observational surveillance system in 2017, with case numbers more than twice that reported in 2016.

Keywords: Influenza, public health surveillance, influenza vaccines, vaccination coverage, vaccine effectiveness

Introduction

Influenza is a common respiratory virus that affects up to 5–10% of the population each year.¹ Although most infection with influenza results in a relatively mild self-limiting illness, the widespread transmission of this virus means that complications from influenza are a major cause of hospitalisation and death.^{2,3} In this report,

we describe the epidemiology of hospitalisation with laboratory-confirmed influenza in the 2017 season in Australia.

Methods

The Influenza Complications Alert Network (FluCAN) is a national hospital-based sentinel surveillance system.⁴ Since 2011, the participating sites have been Canberra Hospital (ACT), Calvary Hospital (ACT), Westmead

Hospital (NSW), John Hunter Hospital (NSW), Children's Hospital at Westmead (NSW), Alice Springs Hospital (NT), Royal Adelaide Hospital (SA), Mater Hospital (Qld), Princess Alexandra Hospital (Qld), Cairns Base Hospital (Qld), Royal Hobart Hospital (Tas), The Alfred Hospital (Vic), Royal Melbourne Hospital (Vic), Monash Medical Centre (Vic), University Hospital Geelong (Vic), Royal Perth Hospital (WA), and Princess Margaret Hospital (WA). In 2017, additional specialist paediatric hospitals also participated, but data from these sites were not included in this report to facilitate comparisons with previous years. Ethical approval has been obtained at all participating sites and at Monash University. Hospital bed capacity statistics were obtained from each participating hospital, and national bed capacity was obtained from the last published AIHW report.⁵

An influenza case was defined as a patient admitted to hospital with influenza confirmed by nucleic acid testing (NAT). Surveillance is conducted from early April to the end of October (with follow-up continuing to the end of November) each year. Data on a frequency-matched group of test-negative controls were also collected. Admission or transfer to an intensive care unit (ICU) included patients managed in a high dependency unit (HDU). 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. The presence of risk factors and comorbidities was ascertained from the patient's medical record. Restricted functional capacity was defined as those who were not fully active and not able to carry out all activities without restriction prior to the acute illness.⁶

We examined factors associated with ICU admission using multivariable regression. Factors independently associated with ICU admission were determined using a logistic regression model with no variable selection process, as all factors were plausibly related to ICU admission.

The presentation delay was defined as the time from onset of illness to admission to hospi-

tal. The treatment delay was defined as the time from onset of illness to prescription of oseltamivir (in patients that received treatment). Patients were categorised into those that (a) did not receive oseltamivir (b) received oseltamivir within 2 days of symptom onset and (c) received oseltamivir more than 2 days of symptom onset. We modelled factors associated with length of hospital stay, including antiviral use, using a negative binomial regression. In this variant of a Poisson model, the coefficient represents the relative increase in hospital length of stay.

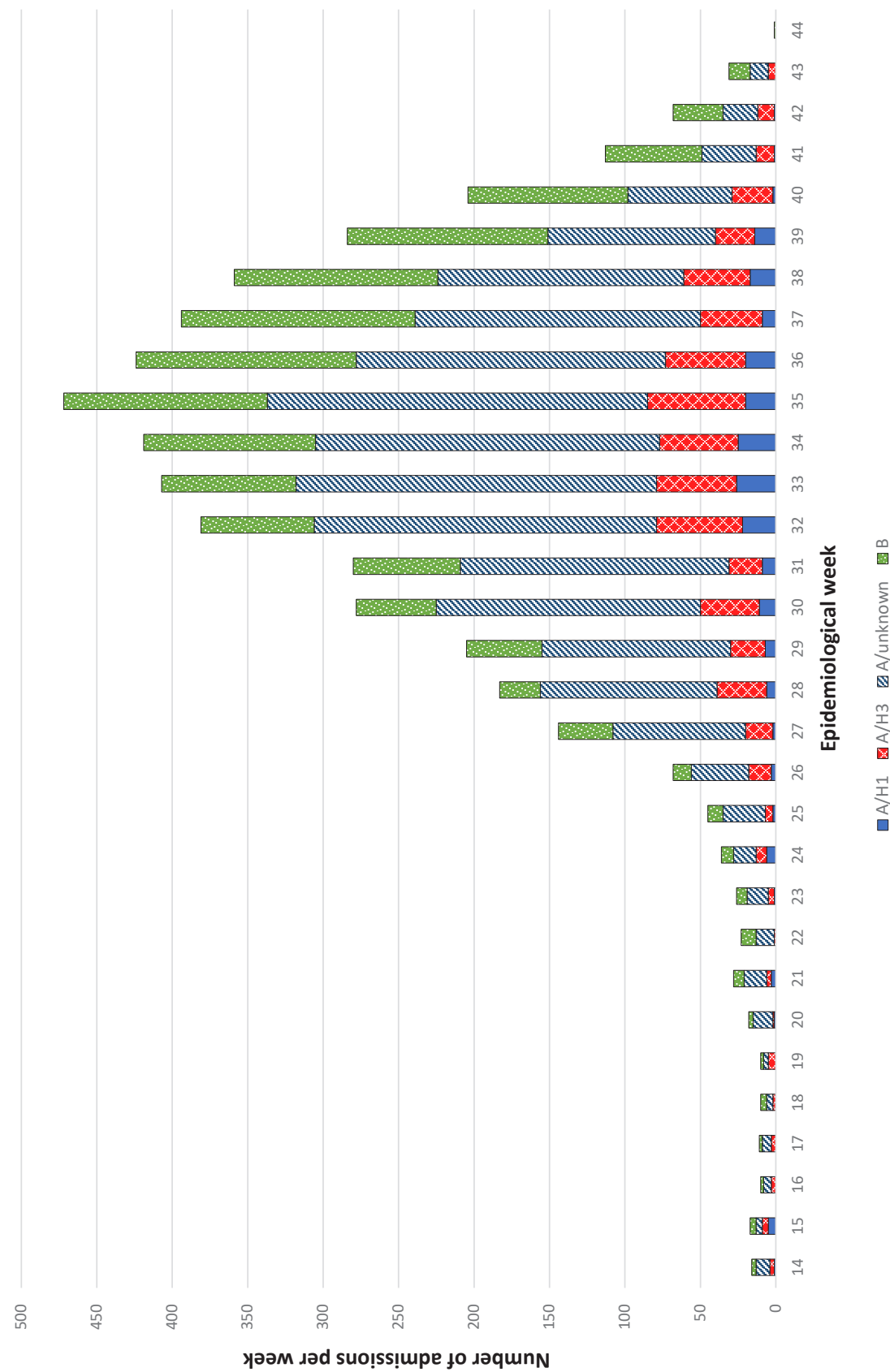
Vaccine coverage was estimated from the proportion of vaccinated individuals in test-negative controls in each age group, stratified by the presence of chronic comorbidities. Vaccine effectiveness was estimated from the odds ratio of vaccination in cases vs controls using the formula, with the odds ratio calculated from a conditional logistic regression, stratified by site and month and adjusted for age group, the presence of chronic comorbidities, pregnancy and Aboriginal or Torres Strait Islander ethnicity.

Results

During the period 3 April to 31 October 2017 (the 2017 influenza season), 4,259 patients were admitted with laboratory-confirmed influenza to the 17 FluCAN sentinel hospitals. The peak weekly number of admissions was in mid-August (week 35) (Figure 1). The majority of cases were due to influenza A (n=2,949, 69%). The proportion due to influenza B was similar across all jurisdictions, ranging from 19% in WA to 34% in NSW.

Of these 4,259 patients admitted with confirmed influenza, 2,228 (52%) were >65 years of age, 587 (14%) were children (<16 years), 277 (6.5%) were Aboriginal and Torres Strait Islander peoples, and 3,310 (78%) had chronic comorbidities (Table 1; Table 2). There were 69 pregnant women which represented 16% of the 412 female patients aged 16–49, or 1.6% of the total. Of the 3,082 patients (73%) where influenza vaccination status was ascertained, 1,531 (50%) had been vaccinated.

Figure 1: Date of admission^a in patients hospitalised with confirmed influenza



^a By week beginning on listed date; representing date of admission (or date of influenza diagnosis if acquired >7 days in hospital).

Table 1: Demographic characteristics of hospitalised patients with confirmed influenza

	Influenza type/subtype				Total
	A/H1N1	A/H3N2	A/unknown	B	
Number	183	532	2,234	1,310	4,259
Age group					
<16 years	51 (27.9%)	1 (0.2%)	296 (13.2%)	239 (18.2%)	587 (13.8%)
16–49 years	47 (25.7%)	111 (20.9%)	342 (15.3%)	273 (20.8%)	773 (18.1%)
50–64 years	30 (16.4%)	100 (18.8%)	336 (15.0%)	205 (15.6%)	671 (15.8%)
65–79 years	38 (20.8%)	173 (32.5%)	642 (28.7%)	309 (23.6%)	1,162 (27.3%)
80+ years	17 (9.3%)	147 (27.6%)	618 (27.7%)	284 (21.7%)	1,066 (25.0%)
Male ^a	101 (55.2%)	262 (49.2%)	1,135 (50.8%)	658 (50.3%)	2,156 (50.6%)
Pregnant	3 (1.6%)	13 (2.4%)	34 (1.5%)	19 (1.5%)	69 (1.6%)
Indigenous	13 (7.1%)	59 (11.1%)	136 (6.1%)	69 (5.3%)	277 (6.5%)
Jurisdiction					
ACT	4 (2.2%)	36 (6.8%)	339 (15.2%)	172 (13.1%)	551 (12.9%)
NSW	25 (13.7%)	3 (0.6%)	597 (26.7%)	328 (25.0%)	953 (22.4%)
NT	10 (5.5%)	59 (11.1%)	57 (2.6%)	57 (4.4%)	183 (4.3%)
Qld	30 (16.4%)	61 (11.5%)	282 (12.6%)	120 (9.2%)	493 (11.6%)
SA	1 (0.5%)	10 (1.9%)	350 (15.7%)	151 (11.5%)	512 (12.0%)
Tas	32 (17.5%)	148 (27.8%)	47 (2.1%)	105 (8.0%)	332 (7.8%)
Vic	50 (27.3%)	164 (30.8%)	526 (23.5%)	348 (26.6%)	1,088 (25.5%)
WA	31 (16.9%)	51 (9.6%)	36 (1.6%)	29 (2.2%)	147 (3.5%)

a Sex missing in two patients

Table 2: Risk factors, severity and outcomes in hospitalised adult patients with confirmed influenza

	Not admitted to ICU	Admitted to ICU	Total
Pregnant	64 (1.7%)	5 (1.0%)	69 (1.6%)
Chronic comorbidities	2,903 (77.1%)	407 (82.6%)	3,310 (77.7%)
Chronic respiratory illness	1,199 (31.8%)	188 (38.1%)	1,387 (32.6%)
Diabetes	881 (23.4%)	121 (24.5%)	1,002 (23.5%)
Chronic liver disease	156 (4.1%)	22 (4.5%)	178 (4.2%)
Immunosuppressed	531 (14.1%)	64 (13.0%)	595 (14.0%)
Malignancy	450 (11.9%)	46 (9.3%)	496 (11.6%)
Chronic cardiac disease	1,408 (37.4%)	170 (34.5%)	1,578 (37.1%)
Obesity	356 (9.5%)	77 (15.6%)	433 (10.2%)
Chronic neurological illness	717 (19.0%)	56 (11.4%)	773 (18.1%)
Chronic renal disease	453 (12.0%)	67 (13.6%)	520 (12.2%)
Nursing home resident	270 (7.2%)	15 (3.0%)	285 (6.7%)
Received influenza vaccine	1,395/2,752 (50.7%)	136/330 (41.2%)	1,531/3,082 (49.7%)
Influenza subtype			
A/H1	152 (4.0%)	31 (6.3%)	183 (4.3%)
A/H3	486 (12.9%)	46 (9.3%)	532 (12.5%)
A/unk	1,964 (52.2%)	270 (54.8%)	2,234 (52.5%)
B	1,164 (30.9%)	146 (29.6%)	1,310 (30.8%)
In hospital mortality	96/3,752 (2.6%)	59/484 (12.2%)	155/4,236 (3.7%)

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

Variable	Crude OR	<i>p</i> value	Adjusted OR ^a	<i>p</i> value
Age				
<16 years	0.86 (0.65, 1.14)	0.292	0.86 (0.61, 1.21)	0.382
16–64 years	1 (referent)		1 (referent)	
65+ years	0.58 (0.47, 0.71)	<0.001	0.52 (0.42, 0.66)	<0.001
Medical comorbidities	1.41 (1.10, 1.80)	0.006	1.79 (1.37, 2.33)	<0.001
Aboriginal or Torres Strait Islander peoples	1.00 (0.68, 1.46)	0.99	0.89 (0.61, 1.32)	0.575
Pregnancy	0.59 (0.24, 1.48)	0.262	0.42 (0.17, 1.07)	0.069
Restricted functional status	1.04 (0.87, 1.26)	0.653	0.91 (0.72, 1.14)	0.405
Nursing home resident	0.41 (0.24, 0.69)	0.001	0.44 (0.26, 0.76)	0.003
Influenza type/subtype				
A/H1	1.63 (1.07, 2.48)	0.024	1.62 (1.05, 2.48)	0.028
A/H3	0.75 (0.53, 1.07)	0.113	0.80 (0.56, 1.15)	0.226
A/unk	1.10 (0.88, 1.36)	0.401	1.15 (0.92, 1.42)	0.215
B	1 (referent)		1 (referent)	

a all variables included in multivariate model

Table 4: Oseltamivir treatment, by age group in patients with confirmed influenza

Factor	Age <16 years	Age 16–64 years	Age 65+ years	<i>p</i> value
Number of patients	528	1,273	1,899	
Oseltamivir not received	435 (83.2%)	520 (41.1%)	615 (32.5%)	<0.001
Oseltamivir received	88 (16.8%)	746 (58.9%)	1,276 (67.5%)	<0.001
received <48h of onset	35 (6.7%)	278 (22.0%)	452 (23.9%)	
received ≥48h of onset	53 (10.1%)	468 (37.0%)	824 (43.6%)	
Delay between onset and admission, median (IQR)	3 (1, 5)	3 (2, 5)	3 (2, 5)	0.34
Delay between onset and treatment, ^a median (IQR)	3 (2, 6)	3 (2, 5)	3 (2, 5)	0.74
Length of stay, median (IQR)	2 (1, 3)	3 (1, 5)	4 (2, 7)	<0.001

a of patients who received oseltamivir

Table 5: Factors associated with length of stay in patients with confirmed influenza

Variable	Crude rate ratio ^a	p value	Adjusted rate ratio	p value
Oseltamivir treatment				
no oseltamivir	1 (referent)		1 (referent)	
received <48h of onset	1.30 (1.12, 1.52)	0.001	1.11 (0.98, 1.26)	0.089
received ≥48h of onset	1.54 (1.26, 1.89)	<0.001	1.21 (1.02, 1.44)	0.028
Age group				
<16 years	0.69 (0.45, 1.05)	0.085	0.78 (0.57, 1.06)	0.112
16–64 years	1 (referent)		1 (referent)	
65+ years	1.28 (1.09, 1.50)	0.003	1.30 (1.14, 1.49)	<0.001
Comorbidities	1.70 (1.43, 2.03)	<0.001	1.43 (1.24, 1.66)	<0.001
ICU admission	2.27 (1.82, 2.83)	<0.001	2.38 (1.91, 2.96)	<0.001

a Represents relative difference in length of stay; RR>1 indicates longer stay associated with factor

Incidence of hospital admissions with influenza

Overall, the peak incidence of admissions with confirmed influenza was 5.9 per 100 hospital beds (Figure 2; in epidemiological week 35), but varied from a high of 14.5 per 100 hospital beds at the Royal Hobart Hospital to a low of 2.4 per 100 hospital beds at Royal Perth Hospital (Figure 3).

Presentation and management

Of all cases, 3,920 patients had a known date of onset of illness documented. Of these, 263 cases (6.2%) were diagnosed more than 7 days after admission and therefore were likely to be hospital-acquired. For the remaining 3,657 patients with community-onset laboratory-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 these patients, the delay from onset of illness to admission was >2 days in 57%, and was similar in children (54%), non-elderly adults (58%) and the elderly (58%).

Radiological evidence of pneumonia was present in 754 patients (18%). Pneumonia was less common in children (11%) than in non-elderly adults

(18%) and in the elderly (19%). A higher proportion of patients with pneumonia were admitted to ICU (25%) than those without pneumonia (8.7%).

Of all cases, 493 (11.6%) patients were admitted to ICU, including 408 patients (9.6%) initially admitted to ICU and a further 85 (2.0%) subsequently transferred to ICU after initial admission to a general ward. The elderly (>65 years) and residents of nursing homes were less likely, and those with chronic comorbidities were more likely to be admitted to intensive care. Compared to patients admitted to hospital with influenza B, patients admitted with confirmed A/H1 infection were more likely to be admitted to ICU after adjustment for age and other factors (Table 3).

Use of antivirals

Of patients where the date of onset was reported, 42% did not receive oseltamivir, 22% received oseltamivir within 2 days of symptom onset and 36% received oseltamivir more than 2 days after the onset of illness. Oseltamivir use was lower in children (6.7% within 2 days; 10% more than 2 days) than in non-elderly adults (22%, 37%) and the elderly (24%, 44%) (Table 4).

Figure 2: Incidence of confirmed influenza (per 100 hospital beds) by week

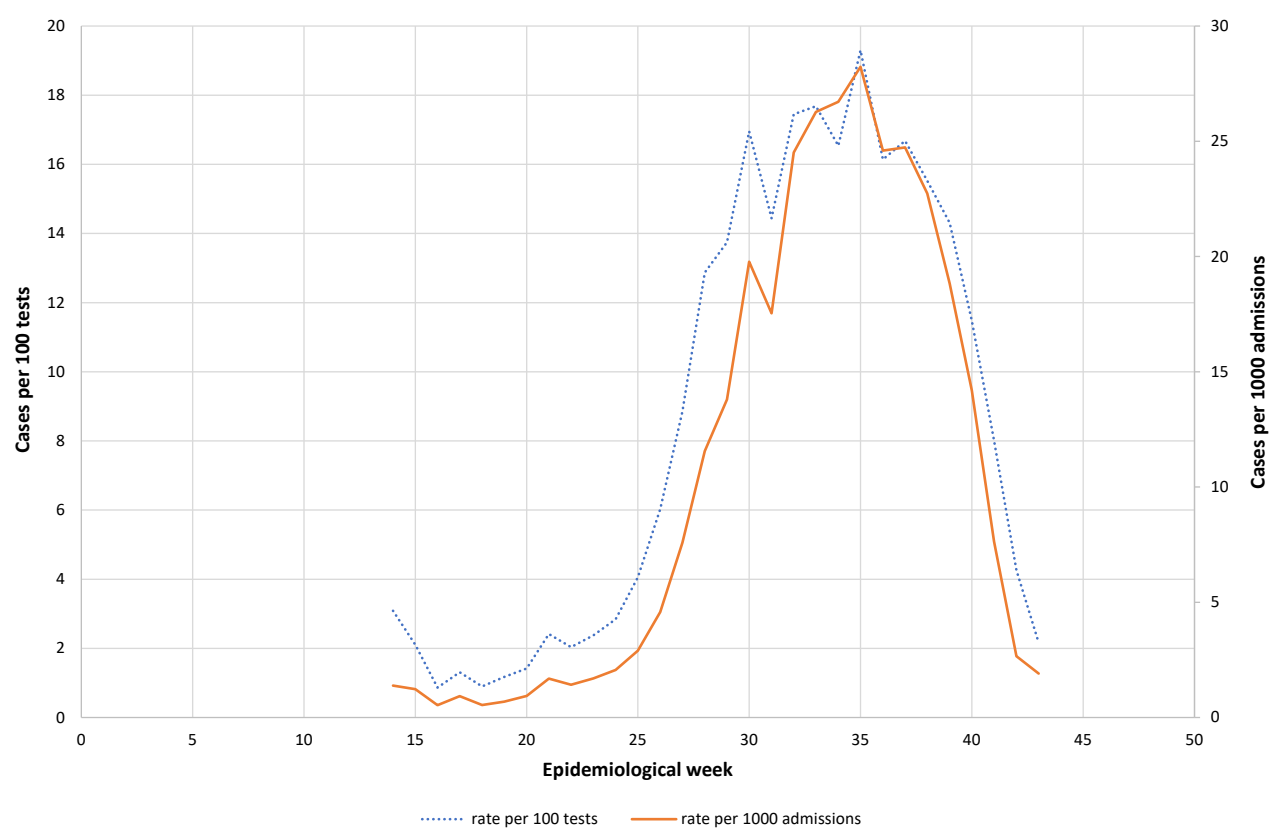


Figure 3: Peak incidence of confirmed influenza (per 100 hospital beds per week) by hospital



CA: Canberra and Calvary Hospitals
 CHW: Children's Hospital at Westmead
 JHH: John Hunter Hospital
 WE: Westmead Hospital
 AS: Alice Springs Hospital
 CB: Cairns Base Hospital
 MA: Mater Hospital
 PA: Princess Alexandra Hospital
 RA: Royal Adelaide
 RH: Royal Hobart Hospital
 AH: Alfred Hospital
 GL: University Hospital Geelong
 MMC: Monash Medical Centre
 RM: Royal Melbourne
 PMH: Princess Margaret Hospital
 RP: Royal Perth Hospital

Outcome

The mean length of hospital stay for all patients was 6.2 days. Admission to ICU was associated with a mean hospital length of stay of 12.4 days, compared to those not admitted to ICU (5.5 days). Of the 4,236 patients where hospital mortality status was documented, 155 patients died (3.7%), which included 59 patients in ICU. Case fatality was higher in the elderly (5.8%) than in non-elderly adults (1.9%) and children (none). Of the 155 deaths, 151 (97%) occurred in patients with comorbidities. The case fatality of influenza-associated pneumonia was 10%, compared to 2.3% in those without pneumonia.

Length of hospital stay was shorter in patients that did not receive oseltamivir (median 2 days, IQR 1, 5 days), than those that received oseltamivir within 2 days (median 4 days, IQR 2, 8 days) or those who received oseltamivir after 2 days (median 4 days, IQR 2, 9 days; Kruskal-Wallis test $p < 0.001$). In a multivariate negative binomial regression model, patients that received late antivirals had a longer length of hospital stay, after adjusting for other factors associated with length of stay including age group, chronic comorbidities and ICU admission (Table 5).

In the 3,669 patients where date of onset of illness and mortality status were reported, mortality was similar in patients that did not receive oseltamivir (44/1,566; 2.8%), those that received oseltamivir within 2 days (28/765; 3.7%) and those that received oseltamivir more than 2 days after onset (42/1,338; 3.14%).

Vaccine coverage and effectiveness

Vaccination status was ascertained in 3,082 of 4,259 cases (72 %) and 1,240 of 1,533 test-negative control patients (81%). Estimated vaccine coverage was 72 % (377/521) in the elderly (≥ 65 years), 50% (161/321) in non-elderly adults with medical comorbidities and 24% (33/140) in children (< 16 years) with medical comorbidities. In the target population, the crude odds ratio of vaccination in cases vs controls was 0.81 (95% CI: 0.67, 0.97) and the adjusted odds ratio of vaccination was

0.77 (95% CI: 0.64, 0.93). The estimated vaccine effectiveness in the target population was therefore 23% (95% CI: 7%, 36%). In the elderly (> 65 years), there was no evidence of vaccine effectiveness (estimated VE 8%; 95% CI: -19%, 30%)

Discussion

In the 2017 season, we have documented 4,259 cases of severe influenza, which represents more than twice the number of admissions in each of 2014 ($n=2,097$), 2015 ($n=2,070$) and 2016 ($n=1,952$). Based on the bed capacity of sentinel hospitals, this represents around 31,000 admissions with confirmed influenza nationally. However, as influenza testing is not performed on all patients with acute respiratory presentations, and influenza may also trigger delayed respiratory presentations (eg secondary bacterial pneumonia) and non-respiratory complications (eg acute myocardial infarction), this should be regarded as a minimum estimate. Estimates of the indirect burden of influenza complications, based on methods that examine excess admissions correlated with influenza activity, suggest that this gap is large.^{2,7}

The peak rate of influenza hospitalisations relative to hospital size provides a measure of impact. Based on the mean duration of hospital stay (6.2 days) and the peak incidence (5.9 per 100 hospital beds per week), we estimate that at the peak of the season, around 5.2% of Australian hospital beds were occupied by patients with confirmed influenza. At Royal Hobart Hospital, where the peak rate of admissions was 14.5 per 100 beds/week, around 12.8% of hospital beds were occupied by patients with confirmed influenza.

Our estimates of vaccine coverage have been similar over several years,⁸⁻¹¹ and consistent with other studies estimating vaccine coverage in the Australian population.^{12,13} Of interest in 2018 will be the impact of new state-based pre-school influenza vaccination programs in Queensland, New South Wales, Victoria, Tasmania, South Australia and the Australian Capital Territory, in addition to the existing program in Western Australia and the national

program for Indigenous children. The utility of an immunisation program for young children is reinforced by the high rate of hospitalisation in this age group¹⁴ and rare but clinically significant complications.¹⁵ Current programs that provide free vaccine for children with chronic comorbidities would not cover the majority of admissions that occur in otherwise healthy children (58% of the 287 children aged between 6 months and 5 years reported to FluCAN in 2017). Additionally, modelling studies in the UK suggest that the influenza campaigns targeting 2–3 year olds resulted in a reduction of 6.1–10.7% in influenza-attributable respiratory hospitalisations, and 5.7–9.4% in influenza-attributable deaths in all age groups.¹⁶

Our estimates of vaccine effectiveness were again relatively low in the target population (point estimate VE 23%) and in the elderly (VE 8%). By comparison, we estimated vaccine effectiveness in the target population in 2016 at 13% (95% CI: -4.7%, 27%), and in the elderly (>65 years) at -19%, (95% CI: -52%, 8.0%). This is lower than interim estimates reported from Australian primary care surveillance systems (33%) but notably these systems focus on younger adults, and our estimates are more consistent with the primary care estimates of VE against A/H3 which was the predominant subtype in the elderly.¹⁷ Primary care surveillance in United States have made interim VE estimates for the 2017/18 season in the elderly at 18% (95% CI: -25% to 47%).¹⁸ Vaccine effectiveness against A/H3 in all population groups was estimated at 25% (13% to 36%) in US primary care, similar to Canadian interim estimates of 17% (95% CI: -14% to 40%).^{18,19}

A confluence of factors may be contributing to this finding; it has long been known that influenza vaccines are less immunogenic in the elderly,²⁰ and this group is disproportionately infected with A/H3N2 influenza subtypes, which are more genetically diverse.¹⁷ Compounding this problem are the well-documented problems associated with egg adaptation of A/H3N2 vaccine strains, which was unchanged from the 2016 vaccine.^{21–23}

The Australian government has recently announced access to two new vaccine formulations in the elderly for 2018. The high dose vaccine has been shown to be more immunogenic, and provide greater protection than standard inactivated influenza vaccine in clinical trials.^{24,25} However, estimates of incremental benefit over standard vaccines in vaccine effectiveness studies have been mixed and may depend on the circulating strains and the degree of match.²⁶ The MF-59 adjuvanted vaccine has also been shown to be more immunogenic in the elderly,²⁷ and one observational study suggests greater protection over several seasons against hospitalisations with influenza and pneumonia.²⁸ While the missing B strain in these trivalent vaccines would have been expected to have minimal impact in the 2017 season where other surveillance suggested that B/Yamagata lineage predominated, mismatch or co-circulation of B lineage strains has occurred previously, most recently in 2015 where more than half of admissions were due to influenza B and both Victorian and Yamagata lineages circulated.

The effectiveness of neuraminidase inhibitors in hospitalised patients remains a controversial topic. Current national guidelines recommend the use of oseltamivir in patients with severe influenza, and this is supported by systematic reviews of observational studies.²⁹ While we did not have sufficient statistical power to detect any impact of oseltamivir on the duration of hospitalisation or mortality, the clinical impact of oseltamivir is likely to be hampered by both under-utilisation and late administration (in turn attributable to late presentation to hospital). A trial of early oseltamivir in high risk patients in primary care (the ALIC4E trial)³⁰ has recently commenced in the UK and will provide more definitive evidence on the effectiveness of this strategy.

There are several limitations to the surveillance system used in the present work. Under-ascertainment of influenza cases may result from the lack of use of influenza laboratory testing or from poor quality sample collection. Delayed presentations or secondary bacterial pneumonia

may be associated with false negative influenza tests as the influenza infection may be cleared by the time of presentation. Ascertainment in tropical regions is limited by surveillance in the winter/dry season only. Estimates of vaccine effectiveness may be biased if an unmeasured confounder disproportionately affects the probability of influenza, compared to non-influenza respiratory illnesses.³¹

In summary, we detected a large number of hospital admissions with laboratory-confirmed influenza in a national observational study in 2017, which was much larger than in any previous season under surveillance since 2010. A consistent finding over several years is that a high proportion of patients with severe influenza, and almost all deaths, occurred in patients with chronic comorbidities.

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Author details

Prof Allen C Cheng¹
Prof Mark Holmes²
Prof Dominic E Dwyer³
A/Prof Sanjaya Senenayake⁴
Dr Louise Cooley⁵
A/Prof Louis Irving⁶
Dr Graham Simpson⁷
A/Prof Tony Korman⁸
Prof Kristine Macartney⁹
A/Prof N. Deborah Friedman¹⁰
Prof Peter Wark¹¹
Dr Anna Holwell¹²
A/Prof Christopher Blyth¹³
Dr Simon Bowler¹⁴
Prof John Upham¹⁵
Prof Grant Waterer¹⁶
A/Prof Tom Kotsimbos¹⁷
Adjunct Prof Paul Kelly¹⁸

1. Alfred Health; Monash University
2. University of Adelaide, Royal Adelaide Hospital
3. University of Sydney, Westmead Hospital
4. Australian National University, The Canberra Hospital
5. Royal Hobart Hospital
6. Royal Melbourne Hospital, University of Melbourne
7. Cairns Base Hospital
8. Monash Medical Centre; Monash University
9. Children's Hospital at Westmead
10. University Hospital Geelong

11. University of Newcastle, John Hunter Hospital
12. Alice Springs Hospital
13. Princess Margaret Hospital, University of Western Australia, Telethon Kids Institute
14. Mater Hospitals
15. Princess Alexandra Hospital, University of Queensland
16. University of Western Australia, Royal Perth Hospital
17. Alfred Health; Monash University
18. ACT Government Health Directorate; Australian National University Medical School

Corresponding author

Prof Allen Cheng, Department of Epidemiology and Preventive Medicine, Monash University, Commercial Road, Melbourne Vic 3004. Email: allen.cheng@monash.edu

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