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Intraseason decline in influenza vaccine effectiveness during the 2016 southern hemisphere influenza season: A test-negative design study and phylogenetic assessment

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ABSTRACT

Background: We estimated the effectiveness of seasonal inactivated influenza vaccine and the potential influence of timing of immunization on vaccine effectiveness (VE) using data from the 2016 southern hemisphere influenza season.
Methods: Data were pooled from three routine syndromic sentinel surveillance systems in general practices in Australia. Each system routinely collected specimens for influenza testing from patients presenting with influenza-like illness. Next generation sequencing was used to characterize viruses. Using a test-negative design, VE was estimated based on the odds of vaccination among influenza-positive cases as compared to influenza-negative controls. Subgroup analyses were used to estimate VE by type, subtype and lineage, as well as age group and time between vaccination and symptom onset.
Results: A total of 1085 patients tested for influenza in 2016 were included in the analysis, of whom 447 (41%) tested positive for influenza. The majority of detections were influenza A/H3N2 (74%). One-third (31%) of patients received the 2016 southern hemisphere formulation influenza vaccine. Overall, VE was estimated at 40% (95% CI: 18–56%). VE estimates were highest for patients immunized within two months prior to symptom onset (VE: 60%; 95% CI: 26–78%) and lowest for patients immunized >4 months prior to symptom onset (VE: 19%; 95% CI: −73–62%).
Discussion: Overall, the 2016 influenza vaccine showed good protection against laboratory-confirmed infection among general practice patients. Results by duration of vaccination suggest a significant decline in effectiveness during the 2016 influenza season, indicating immunization close to influenza season offered optimal protection.

1. Introduction

Influenza is a potentially serious disease, causing an estimated 3–5 million severe infections and 291,000–646,000 deaths annually [1]. Seasonal influenza vaccines are available to prevent influenza infection, and in Australia are funded by the Australian Government Department of Health under the National

Abbreviations: ASPREN, Australian Sentinel Practices Research Network; HA, haemagglutinin; ILI, influenza-like illness; NA, neuraminidase; RT-PCR, reverse transcriptase-polymerase chain reaction; SPNWA, Sentinel Practitioners Network of Western Australia; VE, vaccine effectiveness; VicSPIN, Victoria Sentinel Practice Influenza Network.

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Immunisation Program. This program provides free vaccine to adults ≥65 years of age, individuals with chronic medical conditions predisposing them to severe illness, pregnant women, and Indigenous individuals 6 months to 4 years of age and 15 years and older [2]. State-specific programs in Western Australia and Queensland additionally offer free influenza vaccine to all children 6 months to 4 years of age [3,4].

Annually, the antigenic composition of seasonal influenza vaccines can change to provide the best match to expected circulating virus strains. As a result, routine monitoring of genetic drift and vaccine effectiveness is warranted. The 2016 southern hemisphere formulation of inactivated influenza vaccine offered under the National Immunisation Program in Australia contained four antigens, including A/California/7/2009(H1N1)pdm09-like virus, A/Hong Kong/4801/2014 (H3N2)-like virus, B/Brisbane/60/2008-like virus (B/Victoria lineage), and B/Phuket/3073/2013-like virus (B/Yamagata lineage) [5].

In 2016, the Australian influenza season was characterised by early influenza A/H1N1pdm09 activity, followed by an increase in influenza A/H3N2 activity, which predominated throughout the season [6]. Data from three general practice sentinel surveillance systems with national coverage were pooled to estimate the effectiveness of the 2016 southern hemisphere influenza vaccine, with particular focus on the impact of timing of vaccination.

2. Methods

Data from three sentinel surveillance systems were collected: the Australian Sentinel Practices Research Network (ASPREN), the Sentinel Practitioners Network of Western Australia (SPNWA), and the Victoria Sentinel Practice Influenza Network (VicSPIN). These systems have been described elsewhere [7,8] and in 2016 included 24 general practices in Western Australia (SPNWA), 32 practices in Victoria (VicSPIN), and 97 practices from the remaining states (ASPREN). Sentinel GPs collected information on patients presenting with influenza-like illness (ILI) during the influenza season. Cases of ILI included patients presenting with fever, cough and fatigue. Nasal/throat swabs were taken from a systematic selection of ILI patients for influenza testing by multiplex reverse transcriptase-polymerase chain reaction (RT-PCR). Additional information was collected at the time of testing, including the patient's age, sex, comorbid medical conditions, and receipt and date of the current year's influenza vaccine.

2.1. Influenza testing and phylogenetic analysis

Real-time RT-PCR targeting the haemagglutinin (HA) gene was used to determine subtype of influenza A viruses (A/H3N2 or A/H1N1pdm09) and the lineage of influenza B viruses (Yamagata or Victoria). All original clinical samples testing positive in ASPREN and VicSPIN and all virus isolates recovered from samples collected in SPWNA were referred to the WHO Collaborating Centre for Reference and Research on Influenza (Melbourne, Australia) for antigenic and phylogenetic characterisation. Haemagglutination inhibition assays against the 2016 vaccine virus strains were used to assess antigenic similarity between the viruses collected from patients and the vaccine viruses; i.e. A/California/7/2009 (H1N1pdm09), A/Hong Kong/4801/2014 (H3N2), B/Brisbane/60.2008 (B/Victoria lineage), and B/Phuket/3078/2013 (B/Yamagata lineage). Next generation sequencing was used to characterise the HA and neuraminidase (NA) genes of all the A/H3N2 viruses as previously described [9]. A phylogenetic tree was constructed based on HA sequences using the maximum likelihood method to determine the clades of each A/H3N2 viruses.

2.2. Estimating vaccine effectiveness

To estimate vaccine effectiveness, we calculated the odds of vaccination in influenza-positive cases as compared to influenza-negative controls. A vaccinated patient was defined as a patient with a record of receiving the 2016 influenza vaccine with a date of vaccination ≥14 days prior to symptoms onset. We excluded patients with indeterminable vaccination status, vaccination <14 days prior to testing, patients presenting more than seven days since symptoms onset or outside the influenza season, and patients with missing information on age. The start of the influenza season was defined as the third consecutive week where the number of influenza detections exceeded the annual mean number of detections; the end date was defined as the third consecutive week where the number of influenza detections was less than the annual mean. The period of peak influenza activity was defined as weeks falling within one standard deviation of the peak number of detections for the season.

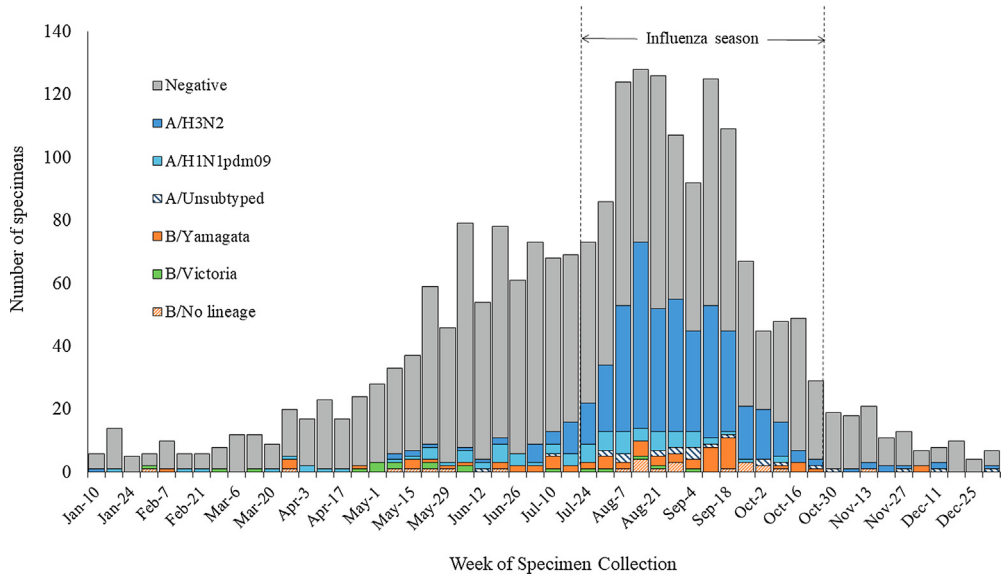

Fig. 1. Weekly influenza tests submitted to sentinel general practices – Australia, 2016.

Table 1
Characteristics of patients testing positive for influenza (n = 1085) – Australia 2016.

Characteristic	Test positive cases							Test negative controls
	Total positive cases *n (%)*	A/Untyped *n (%)*	A/H1N1 *n (%)*	A/H3N2 *n (%)*	B/No lineage *n (%)*	B/Yamagata *n (%)*	B/Victoria *n (%)*	*n (%)*
Overall	447 (41)	15 (1)	43 (4)	329 (30)	14 (1)	43 (4)	3 (<1)	638 (59)
By age group								
<18 years	116 (47)	2 (1)	11 (5)	84 (34)	4 (2)	14 (6)	1 (<1)	128 (53)
18–64 years	290 (41)	11 (1)	29 (4)	214 (30)	10 (1)	24 (3)	2 (<1)	423 (59)
≥65 years	41 (32)	2 (1)	3 (2)	31 (24)	0 (0)	5 (4)	0 (0)	87 (68)
Sex[*]								
Male	208 (42)	4 (1)	23 (5)	151 (31)	7 (1)	21 (4)	2 (<1)	286 (58)
Female	238 (40)	11 (2)	20 (3)	177 (30)	7 (1)	22 (4)	1 (<1)	351 (60)
Comorbidity[†]								
≥One condition	123 (40)	5 (2)	13 (4)	90 (29)	4 (1)	10 (3)	1 (<1)	183 (60)
No condition identified	293 (42)	7 (1)	25 (4)	221 (31)	8 (1)	30 (4)	2 (<1)	408 (58)
Timing of season[§]								
Early season	105 (36)	3 (1)	20 (7)	70 (24)	1 (<1)	9 (3)	2 (1)	185 (64)
Peak season	298 (46)	9 (1)	21 (3)	228 (35)	10 (1)	29 (5)	1 (<1)	344 (54)
Late season	44 (29)	3 (2)	2 (1)	31 (20)	3 (2)	5 (3)	0 (0)	109 (71)

[*] 2 specimens missing patient's sex.
[†] 78 specimens missing information on comorbid medical conditions.
[§] Timing of influenza testing in relation to seasonal activity. Cut-points for early and late influenza season were defined based on two standard deviations from the peak of the season.

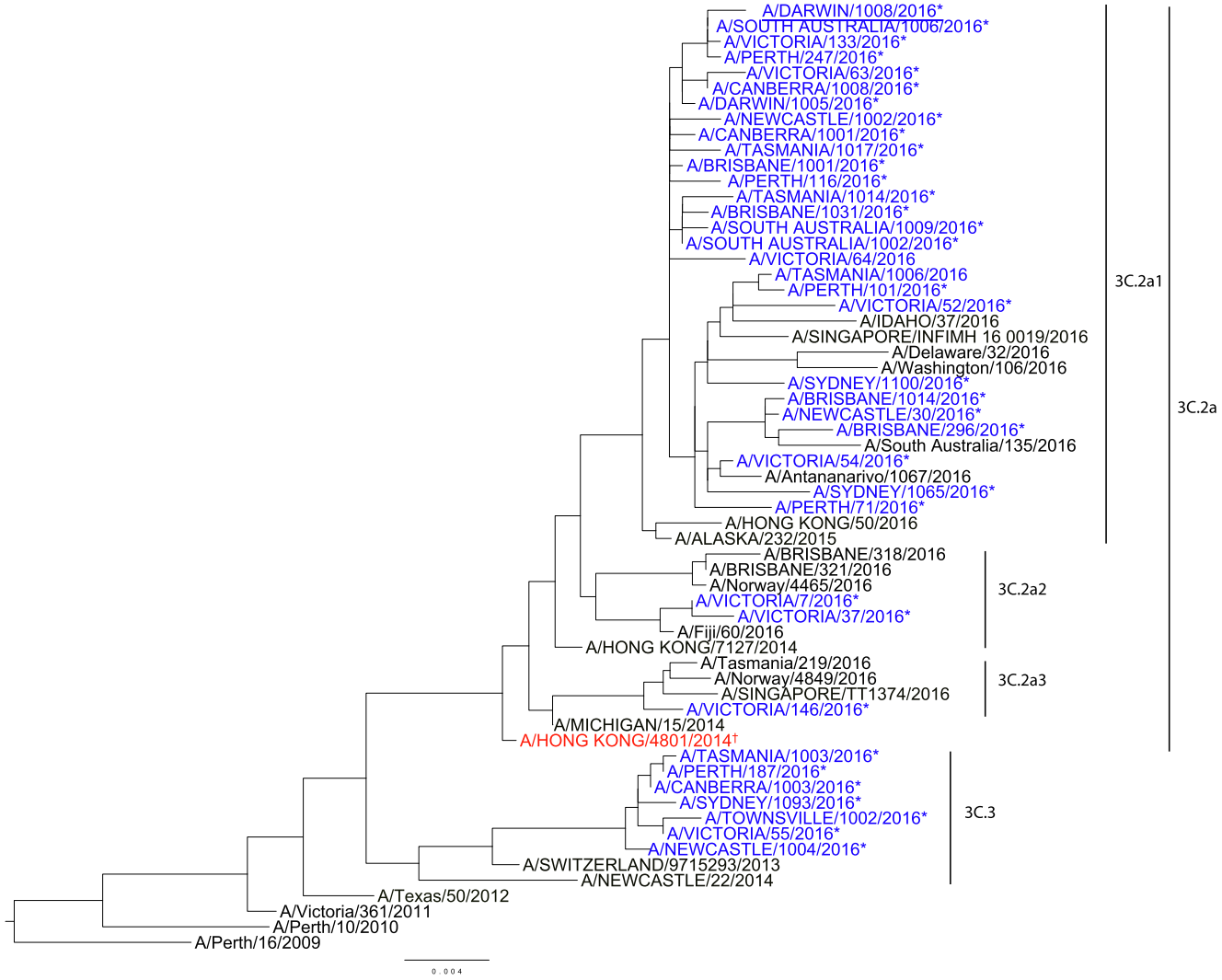

Fig. 2. Phylogenetic analysis of representative circulating southern hemisphere seasonal influenza A/H3N2 viruses[*] – Australia, 2016. Footnote: [*]Viruses sequenced in this study; [†]viruses in red are the 2016 southern hemisphere vaccine virus.

Adjusted odds ratios were estimated by logistic regression, which included a dummy variable for surveillance system, a cubic spline term for patient's age, and a quadratic spline term for week of influenza testing. Vaccine effectiveness was calculated as one minus the adjusted odds ratio. Stratified models were used to estimate effectiveness by age group, virus subtype and lineage, and time between vaccination and symptom onset (<3 months, 3 months, 4 months, and >4 months). For A/H3N2, estimates were also attempted for the major genetic groups. Analyses were performed in R.

3. Results

Among the 294 GPs at 153 general practices participating in the surveillance systems in 2016 (ASPREN: 147 GPs, SPNWA: 51 GPs, and VicSPIN: 96 GPs), 5157 patients presented with influenza-like illness (ASPREN: 3567 patients, SPNWA: 1061 patients, and VicSPIN: 529 patients). Among these patients, nasal/throat swabs were taken from 2189 (42%) patients (ASPREN: 1130 specimens, SPNWA: 647 specimens, and VicSPIN: 412 specimens) (Supplemental Fig. 1). Both influenza positivity and the number of specimens collected peaked in week 33 (week beginning 15 August), with influenza A/H3N2 constituting the majority of detections (Fig. 1). A total of 1242 specimens were collected during the southern hemisphere influenza season (weeks 28–42 or 11 July to 21 October); 157 specimens were excluded from patients where the symptom onset was missing or exceeded seven days prior to clinical testing, or due to indeterminable vaccination status or missing information. A total of 1085 specimens with complete information included in the final analysis (Supplemental Fig. 2). Among these, 447 (41%) were positive for influenza: 329 (30%) with influenza A/H3N2, 43 (4%) with influenza A/H1N1pdm09, 43 (4%) with influenza B/Yamagata, and 3 (<1%) with influenza B/Victoria (Table 1). The remaining specimens testing positive for influenza were unsubtyped influenza A (n = 15) or influenza B viruses with no lineage information (n = 14). Isolates were recovered from 162 specimens. A/H1N1, A/H3N2, and B virus isolates were antigenically similar to vaccine strains. Sequencing was performed on 153 A/H3N2 viruses and indicated substantial genetic diversity among viruses (Fig. 2). 131 viruses were identified as clade 3C.2a1, 5 as clade 3C.2a2, 1 as 3C2a3, and 16 as 3C.3a. The 3C.2a1 and 3C.2 clades viruses showed significant genetic differences to 3C.2a clades that the 2016 southern hemisphere vaccine (A/Hong Kong/4801/2014) belongs to, however, they are still similar antigenically.

In total, 31% (n = 332) of patients received the 2016 southern hemisphere influenza vaccine. Influenza vaccination was most common among adults 65 years of age and older, women and those with a chronic medical condition (Table 2). On average, patients received their influenza vaccine within four months prior to ILI symptom onset (median: 117 days; interquartile range [IQR]: 92–142 days); 108 (24%) influenza-positive cases received an influenza vaccine, and 224 (35%) influenza-negative controls were vaccinated against influenza in 2016. Older adults (≥65 years) were associated with a longer time between vaccination and symptom onset (chi-square value = 14.8, $P = 0.02$).

Estimates of vaccine effectiveness by type/subtype and age group are presented in Fig. 3. We estimated the 2016 influenza vaccine was 40% (95% CI: 18–56%) effective against any medically-attended influenza infection. For influenza A viruses, influenza vaccine effectiveness in 2016 was 67% (95% CI: 15–87%) for A/H1N1pdm09, 42% (95% CI: 17–59%) for A/H3N2, 49% (95% CI: 13–70%) for A/H3N2 clade 3c.2a, and 52% (95% CI: 16–73%) for A/H3N2 clade 3C.2a1. For influenza B viruses, data suggested vaccination was not effective in these tested patients (VE: 1%; 95% CI, −93–49%).

When considering the timing of influenza vaccination, a shorter time period between vaccination and onset of ILI symptoms was not associated with fewer influenza detections (chi-square value = 6.03; $P = 0.11$). However, VE was highest against influenza infection among patients with a record of vaccination < 3 months prior to symptom onset (VE: 60%; 95% CI: 26–78%) (Fig. 4). At three months, VE was 42% (95% CI: 1–66%); by four months, we estimated influenza vaccination to be 25% effective and confidence limits overlapped the null (95% CI: −30–57%). On average, influenza-positive cases had a longer period of time between

Table 2
Seasonal inactivated influenza vaccination among test-positive cases (n = 447) and test-negative controls (n = 638) – Australia, 2016.

Characteristic	Total	Test positive cases (n = 447)			Test negative controls (n = 638)		
		Unvaccinated	Vaccinated		Unvaccinated	Vaccinated	
				Days between vaccination and symptom onset			Days between vaccination and symptom onset
		n (%)	*n (%)*	*Median (IQR)*	*n (%)*	*n (%)*	*Median (IQR)*
Overall	1085	339 (76)	108 (24)	123 (98–141)	414 (65)	224 (35)	116 (89–142)
By age group							
<18 years	244	108 (93)	8 (7)	105 (97–110)	113 (88)	15 (12)	89 (51–103)
18–64 years	713	219 (75)	71 (25)	115 (92–138)	289 (68)	134 (32)	116 (80–142)
≥65 years	128	12 (29)	29 (71)	135 (120–145)	12 (14)	75 (86)	119 (99–146)
Sex[*]							
Female	589	175 (73)	63 (27)	123 (99–139)	211 (60)	140 (40)	118 (91–146)
Male	494	163 (78)	45 (22)	124 (94–147)	202 (71)	84 (29)	108 (85–131)
Comorbidity[†]							
≥One condition	306	74 (60)	49 (40)	133 (106–145)	70 (38)	113 (62)	121 (96–145)
No condition reported	701	239 (82)	54 (18)	115 (98–128)	311 (76)	97 (24)	108 (77–137)
Timing of influenza-like illness[§]							
Early season	290	84 (80)	21 (20)	91 (80–105)	122 (66)	63 (34)	86 (68–97)
Peak season	642	224 (75)	74 (25)	124 (108–139)	217 (63)	127 (37)	122 (100–138)
Late season	153	31 (70)	13 (30)	159 (139–177)	75 (69)	34 (31)	160 (151–170)

[*] 2 specimens missing patient's sex.
[†] 78 specimens missing information on comorbid medical conditions.
[§] Timing of influenza testing in relation to seasonal activity. Cut-points for early and late influenza season were defined based on one standard deviations from the peak of the season. The beginning and end of influenza season was defined as two standard deviations from the mean number of annual influenza detections.

vaccination and symptom onset (median: 123 days; IQR: 98–141 days) compared to influenza-negative controls (median: 116 days; IQR: 89–142 days) (Kruskal-Wallis chi-squared: 2.30; $P = 0.13$) (Supplemental Fig. 3).

4. Discussion

In the 2016 Australian influenza season, which was predominated by the influenza A/H3N2 virus, we estimated that influenza vaccination was 40% effective against laboratory-confirmed influenza and 42% effective against influenza A/H3N2. Circulating influenza A/H3N2 viruses were most commonly identified as clade 3C.2a1. Our estimates are similar to those from the 2015–2016 northern hemisphere influenza season formulation of 10–48% [10,11] and the 2015 southern hemisphere formulation of 54% [8].

Although we observed significant protection against influenza A viruses, we estimated low VE against influenza B viruses (1%). Low vaccine effectiveness against influenza B from the 2015/16 northern hemisphere has been documented in previous studies from the 2015/16 and 2016/17 northern hemisphere seasons [12–14]. In Japan, the 2015/16 northern hemisphere formulation was estimated to be just 37% (95% CI: −12% to 64%) effective against influenza B among children aged 6 months to 15 years [12]. Crude vaccine effectiveness estimates against influenza B less than 35%

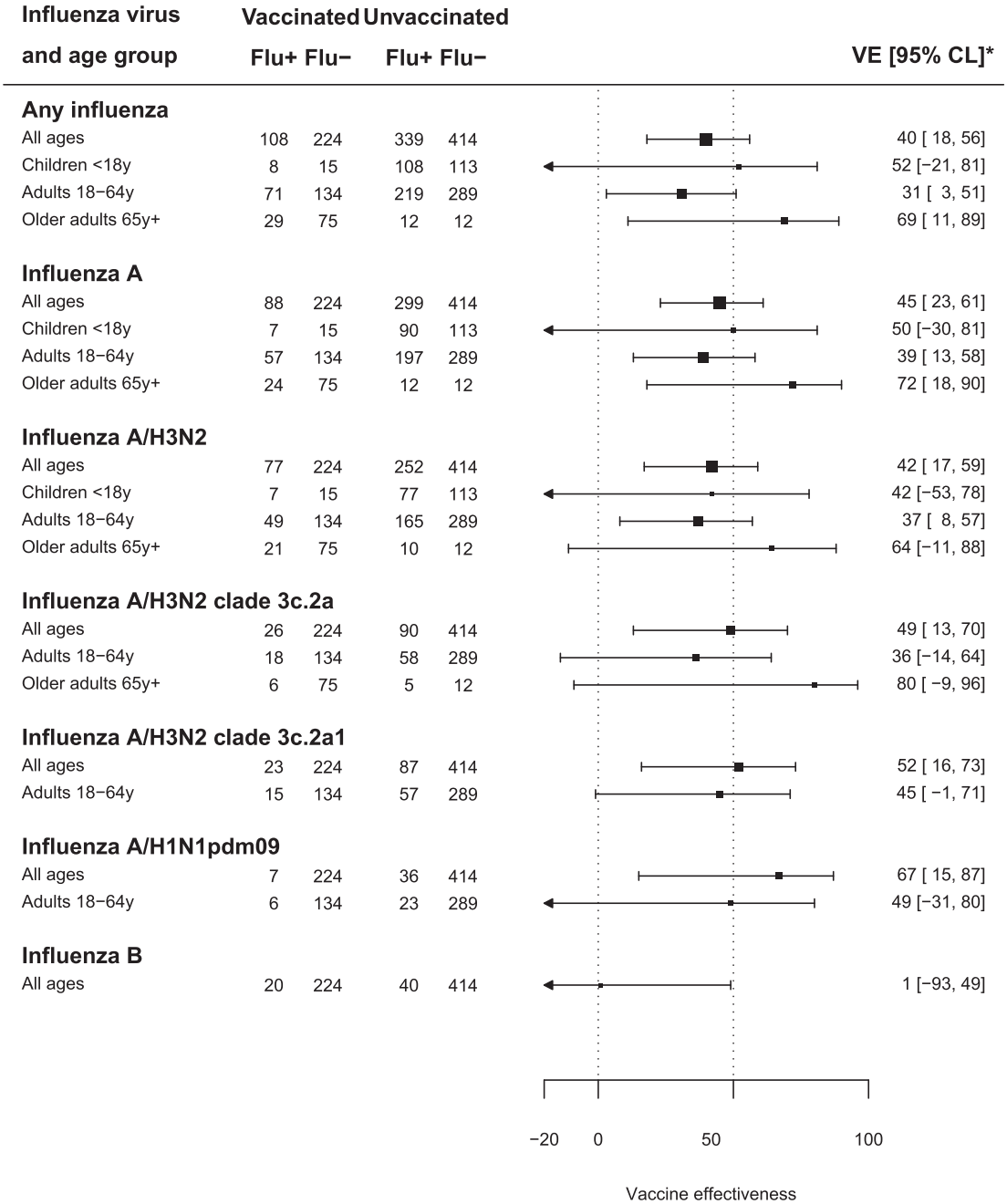

Fig. 3. Estimates* of 2016 southern hemisphere influenza vaccine effectiveness (VE) by virus type/subtype and age group – Australia, 2016†. Footnotes: *Vaccine effectiveness and corresponding 95% confidence intervals, adjusted by cubic spline for age, a quadratic spline for week of collection, and sentinel surveillance system. †Reliable estimates could not be computed for influenza B lineages due to wide confidence intervals (>100) or for all age groups for influenza A/H1N109, influenza A/H3N2, or influenza B due to small cells (n < 5).

were also documented among adults during the 2016/17 influenza season in the United Kingdom [13].

The reasoning for such low vaccine effectiveness estimates for influenza B viruses is difficult to disentangle. On the one hand, low VE may be attributed to lineage mis-match in trivalent influenza vaccines. Although quadrivalent influenza vaccines were made available under the National Immunisation Program in 2016 [17], trivalent influenza vaccines were available for private purchase in Australia [18]. In our setting, the 2016 southern hemisphere trivalent influenza vaccine included a Victoria lineage influenza B virus (B/Brisbane/60/2008-like virus), but 68% of influenza B viruses detected were Yamagata lineage. We do not know what proportion of participants in our study received each type of vaccine; however, 72% of individuals with influenza B had no chronic medical condition recorded and were <65 years of age, suggesting immunisation through the private market was possible in this study. While some studies support the existence of cross-lineage protection [8,15–17], this evidence is somewhat inconsistent [18].

During the 2016 southern hemisphere season, we observed a significant within-season decline in influenza vaccine effectiveness as the time from vaccination to symptom onset increased. Vaccine effectiveness was highest among patients who were immunised <3 months prior to symptom onset (60%). Between two and four months post-vaccination, we observed an absolute monthly reduction of 7–18%. Several studies in primary care settings have identified a similar decline in effectiveness by days between vaccination and symptom onset [11,19]. A recent study by the US Influenza Vaccine Effectiveness Network showed that for every month after vaccination, effectiveness was reduced by 6–11%.[20] Likewise, a large case-control study from the European I-MOVE group demonstrated declining effectiveness over multiple influenza seasons. Their results showed that by 111 days post-vaccination, limited effectiveness of influenza vaccination could be observed [19]. The decline in vaccine effectiveness occurred across seasons and virus subtypes [19], and similar results have been observed in hospital settings [21].

It remains unclear whether the cause of within-season declines in vaccine effectiveness is due to waning immunity as the influenza season progresses [19], is a result of uncontrolled confounding, or is induced by a "leaky" vaccine effect [22]. Several potential biasing factors may influence observations of an intraseason decline in VE. Shifts in the prevalence of circulating virus strains will influence VE estimates and can draw an overall VE estimate towards the predominant strain's estimate for each period. For example, in our data, influenza A/H1N1pdm09 circulated early in the season, while influenza A(H3N2) (for which VE was lower) circulated later in the season. This argument may be somewhat contradicted by the circulation of influenza B early in the season, but we note that the relative frequency of influenza B may have been too low to influence the overall VE estimate. Although most analyses, including our own, control for the week of specimen collection, it is possible that the temporal pattern in circulating influenza viruses may have influenced VE estimation. Another important side-effect of this temporal change is that the source population from which cases arise changes throughout a season. For example, many of the cases occurring later in the season (with a longer period of time between vaccination and symptom onset) were ≥65 years old, a group in which influenza vaccines are known

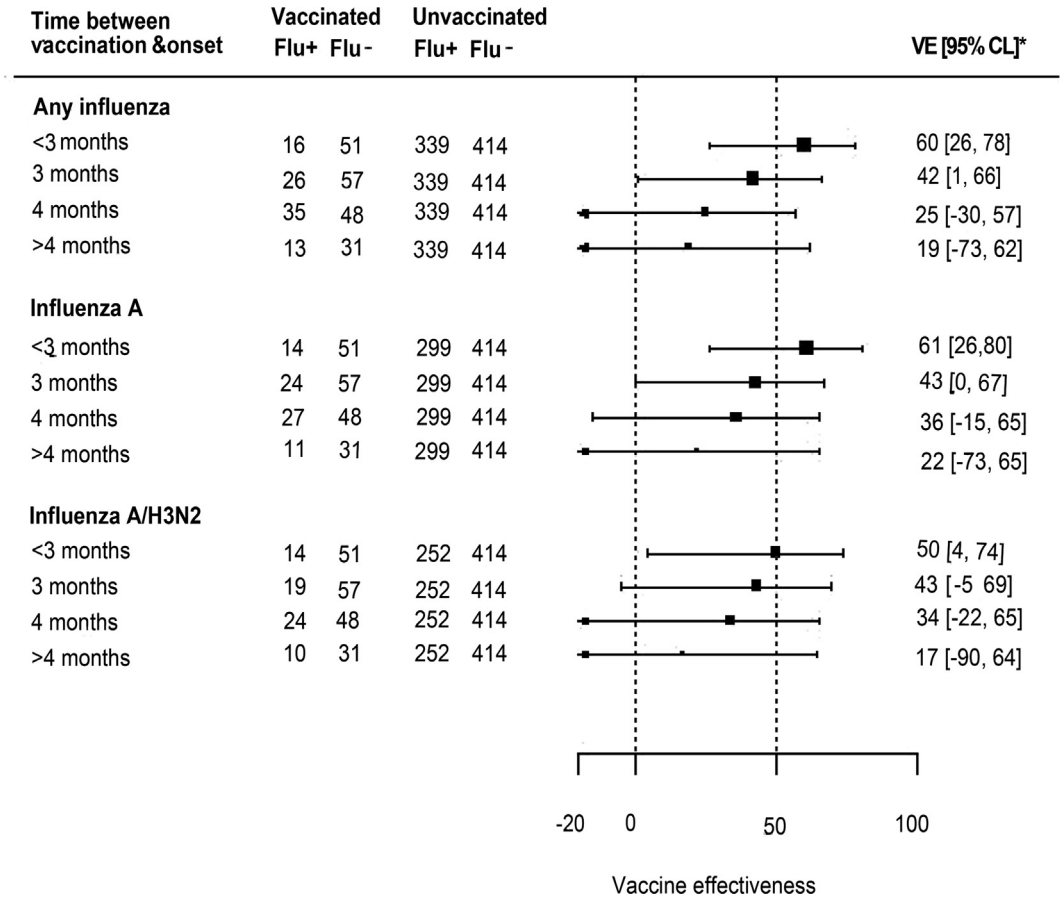

Fig. 4. Estimates of vaccine effectiveness (VE)* of 2016 southern hemisphere influenza vaccine, stratified by time between vaccination and symptom onset – Australia, 2016.
*Vaccine effectiveness was adjusted by cubic spline for age, a quadratic spline for week of collection, and sentinel surveillance system.

to perform sub-optimally [13,16,23,24]. Therefore, estimation across a season may in fact be influenced by these other factors [25]. A recent modelling study by Lewnard et al. [25] suggests that the test-negative design may produce biased estimates of "waning" VE. As a result, the source of declining VE within a season remains uncertain. Further work is needed to understand these potential biases and the valid use of statistics for estimating VE when the source population is not stable.

In future, if a true "waning" effect is confirmed, these findings would have implications for the optimal timing of influenza vaccination programs. Immunisation as near to the influenza season as possible, rather than months prior to the season, may offer the community the best level of protection. In Australia, the Australian Technical Advisory Group on Immunisation currently recommends that optimal protection is offered within the first 3–4 months following influenza vaccination [26]. Our results may suggest that optimal protection is restricted to a shorter time period (<3 months) and that clinical protection may not persist as long as four months following immunization. However, if a true "leaky" effect is confirmed through further study, changing the timing of vaccination would not impact the vaccine's ability to prevent infection and reduce the burden of influenza. Further investigation into the causes of intra-season declines in vaccine effectiveness is needed.

There were several limitations to this analysis. Although these three systems are collaborative and work to harmonize data collection methods, there is some useful information not consistently collected by all these systems, including Indigenous status, vaccine brand, vaccination history, and previous influenza infection. Without such information, consideration for prior infection or vaccination receipt could not be considered and we could not estimate effectiveness by Indigenous status. While all three systems use the same ILI case definition, the swabbing scheme differs in terms of the proportion swabbed, which has resulted in uneven representativeness across jurisdictions. Therefore, while these results represent an average across Australia, their applicability to each jurisdiction may vary.

5. Conclusions

The study provides national estimates of the effectiveness of the 2016 southern hemisphere influenza in a primary care setting based on a test-negative design. Overall, the vaccine was moderately effective against influenza A viruses, and vaccination within two months of symptom onset offered optimal protection against medically-attended laboratory-confirmed influenza. Our findings support continued provision of influenza vaccines to prevent influenza infection.

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Disclosure of conflicts of interest

The authors have no potential conflicts of interest to disclose.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2019.02.027.

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