Effectiveness of seasonal influenza vaccine in preventing influenza primary care visits and hospitalisation in Auckland, New Zealand in 2015: interim estimates

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Preliminary results for influenza vaccine effectiveness (VE) against acute respiratory illness with circulating laboratory-confirmed influenza viruses in New Zealand from 27 April to 26 September 2015, using a case test-negative design were 36% (95% confidence interval (CI): 11–54) for general practice encounters and 50% (95% CI: 20–68) for hospitalisations. VE against hospitalised influenza A(H3N2) illnesses was moderate at 53% (95% CI: 6–76) but improved compared with previous seasons.

Introduction

Seasonal influenza vaccines are used widely to reduce the burden of influenza, but effectiveness measures vary by a range of factors including season, age and underlying co-morbidities [1,2]. The Southern Hemisphere Influenza and Vaccine Effectiveness, Research and Surveillance (SHIVERS) study [3], running since 2012, allows estimation of vaccine effectiveness (VE) against patients presenting with influenza illness to general practice (primary care) and against influenza requiring hospitalisation. Reports were published for 2012, 2013 and 2014 [4–6]. Here we report the preliminary VE results for the 2015 influenza season in New Zealand.

Methods

We used the case test-negative design, as previously described [4], to estimate VE of southern hemisphere trivalent inactivated influenza vaccine (IIV3) against laboratory-confirmed influenza in patients presenting during the 2015 winter season. We included patients who had presented to selected general practices with an influenza-like illness (ILI) or who had been hospitalised with a severe acute respiratory infection (SARI).

Both syndromes were defined as onset of an acute illness with a cough and a history of fever or measured temperature ≥ 38 °C; illnesses with onset within the past seven days before presentation were included in this report.
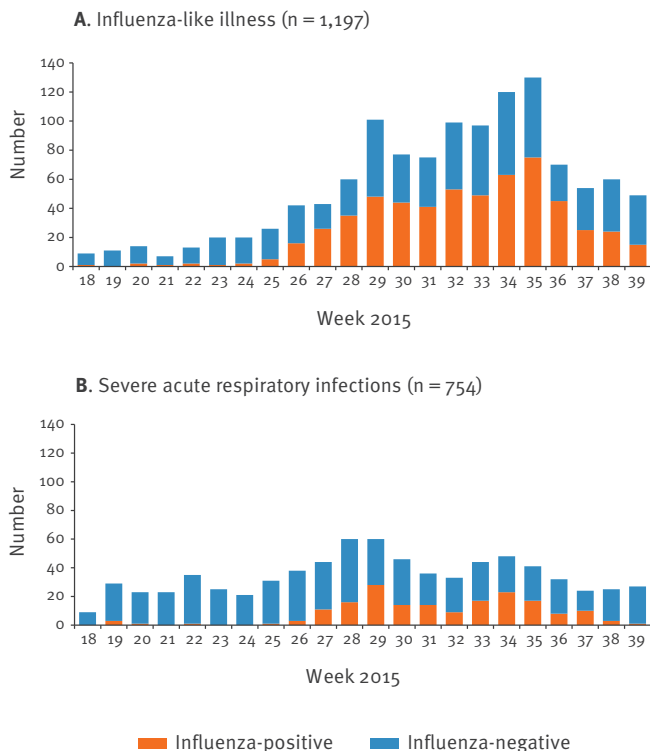
Ethics approval was obtained from the Northern A Health and Disability Ethics Committee (11/11/102/ AM02). The analysis was done on data collected between 27 April and 26 September 2015. The study population for both ILI and SARI came from the Central, South and East Auckland city districts with a population of ca 900,000.

ILI patients were recruited from 16 sentinel general practices that serve ca 100,000 enrolled patients. All identified ILI patients were screened for influenza by a general practitioner or practice nurse, and data were entered through an electronic form into the practice management system. SARI patients were recruited by a research nurse screening all patients admitted overnight with a respiratory illness, and data were collected on a case report form and completed with information from electronic hospital records. All consenting patients had a nasopharyngeal or throat swab collected for influenza virus testing.

Confirmed cases of influenza were defined as those with a positive laboratory result for any influenza virus detected by real-time reverse transcription PCR (rRT-PCR). As per previous years, all swabs were tested using the United States Centers for Disease Control and Prevention (CDC) protocol [7] or the AusDiagnostic PCR protocol [8]. The assays detected influenza virus types A and B, A subtypes and B lineages. A screening

Figure 1

Study participants with influenza-like illness (n = 1,197) and severe acute respiratory infection (n = 754) who were influenza virus-positive or -negative, by week, Auckland, New Zealand, 27 April–26 September 2015

A. Influenza-like illness (n = 1,197)

B. Severe acute respiratory infections (n = 754)

Influenza-positive   Influenza-negative

Figure 2

Flowchart of all patients with influenza-like illness (n = 1,197) and severe acute respiratory infection (n = 754) selected, recruited and tested for influenza vaccine effectiveness analysis, Auckland, New Zealand, 27 April–26 September 2015

ILI: Influenza-like illness; SARI: severe acute respiratory infection.

a A number of SARI patients are admitted to hospital multiple times. The total of 1,243 included multiple admissions, which were removed in this box.

of A(H3N2) viruses for genetic markers associated with six major haemagglutinin (HA) genetic groups (3C.2, 3C.2a, 3C.2b, 3C.3, 3C.3a, and 3C.3b) was done with a pyrosequencing assay. The detailed protocol for the H3 genetic groups pyrosequencing assay is available upon request (fluantiviral@cdc.gov).
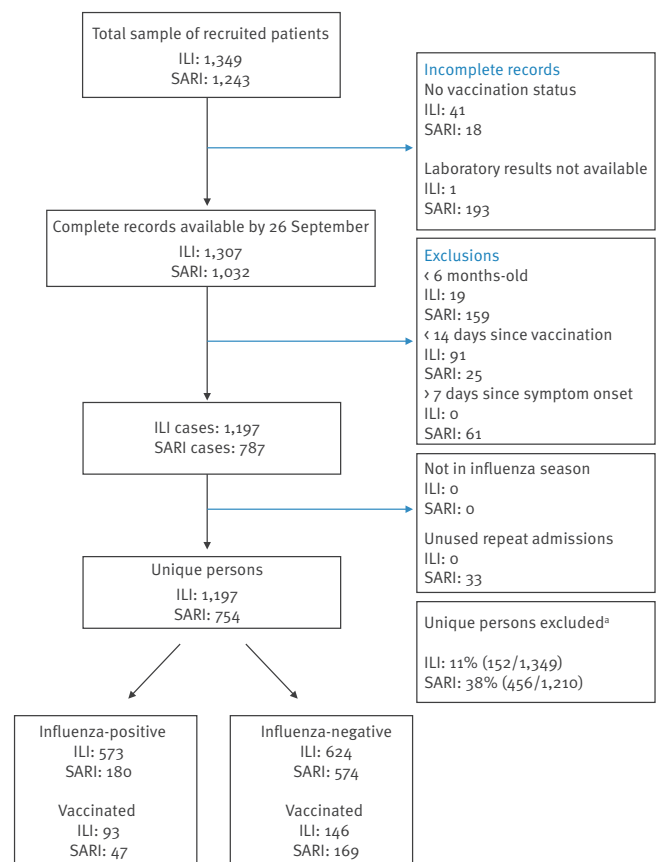
Vaccination status for ILI patients was ascertained from electronic documentation in the general practice records. For SARI patients, vaccination status was based on self-report. A patient was considered fully vaccinated if they had received at least one self-reported or documented dose of the 2015 influenza vaccine.

We excluded infants younger than six months, those vaccinated less than 14 days before illness onset and those with symptom onset more than seven days before presentation. For patients with multiple illness presentations, the first influenza virus-positive episode was used for the analysis or, when there was no influenza virus-positive episode, the first illness episode.

VE was analysed for all influenza viruses, subtypes and clades. Unconditional logistic regression was used to compare the odds of vaccination among influenza virus-positive vs influenza virus-negative participants for both ILI and SARI datasets, with VE estimated as 100% x (1−OR). VE estimates were adjusted for age

group, calendar week, any underlying health condition and days since illness onset at swab collection.

Results

In total, 1,197 ILI and 754 SARI patients were included for analysis (Figure 1 and Figure 2).

Of these, 573 (47.9%) of the ILI and 180 (23.9%) of the SARI were influenza virus-positive (Figure 2). Of all influenza infections, 399 were with influenza A viruses (285 ILI and 114 SARI); 281 were influenza A(H3N2), one was A/California/7/2009(H1N1) and 117 were not subtyped at the time of reporting. All 101 pyrosequenced influenza A(H3N2) samples were identified as clade 3C.2a (86 ILI and 15 SARI), which is like the vaccine component. There were 354 influenza B viruses (288 ILI and 66 SARI); 140 were B/Yamagata (including 95 B/Phuket/3073/2013 lineage), 159 were B/Victoria (including 52 B/Brisbane/60/2008 lineage) and 55 were not genotyped at the time of reporting.

Crude and adjusted estimated influenza vaccine effectiveness by age group and influenza virus type and subtype, Auckland, New Zealand, 27 April–26 September 2015

Influenza type or Age groups	Influenza-positive			Influenza-negative			Unadjusted		Adjusted[a]	
	Number vaccinated	Total	%	Number vaccinated	Total	%	VE %	95% CI	VE %	95% CI
ILI										
Overall	93	573	16	146	624	23	37	15 to 52	36	11 to 54
6 months–17 years	15	260	6	26	258	10	45	−6 to 72	50	1 to 75
18-64 years	59	287	21	89	331	27	30	−2 to 52	27	−8 to 51
≥ 65 years	19	26	73	31	35	89	65	−36 to 91	67	−41 to 92
Influenza A	54	285	19	146	624	23	23	−9 to 46	24	−15 to 50
A(H3N2)	45	216	21	146	624	23	14	−26 to 41	22	−23 to 51
Influenza B	39	288	14	146	624	23	49	25to 65	46	17 to 65
B/Yamagata	18	131	14	146	624	23	48	11 to 69	35	−18 to 64
B/Victoria	19	145	13	146	624	23	56	22 to 75	56	22 to 75
SARI										
Overall	47	180	26	169	574	29	15	−24 to 42	50	20 to 68
6 months–17 years	3	55	5	30	312	10	NA	NA	NA	NA
18-64 years	25	92	27	61	154	40	43	0 to 68	46	1 to 70
≥ 65 years	19	33	58	78	108	72	48	−17 to 77	52	−14 to 79
Influenza A	33	114	29	169	574	29	2	−52 to 37	54	21 to 73
A(H3N2)	19	65	29	169	574	29	1	−74 to 44	53	6 to 76
Influenza B	14	65	22	169	574	29	34	−22 to 65	40	−24 to 71

CI: Confidence interval; ILI: Influenza-like illness; NA: not applicable; SARI: severe acute respiratory infections; VE: vaccine effectiveness.

Overall: includes any influenza and all ages ≥ 6 months; B/Yamagata: B/Yamagata lineage + B/Phuket/3073/2013-like; B/Victoria: B/Victoria lineage + B/Brisbane/60/2008-like.

[a] Adjusted for six age groups (<6, 6–17, 18–45, 46–64, 65–79 and ≥80 years), week in season, any underlying health condition and days since illness onset at swab collection.

Data source: SHIVERS 27 April to 26 September 2015 (week 18–week 39).

Among ILI patients of all ages, 93 of 573 (16%) influenza virus-positive persons and 146 of 624 (23%) influenza virus-negative persons were vaccinated, resulting in a crude VE against all circulating influenza strains of 37% (95% confidence interval (CI): 15–52); VE adjusted for variables listed in the methodology was 36% (95% CI: 11–54). Adjusted VE point estimates by age group were 50%, 27% and 67% for patients aged 6 months to 17 years, 18–64 years and ≥ 65 years, respectively, but with wide confidence intervals (Table).

For all ages, the adjusted VE against ILI with influenza A(H3N2) viruses was 22% (95% CI: −23 to 51), but the VE point estimate, though not statistically significant, was slightly higher for the subset identified as Clade 3C.2a: 27% (95% CI: −46 to 63). For all ages, the adjusted VE against ILI with any influenza B virus was 46% (95% CI: 17–65), but the VE point estimate, though not statistically significant, was slightly higher for the B/Victoria than for B/Yamagata lineage.

Among hospitalised SARI patients of all ages, 47 of 180 (26%) influenza-positive persons and 169 of 574 (29%) influenza-negative persons were vaccinated, resulting in a crude VE of 15% (95% CI: −24 to 42) against circulating influenza viruses. VE adjusted for age, week, underlying conditions and days since onset was higher at 50% (95% CI: 20−68). Adjusted VE point estimates against SARI influenza by age were 49%, 46% and 52% for patients aged 6 months to 17 years, 18−64 years and ≥ 65 years, respectively, but with wide confidence intervals (Table) (p interaction = 0.99). Age-adjusted VE for influenza A(H3N2) virus-associated SARI was 53% (95% CI: 6–76); we did not have a sufficient number of Clade 3C.2a identified viruses to date to do a clade-specific SARI VE estimate. Finally, for SARI associated with influenza B (of either lineage), adjusted VE was 40% (95% CI: −24 to 71).

Background

In New Zealand, the influenza season occurs between March and September, and southern hemisphere IIV3 is offered annually free of charge from early March to all those older than six months with high risk medical conditions, to pregnant women and to those 65 years and older. The influenza strains in the 2015 trivalent vaccine were A/California/7/2009 (H1N1)-like virus, A/Switzerland/9715293/2013 (H3N2)-like virus and B/Phuket/3073/2013-like virus.

Discussion

The 2015 New Zealand influenza season was dominated by influenza A(H3N2) and B viruses (including both B/Victoria and B/Yamagata lineages). Our interim results suggest that IIV3 was ca 37–50% effective at preventing influenza-associated acute respiratory illnesses (with fever and cough) that resulted in general practice visits or hospitalisation. If this trend continues, the overall VE observed in 2015 will be similar to the moderate VE reported during the previous three influenza seasons in New Zealand, even though the virus mix was different. VE point estimates have been consistently around 50% with minimal differences between ambulatory and inpatient medical care [4-6].

In 2014, although influenza A(H1N1)pdm09 was the predominant circulating strain, A(H3N2) viruses were also in circulation. During 2014, we observed no measureable protection of southern hemisphere IIV3 against influenza A(H3N2) virus-associated ILI or SARI [9]. This was consistent with reports from the northern hemisphere during the 2014/15 season, when the A/Texas/50/2012 (H3N2)-like component of the vaccine was not a good match to the circulating strains [10-13]. The influenza A(H3N2) IIV3 component was subsequently changed to A/Switzerland/9715293/2013 (H3N2)-like virus. In this interim 2015 report, all influenza A(H3N2) viruses with pyrosequencing performed to date belonged to the genetic clade 3C.2a, which is antigenically related to the vaccine clade 3C.3a.

We are encouraged by our interim observation of positive VE point estimates for influenza A(H3N2) virus-associated ILI (22%; 95% CI: −23 to 51) and SARI (53%; 95% CI: 6–76), which may indicate that VE improved with the change in vaccine strain.

The precision of our interim estimates was limited by relatively small numbers of observations for some ages and outcomes. Large differences in vaccination uptake and influenza positivity between age groups also resulted in substantial differences between our crude and adjusted VE estimates for SARI. Specifically, when we combined the data across ages, the lower vaccination coverage among children and greater likelihood of older age groups testing positive for influenza virus biased the crude VE estimate towards the null (i.e. Simpson's paradox which occurs because vaccination and the likelihood of testing positive are both correlated with age [14]).

Our interim results are subject to at least four other limitations. Firstly, the hospitalised patient results are based on self-reported vaccination status. However self-reporting has been shown to be generally accurate, especially among hospitalised elderly patients [15], and when comparing self-reporting with documented vaccination status, VE estimates have been shown to be very similar [16]. Secondly, the precision of our age and (sub)type-specific estimates was low given the use of preliminary data with few observations

in many categories. Thirdly, we adjusted for covariates included in prior VE analyses, but a complete examination of potential confounders, including confirmation of chronic medical conditions must await our final report. Finally, we examined VE for a single dose only and because of pending vaccination records and small numbers of children enrolled to date we could not examine VE for the two-dose regimen recommended for children under the age of nine years.

Similar to previous SHIVERS studies, this study suggests that inactivated influenza vaccines provided moderate protection against laboratory-confirmed influenza virus illness in general practice and hospital settings.

Southern Hemisphere Influenza Vaccine Effectiveness, Research and Surveillance (SHIVERS) investigation team (listed in an alphabetical order)

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Conflict of interest

None declared.

Authors' contributions

Ange Bissielo: involved in study design, data collection and analysis, interpretation and manuscript development. Nevil Pierse: involved in study design, methodological design, data analysis, interpretation and manuscript development. Q Sue Huang: principal investigator for the larger SHIVERS study, involved in study design, implementation, and manuscript development. Mark Thompson: involved in study design, interpretation and manuscript development. Heath Kelly: involved in study design, methodological analysis, data analysis and interpretation, manuscript development and editing. Vasiliy Mishin: involved in methodological and data analysis analysis, Nikki Turner: involved in study design, implementation, analysis, manuscript development.

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