Influenza epidemiology, vaccine coverage and vaccine effectiveness in children admitted to sentinel Australian hospitals in 2017: Results from the PAEDS-FluCAN Collaboration

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Summary: Significant influenza-associated pediatric morbidity was observed in Australia in 2017. This has prompted multiple Australian states to introduce funded preschool vaccination in 2018. In 2017, inactivated quadrivalent vaccine was protective but with lower effectiveness than observed in previous seasons.

Abstract

Background: In 2017, Australia experienced record influenza notifications. Two sentinel surveillance programs combined to summarise the epidemiology of hospitalised influenza in children and report on vaccine effectiveness (VE) in the context of a limited nationally-funded pediatric influenza vaccination program.

Methods: Subjects were prospectively recruited from April until October. Cases were children aged ≤16 years admitted to eleven hospitals with an acute respiratory illness (ARI) and laboratory-confirmed influenza. Controls were hospitalised children with ARI testing negative for influenza. VE estimates were calculated using the test-negative-design.

Results: 1268 children were hospitalised with influenza: 31.5% were <2 years, 8.2% were Indigenous, and 45.1% had comorbidities predisposing to severe influenza. Influenza B was detected in 34.1% with Influenza A/H1N1 and A/H3N2 detected in 47.2% and 52.8% of subtyped Influenza A specimens. The median length of stay was 3 days (IQR: 1,5), 14.5% were admitted to ICU and 15.9% received oseltamivir. Four in-hospital deaths occurred (0.3%), one considered to be influenza-associated. Only 17.1% of test-negative-controls were vaccinated with poor coverage in children eligible for free vaccine. The VE of inactivated quadrivalent influenza vaccine (QIV) for preventing hospitalised influenza was estimated at 30.3% (95%CI: 2.6%;50.2%).

Conclusions: Significant influenza-associated morbidity was observed in 2017 in Australia. Most hospitalised children had no comorbidities predisposing to severe influenza. Vaccine coverage and antiviral use was inadequate. QIV was protective in 2017 yet VE was lower than previous seasonal estimates. Multiple Australian states have introduce funded preschool vaccination programs in 2018. Additional efforts to promote vaccination and monitor effectiveness are required.

Introduction

Influenza is a common respiratory viral infection that affects up to 10% of the population each year (1, 2). Previous studies demonstrate that young children have the highest rate of hospitalisation (3). The Influenza Complications Alert Network (FluCAN), a national sentinel surveillance program for severe influenza, was established in 2009 to monitor hospitalisations in Australian adults with confirmed influenza (4). Comprehensive clinical data were collected from Australian children admitted to six tertiary pediatric hospitals during the 2009 influenza pandemic (5). However, from 2010-13, insufficient numbers of children were prospectively enrolled in surveillance programs to ascertain pediatric seasonal influenza activity and severity in Australia. In 2014, two tertiary pediatric hospitals in New South Wales (NSW) and Western Australia (WA) from the separate Paediatric Active Enhanced Disease Surveillance network (PAEDS (6)) were included in the existing FluCAN sentinel system (7). In 2017, this collaboration was extended to include four further PAEDS hospitals resulting in a nationally representative pediatric influenza surveillance program.

Inactivated influenza vaccination is recommended by the Australian Technical Advisory Group on Immunisation (ATAGI) for all children 6 months and older. Despite this recommendation, influenza vaccine was only provided free of charge in 2017 under the National Immunisation Program (NIP) for all children ≥6 months of age with comorbidities predisposing them to severe outcomes following influenza infection and Indigenous children aged 6-59 months (8). In a single state, Western Australia, a state funded program has provided free influenza vaccine to all children 6-59 months of age from 2008 (9-11).

The 2017 Southern Hemisphere influenza vaccine contained influenza A/Michigan/45/2015 (H1N1)pdm09 like virus; A/Hong Kong/4801/2014 (H3N2) like virus, B/Brisbane/60/2008 like virus and B/Phuket/3073/2013 like virus (12). Vaccines distributed for children in 2017 included: FluQuadri Junior and FluQuadri (Sanofi-Aventis; FluQuadri Junior provided for children 6-35 months) and Fluarix

Tetra (GlaxoSmithKline; recommended for children 3 years and older) (12). Live attenuated influenza vaccine has not been available in the Southern Hemisphere.

Previous studies have demonstrated that the Southern Hemisphere inactivated influenza vaccine is protective against influenza in children (13, 14). The Western Australian Influenza Vaccine Effectiveness study previously estimated vaccine effectiveness (VE) of TIV in children six to 59 months attending a pediatric emergency department against any laboratory-confirmed influenza at 64.7% (95% confidence interval [CI] 33.7, 81.2) (9). The PAEDS-FluCAN collaboration has previously demonstrated vaccine effectiveness of 55.5% (11.6, 77.6) against hospitalisation in children in 2014 (7).

In this paper, we describe the epidemiology of hospitalisation in children presenting to Australian sentinel sites with confirmed influenza, identify predictors for severe disease (intensive care unit (ICU) admission; prolonged length of stay) and describe vaccine coverage and effectiveness estimates of the 2017 inactivated quadrivalent influenza vaccine (QIV).

Methods

FluCAN is a national hospital-based surveillance system recruiting patients with laboratory-confirmed influenza from 15 sentinel sites (4). In 2017, additional surveillance sites from the PAEDS network joined the surveillance network including five large specialty pediatric hospitals: Children's Hospital at Westmead (NSW), Lady Cilento Children's Hospital (Queensland: QLD), Monash Children's Hospital (Victoria; VIC) Princess Margaret Hospital (WA), Women and Children's Hospital (South Australia: SA); and a large general hospital with an established pediatric unit: Royal Darwin Hospital (Northern Territory: NT). In addition, pediatric patients from other participating FluCAN hospitals were also enrolled; Alice Springs (NT), Cairns Base Hospital (QLD), Canberra Hospital (Australian Capital Territory: ACT), Geelong Hospital (VIC) and Royal Hobart Hospital (Tasmania; TAS).

An influenza case was defined as a patient (≤16 years) admitted to hospital with an acute respiratory illness (ARI) and influenza confirmed by nucleic-acid-testing (NAT). Influenza testing was initiated by clinicians based on local guidelines. All influenza cases were confirmed using real-time reverse transcriptase polymerase chain reaction (PCR) assays using standard primers. Subtype and lineage were not routinely performed in all laboratories. All tests were performed in local or referral laboratories accredited by the National Association of Testing Authorities. An ARI was defined by the presence of new respiratory symptoms including cough, shortness of breath or rhinorrhoea. A hospital admission was defined as requiring inpatient care outside of the emergency department.

Prospective clinician-led surveillance was conducted during the 2017 southern hemisphere influenza season (April to October; follow up continuing to end of November) using a detailed case-report form. Admission to an intensive care unit (ICU) was recorded as well as risk factors predisposing to severe outcomes including race (Indigenous or non-Indigenous) and the presence of underlying conditions (hereafter referred to as comorbidities) (8). Comorbidities assessed included congenital heart disease,

chronic respiratory and neurological disorders, immunocompromising conditions and chronic illnesses such as diabetes mellitus and renal failure (8).

Influenza complications and management

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. Factors associated with length of hospital stay (LOS) were modelled using a negative binomial regression and adjusted length of stay ratios were calculated using the exponential of the LOS regression coefficient. Presentation delay was defined as the time from onset of illness to hospital admission. Treatment delay was defined as the time from onset of illness to oseltamivir prescription (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 >2 days after symptom onset.

Estimation of vaccination coverage and effectiveness

Vaccination status was obtained from the medical record, by parental report and confirmed on the national Australian Immunisation Register (AIR) (15). Immunized was defined as receipt of at least one dose of a licenced influenza vaccine prior to presentation. Vaccination coverage was estimated in control patients' ≥6 months of age admitted with ARI testing negative to influenza by PCR.

We used an incidence density test negative design to estimate vaccine effectiveness, where controls were selected from influenza-test negative subjects with ARI tested contemporaneously with a case: controls could be test-negative for all pathogens or have an alternative respiratory pathogen detected (16-18). Vaccine effectiveness (VE) was estimated as 1 minus the odds ratio of vaccination in influenza positive cases compared to test-negative control patients using methods previously described (4, 19).

Only children ≥6 months of age and tested within seven days of admission were included in VE estimates. A conditional logistic regression model using influenza case status as the dependent outcome was constructed from influenza vaccination. The model was adjusted for potential confounders (age group [6-11months, 12-23months, 2-4years, 5-9years, ≥10 years], indigenous status, comorbidities and stratified by site and month of illness. Sensitivity analyses were performed by i) restricting the cohort to children ≥6months of age tested within seven days of symptom onset and ii) excluding those whose symptoms onset occurred within 14 days of vaccination.

Analyses were performed using Stata 14 for Windows (College Station, Texas, USA). Ethics approval has been obtained at all participating sites and Monash University.

Results

During the period 2 April to 31 October 2017, 1268 children were admitted with PCR-confirmed influenza to eleven hospitals (table 1). The peak rate of admission was in late-August (week 34-35: supplemental figure 1). Of these 1268 children, 400 (31.5%) were <2 years of age, 105 (8.3%) were Indigenous, and 572 (45.1%) had underlying comorbidities (table 1; table 2).

Presentation and treatment

In 1192 patients with confirmed influenza where the duration of symptoms was known, the median duration of symptoms prior to admission was 3 days (IQR 1,5 days). A subset of 42 cases (3.3%) were diagnosed ≥7 days after hospital admission and therefore were likely to be hospital-acquired. Only 199 (15.9%) patients with influenza, received oseltamivir; of these, 82 (6.6% of total) patients were known to have received oseltamivir within 48 hours of symptom onset.

Of all influenza cases, 184 (14.5%) were admitted to ICU. Young infants (<6 months; OR 1.97 [95%CI: 1.21,3.20], p=0.006) and those with comorbidities (OR 2.29 [95%CI: 1.60,3.26], p<0.001] were at increased odds of ICU admission (table 3). The rate of ICU admission was not influenced by Indigenous status, influenza type or vaccination status.

Outcomes

The median length of stay was 3 days (IQR: 1,5). The mean LOS was 4.6 days. LOS was prolonged in Indigenous patients (adjusted length of stay ratio [aLOSR]: 1.51 [95%CI: 1.19,1.92], p=0.001), those admitted to ICU (aLOSR: 3.45 [2.94,4.05], p<0.001), children with comorbidities (aLOSR: 1.34 [1.11,1.61], p=0.002) and those receiving antivirals (aLOSR: 1.76 [1.25, 2.47, p = 0.001]). Vaccination status was not associated with increased length of stay.

In-hospital death was reported in four children (0.3%) ranging in age from <1 month to 13 years. Death occurred 20 to 43 days after influenza diagnosis. Three children had pre-existing comorbidities and all required ICU admission for respiratory support and/or extra corporal membrane oxygenation. One child died of *Staphylococcus aureus* pneumonia related to influenza infection (0.07%) with other deaths unrelated to influenza infection.

Vaccine coverage

Vaccine coverage for all children >6 months of age (figure 1; table 4), was low. Of the 551 children who tested negative for influenza within 7 days of onset of illness, only 94 had received at least one dose of vaccine in 2017 (17.1%; 95%CI: 13.9,20.2; figure 2). Despite a funded influenza program, vaccine coverage remained poor in WA children with only 24.4% (10.7,38.1) of test-negative children aged 6-59 month vaccinated (national average: 14.8%; [11.7; 18.5]). No significant difference between states were observed (figure 2a). Vaccine coverage in influenza test-negative children with comorbidities ranged from 31.6% in WA to 22.9% in SA (figure 2b). Vaccine coverage was increased in older children with comorbidities (33.0% in children ≥5 years compared with 19.8% in children 6-23 months; figure 2c). Higher vaccine coverage was observed in indigenous children (30.0% [12.6;47.4]) compared with non-indigenous children (16.5% [13.1;19.4]). In the age group eligible for funded vaccine (Indigenous children 6-59 months), vaccine coverage was significantly greatly in indigenous children (38.1% [15.4;60.7]) compared with non-Indigenous children (13.5% [10.1;16.9] $p < 0.01$) but overall vaccination coverage was low.

Vaccine effectiveness

After adjusting for age group, comorbidities and Indigenous status, vaccine effectiveness was estimated as 30.3% [95%CI 2.6; 50.2%; table 5]. Vaccine effectiveness did not differ by infecting type (table 5; Influenza A: 28.7% [-3.0; 50.6%], Influenza B: 32.3% [-11.2; 58.8%). Low VE was also demonstrated in children with comorbidities. By restricting the cohort to those tested within 7 days

of symptom onset, vaccine effectiveness was estimated to be 24.3% [-7.1; 46.6%). Following exclusion of those vaccinated within 14 days of symptom onset, vaccine effectiveness was estimated to be 31.7% (2.9; 51.9%)

Discussion

We report on the largest and most comprehensive Australian study to date of pediatric influenza detailing data from 11 sentinel sites. Inclusion of tertiary pediatric hospitals (from the separate PAEDS network (6)) into the existing FluCAN sentinel system has allowed us to report on influenza in 1268 hospitalised children inclusive of metropolitan and regional hospitals, specialist pediatric hospitals and hospitals in tropical and subtropical regions. By collecting data on control patients testing negative for influenza, vaccine coverage (particularly in vulnerable patients) and effectiveness against severe influenza has been accurately estimated (20).

These data demonstrate that the majority of Australian children requiring admission to hospital with influenza are aged <5 years (57.8%) and have no comorbidities (54.9%). Of those hospitalised in 2017, 14% were admitted to ICU and the in-hospital case fatality rate was 0.3%. Despite a significant increase in influenza activity in all age groups in the majority of Australian states in 2017 (21), pediatric influenza outcomes appear similar to those observed in previous years (ICU admission: 11% in 2014 and 10% in 2009 and case fatality rate: 0.3% and 0.9%, respectively (5, 7).) Indigenous children were overrepresented in influenza-associated admissions (8.3% of the total influenza-positive population compared with the national average of 4.4% (22)) as were children with comorbidities (45.1% of the total influenza positive population). These data highlight the ongoing significant burden of influenza in childhood and impact on health-care systems.

The FluCAN network has reported vaccine effectiveness in Australian adults since 2010 but has lacked sufficient recruitment to report separate pediatric VE estimates (19, 20, 23, 24). The addition of large

pediatric sites to the network, has enabled calculation of VE estimates against hospitalised influenza for children aged ≤16 years. In a 2014 pilot study, where two PAEDS sites were included, pediatric VE was estimated at (55% [95%CI 12, 77%]), comparable to that observed in hospitalised adults in the same year (51% [95%CI 42, 60%](7)). Likewise, the 2017 pediatric vaccine effectiveness point estimate (30% [95%CI 3%, 50%]) is comparable to that observed in hospitalised adults (23% [95% CI: 7%, 36%]) (25). These data highlight that VE estimates in children and adults are comparable, providing further evidence of the effectiveness of inactivated vaccines against hospitalised influenza in childhood.

In 2017, Australia experienced record high influenza disease notifications in all age groups (21). Data from the PAEDS-FLuCAN collaboration and other surveillance data have been used by policy makers in states and territories to justify the provision of funded preschool influenza vaccination in 2018. Through these programs, it is anticipated that national influenza vaccine coverage will significantly improve. As the most effective influenza prevention strategy available, vaccination is likely to have a direct impact on the burden of disease in children and potentially an impact on influenza burden more broadly through indirect effects (26-28). The overall benefits of such a program will continue to be influence by the variable and moderate vaccine effectiveness observed with inactivated seasonal influenza vaccines.

The findings of this study highlight ongoing and future challenges with childhood influenza vaccination in Australia. Despite existing funding arrangements, vaccine coverage in children with comorbidities, Indigenous children and children 6-59 months in WA remains inadequate. Free vaccination has been provided through the NIP for children with comorbidities from 2010 yet coverage in those with comorbidities has not significantly changed since 2009(5), remaining well below that observed in adults with risk factors (2015 estimates: 80.2% in the elderly and 57.9% in non-elderly adults with comorbidities(24)). Indigenous Australians are at increased risk of hospital admission with influenza; national hospitalisation discharge data indicate that indigenous children aged <5 years are

hospitalised more than twice as frequently with influenza compared with their non-indigenous peers (29). This finding previously prompted the inclusion of Indigenous children <5 years of age as eligible for NIP-funded influenza vaccination from 2015 onwards: coverage achieved with this program in 2017 continues to be inadequate. 2017 vaccine coverage in WA, the only state with a funded universal vaccination program for children aged 6 to 59 months remains suboptimal. One dose coverage of >50% was initially observed in this age group in WA when introduced in 2008 yet plummeted following suspension of the program in 2010 with adverse events with one brand of influenza vaccine identified (30, 31). Despite ongoing attempts to improve coverage in WA children, coverage remains inadequate. Parents cite ongoing concerns about safety and side effects, despite extensive post marketing surveillance data demonstrating low rates of adverse events (9, 32-35). As Australia moves to improve influenza vaccination coverage in children in 2018, ongoing safety monitoring and community engagement is paramount to the success of such a program (34).

As demonstrated in 2014, antiviral medications are infrequently used in Australian children with influenza (7). Early clinical trials demonstrated more rapid resolution of symptoms and reduced shedding when neuraminidase inhibitors were used early in the illness (36). Although controversial, individual patient level meta-analysis suggest that neuraminidase inhibitors including oseltamivir, when used in seasonal influenza, result in a reduction in illness duration, hospitalization and respiratory complication (37). Early use is expected to have greater impact compared with delayed prescription. Antivirals are currently recommended in national antimicrobial guidelines, regardless of symptom duration, for all individuals with established influenza-associated complications and for patients requiring admission to hospital (38). The finding that oseltamivir receipt was associated with prolonged length of stay needs to be interpreted in this study cautiously due to previously demonstrated residual confounding by severity of illness (39). Future work should focus on ways to improve antiviral use, particularly among children with risk factors for severe influenza.

There are a number of limitations to this study. The decision to test was left to the treating clinician using local guidelines. The impact of this is expected to be small as influenza tests are routinely recommended for infection control purposes in Australian children requiring hospital admission with acute respiratory symptoms. 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. It remains possible, although unlikely, that the decision to test might have been influenced by vaccination status. In this study, we considered receipt of one or more doses of vaccine to equal fully-vaccinated despite recommendations for children aged < 9 years of age to receive two doses in the first vaccination year (8). As in all observational studies, a biased VE estimate may result from unmeasured confounding or mis-ascertainment of vaccination status or outcome. Influenza subtyping was not available for the majority of patients, limiting our ability to determine the relative burden of influenza A types and calculate accurate vaccine effectiveness estimates by strain. Furthermore, the antigenic characteristics of influenza viruses from cases was not performed and as such we are unable to determine the relatedness of circulating strains with influenza strains included in the 2017 seasonal vaccine. Low vaccine uptake was also a major limitation impacting on our ability to more precisely calculate vaccine effectiveness. Inclusion of many, but not all pediatric hospitals precludes estimation of the population at risk and thus the incidence of hospitalised influenza: based on previous estimates from two states, we estimate that this represents 20-40% of pediatric influenza admission nationally in 2017 (40). Despite these limitations, this remains the largest and most comprehensive study to date on pediatric influenza during a single season in Australia.

In summary, we describe more than 1200 children hospitalised with seasonal influenza in Australia, of whom 14% required ICU admission. QIV appeared protective in 2017 but VE was lower than previous estimates. With all states introducing funded pediatric influenza-vaccine programs in 2018, additional efforts to promote vaccination are required. The PAEDS-FLuCAN Network is uniquely placed to monitor the effectiveness of these programs against outcomes of public health importance.

Notes:

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Table 1: Demographic characteristics of hospitalised children with confirmed influenza and influenza negative controls (Epidemiological cohort; April to October 2017, n = 1268)

	Influenza type				Total influenza positive cases	Total influenza negative controls
	A/H1N1	A/H3N2	A/unsubtyped	B		
Number of children	76	85	675	432	1268	885
Age group						
• 0-5 months	11 (14.5%)	10 (11.8%)	94 (13.9%)	38 (8.8%)	153 (12.1%)	252 (28.6%)
• 6-23 months	12 (15.8%)	22 (25.9%)	155 (23.0%)	58 (13.4%)	247 (19.5%)	318 (35.9%)
• 2-4 years	33 (43.4%)	25 (29.4%)	178 (26.4%)	97 (22.5%)	333 (26.3%)	169 (19.2%)
• 5-16 years	20 (26.3%)	28 (32.9%)	248 (36.7%)	239 (55.3%)	535 (42.2%)	143 (16.2%)
Male	43 (56.6%)	48 (56.5%)	353 (52.3%)	221 (51.2%)	664 (52.3%)	515 (58.2%)
Indigenous	5 (6.6%)	19 (22.4%)	53 (7.9%)	28 (6.5%)	105 (8.3%)	58 (6.5%)
State						
• New South Wales	18 (23.7%)	30 (35.3%)	82 (12.1%)	120 (27.8%)	250 (19.7%)	250 (28.3%)
• Victoria	8 (10.5%)	0	80 (11.9%)	62 (14.4%)	150 (11.8%)	93 (10.5%)
• Queensland	12 (15.8%)	1 (1.2%)	268 (39.7%)	89 (20.6%)	370 (29.2%)	179 (20.2%)
• Western Australia	15 (19.7%)	25 (29.4%)	10 (1.5%)	15 (3.5%)	65 (5.1%)	66 (7.5%)
• South Australia	4 (5.3%)	0 (0%)	178 (26.4%)	72 (16.7%)	254 (20.0%)	263 (29.7%)
• Tasmania	10 (13.3%)	9 (10.4%)	3 (0.44%)	17 (3.9%)	39 (3.1%)	0
• Northern Territory	6 (7.9%)	14 (16.5%)	7 (1.0%)	20 (4.6%)	47 (3.7%)	33 (3.7%)
• ACT*	3 (4.0%)	6 (7.1%)	47 (7.0%)	37 (8.6%)	93 (7.3%)	1 (0.1%)

* Australian Capital Territory

Table 2: Risk factors, severity and outcomes in hospitalized children with confirmed influenza (Epidemiological cohort; April to October 2017, n = 1268)

	Not admitted to ICU	Admitted to ICU	Total
Total	1084	184	1268
Age group			
• 0-5 months	118 (77.1%)	35 (22.9%)	153
• 6-23 months	217 (87.9%)	30 (12.1%)	247
• 2-4 years	293 (88.0%)	40 (12.0%)	333
• 5-16 years	456 (85.2%)	79 (14.8%)	535
Chronic medical comorbidities	459 (80.2%)	113 (19.8%)	572
• Prematurity	122 (81.3%)	28 (18.7%)	150
• Chronic respiratory disease	159 (76.1%)	50 (23.9%)	209
• Chronic cardiac disease	56 (69.1%)	25 (30.9%)	81
• Diabetes	13 (50%)	13 (50%)	26
• Chronic neurological disease	95 (73.1%)	35 (26.9%)	130
• Chronic renal disease	24 (85.7%)	4 (14.3%)	28
• Immunosuppressed	99 (88.4%)	13 (11.6%)	112
• Chronic liver disease	26 (81.2%)	6 (18.8%	32
• Genetic abnormality	56 (74.7%)	19 (25.3%)	75
• Inborn error of metabolism	16 (72.7%)	6 (27.3%)	22
• Chronic aspirin use	6 (75.0%)	2 (25.5%)	8
• Obesity (BMI > 30 or body weight >120kg)	7 (87.5%)	1 (12.5%)	8
Influenza vaccination	125 (86.2%)	20 (13.8%)	145
Influenza subtype			
• A/H1N1	67 (88.2%)	9 (11.8%)	76
• A/H3N2	68 (80.0%)	17 (20.0%)	85
• A/unsubtyped	574 (85.0%)	101 (15.0%)	675
• B	375 (86.8%)	57 (13.2%)	432
Mortality	1 (20%)	4 (80%)	5

Table 3: Factors associated with admission to intensive care identified using a multivariable model (Epidemiological cohort; April to October 2017, n = 1268)

Variable		Crude odds ratio (95% CI)	P value	Adjusted odds ratio (95% CI)	P value
Age	<6 months	1.71 (1.10, 2.68)	0.018	1.97 (1.21, 3.20)	0.006
	6-23 months	0.80 (0.51, 1.25)	0.33	0.85 (0.51, 1.40)	0.52
	2-4 years	0.79 (0.52, 1.18)	0.25	0.86 (0.55. 1.35)	0.52
	≥ 5 years	1 (referent)		1 (referent)	
Medical comorbidities	Comorbidities present	2.17 (1.57, 2.99)	<0.001	2.29 (1.60, 3.26)	<0.001
	Comorbidities absent	1 (referent)		1 (referent)	
Indigenous Australian	Indigenous	1.06 (0.61, 1.86)	0.825	1.09 (0.60, 1.98)	0.76
	Non-Indigenous	1 (referent)		1 (referent)	
Influenza type	Influenza A	1.18 (0.84, 1.65)	0.339	1.15 (0.79, 1.66)	0.48
	Influenza B	1 (referent)		1 (referent)	
Influenza vaccination	Vaccinated in 2017	0.93 (0.57, 1.55)	0.801	0.83 (0.49, 1.40)	0.49
	Unvaccinated in 2017	1 (referent)		1 (referent)	

Table 4: Characteristics of vaccinated and unvaccinated cases (n=937) and vaccinated and unvaccinated controls (n=551; Vaccine effectiveness cohort: April to October 2017)

	Influenza positive cases		Influenza negative controls	
	Vaccinated	**Unvaccinated**	**Vaccinated**	**Unvaccinated**
Total	133	804	94	457
Age group				
• 6-23 months	25 (18.8%)	186 (23.1%)	32 (34.0%)	241 (52.7%)
• 2-4 years	43 (32.3%)	236 (29.4%)	31 (33.0%)	119 (26.0%)
• 5-16 years	65 (48.9%)	382 (47.5%)	31 (33.0%)	97 (21.2%)
Chronic medical comorbidities	95 (71.4%)	332 (41.3%)	72 (76.6%)	205 (44.9%)
• Prematurity	20 (15.0%)	82 (10.2%)	11 (11.8%)	69 (15.10%)
• Chronic respiratory disease	40 (30.1%)	126 (15.7%)	35 (37.2%)	86 (18.8%)
• Chronic cardiac disease	15 (11.7%)	35 (4.4%)	14 (14.9%)	29 (6.5%)
• Diabetes	3 (2.3%)	16 (2.0%)	1 (1.1%))	2 (0.4%)
• Chronic neurological disease	31 (24.2%)	73 (9.2%)	20 (21.5%)	39 (8.7%)
• Chronic renal disease	9 (7.0%)	17 (2.1%)	4 (4.3%)	12 (2.7%)
• Immunosuppressed	30 (23.4%)	60 (7.6%)	21 (22.6%)	27 (6.1%)
• Chronic liver disease	12 (9.4%)	13 (1.6%)	5 (5.4%)	9 (2.0%)
• Genetic abnormality	17 (13.3%)	35 (4.4%)	8 (8.7%)	20 (4.5%)
• Inborn error of metabolism	2 (1.6%)	14 (1.77%)	2 (2.1%)	11 (2.5%)
• Chronic aspirin use	0	3 (0.4%)	5 (5.4%)	4 (0.9%)
• Obesity (BMI > 30 or body weight >120kg)	2 (1.6%)	4 (0.5%)	1 (1.1%)	4 (0.9%)

Table 5: Estimated vaccine effectiveness against hospitalisation with influenza in children >6 months (Vaccine effectiveness cohort; April to October 2017)

Strains	Number of cases and controls				Unadjusted VE (95% CI)	Adjusted VE* (95% CI)
	Vaccinated cases	Unvaccinated cases	Vaccinated controls	Unvaccinated controls		
Overall						
All strains†	133	804	94	457	19.6% (-7.3%; 39.7%)	30.3% (2.6%; 50.2%)
A	87	522	94	457	19.0% (-11.3%; 41.0%)	28.7% (-3.0%; 50.6%)
B	46	282	94	457	20.7% (-16.3%; 45.9%)	32.3% (-11.2; 58.8%)
In children with comorbidities						
All strains†	105	343	75	215	12.2% (-23.5%:37.7%)	23.3% (-12.7%; 47.8%)

* adjusted by age group, medical risk factors and indigenous status

† Inclusive of patients with untyped influenza A infection, H1N1, H3N2 and influenza B.

Figure 1: Flowchart of children included in epidemiological and VE cohorts (April to October 2017)

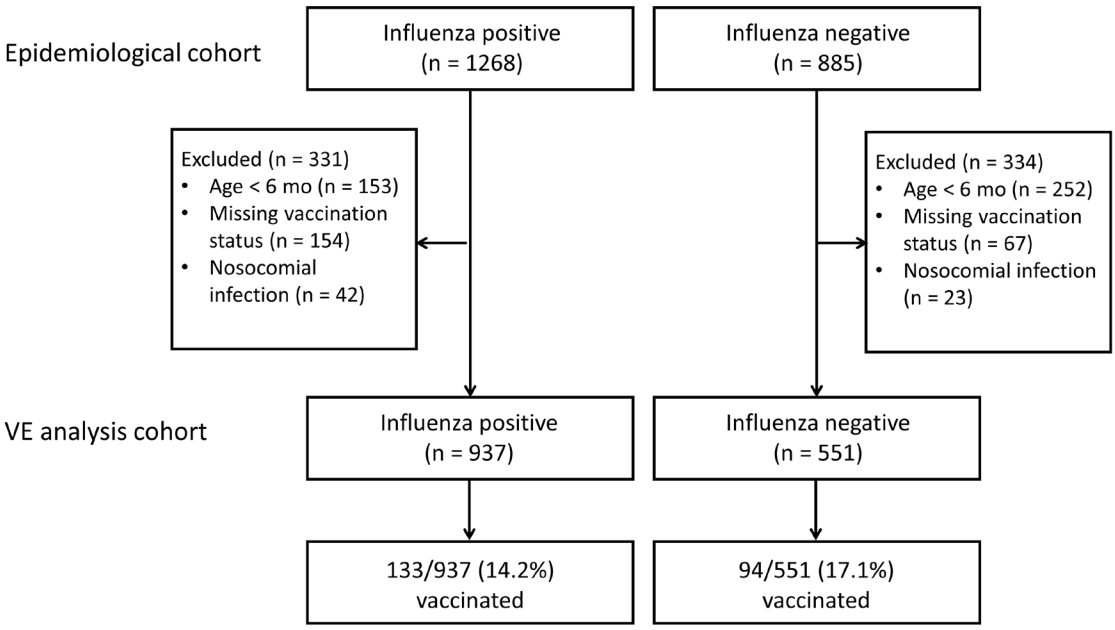
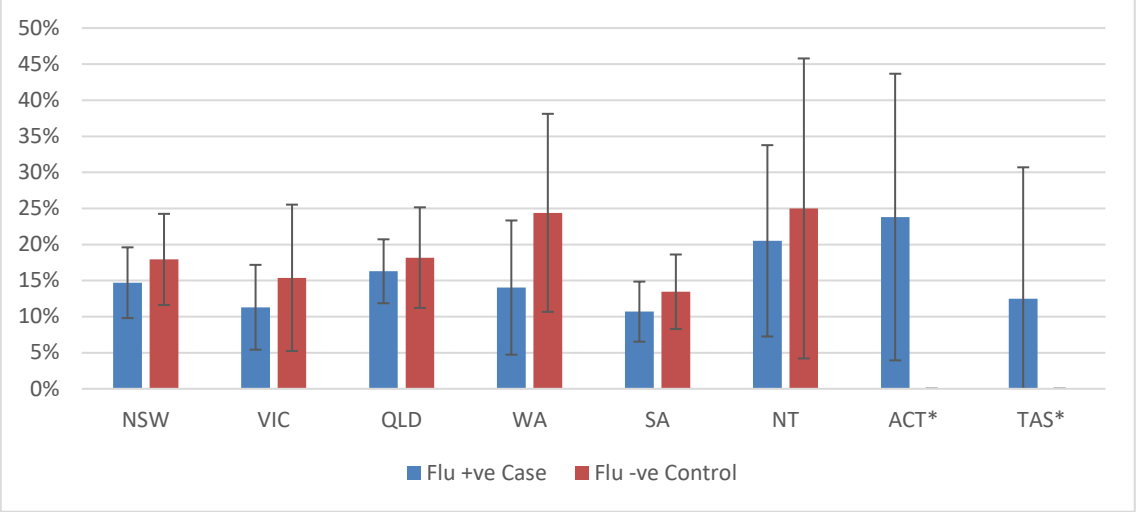


Figure 2a: Influenza vaccine coverage by case-status and state (excluding children <6 months)



*<5 test negative controls recruited in ACT and TAS

Figure 2b: Influenza vaccine coverage by comorbidities and state in test negative controls (excluding children <6 months)

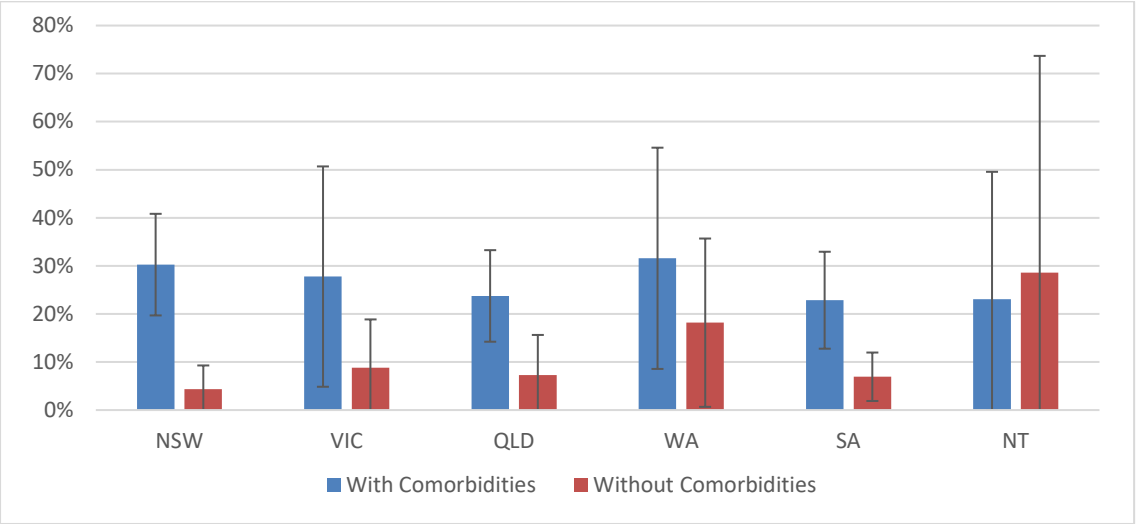
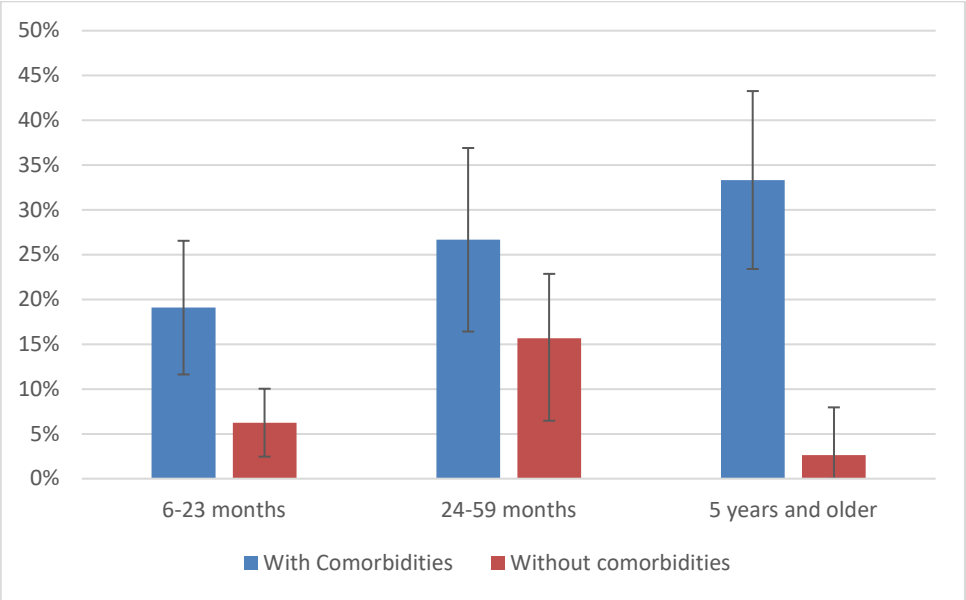


Figure 2c: Influenza vaccine coverage by comorbidities and age group in test negative controls (excluding children <6 months)



Supplemental figure 1: Date of admission in children hospitalized with confirmed influenza (epidemiological cohort; April to October 2017, n = 1268)