

## RAPID COMMUNICATIONS

# Interim estimates of the effectiveness of seasonal trivalent inactivated influenza vaccine in preventing influenza hospitalisations and primary care visits in Auckland, New Zealand, in 2014

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**We present preliminary results of influenza vaccine effectiveness (VE) in New Zealand using a case test-negative design for 28 April to 31 August 2014. VE adjusted for age and time of admission among all ages against severe acute respiratory illness hospital presentation due to laboratory-confirmed influenza was 54% (95% CI: 19 to 74) and specifically against A(H1N1) pdm09 was 65% (95% CI: 33 to 81). For influenza-confirmed primary care visits, VE was 67% (95% CI: 48 to 79) overall and 73% (95% CI: 50 to 85) against A(H1N1) pdm09.**

## Introduction

The SHIVERS (Southern Hemisphere Influenza and Vaccine Effectiveness, Research and Surveillance) study [1] has allowed estimation of vaccine effectiveness (VE) against influenza illness requiring hospitalisation since 2012 and against influenza illness requiring a primary care consultation (sentinel general practices) since 2013. The study captures an ethnically diverse urban population of approximately 838,000 people in Auckland, New Zealand. Patients in the 16 sentinel general practices are part of the population served by the four participating hospitals. VE estimates for 2012 from the hospital arm of the study [2] and from both hospital and community arms in 2013 [3] have been reported previously. Here we report the 2014 influenza season interim estimates of VE against laboratory-confirmed influenza general practice (primary care) visits and hospitalisations in Auckland, New Zealand.

In New Zealand, seasonal trivalent inactivated influenza vaccine is offered annually free of charge to all

adults aged 65 years and over, pregnant women and all individuals over six months of age with chronic medical conditions that are likely to increase the severity of the infection. Influenza vaccines are also available on the private market for all other individuals over six months of age. The influenza season usually occurs between March and September and the vaccine is available from late February.

The influenza strains in the southern hemisphere vaccine in 2014 were A/California/7/2009 (H1N1)-like virus, A/Texas/50/2012 (H3N2)-like virus and B/Massachusetts/2/2012-like virus (B/Yamagata lineage) as recommended by the World Health Organization for trivalent influenza vaccines [4].

## Methods

Using the case test-negative design to estimate VE as previously described [3], we estimated the effectiveness of seasonal trivalent inactivated influenza vaccine against laboratory-confirmed influenza in patients hospitalised with severe acute respiratory infections (SARI) and in patients presenting to a sentinel general practice with an influenza-like illness (ILI) during the 2014 influenza season. Ethics approval was obtained from the Northern A Health and Disability Ethics Committee (NTX/11/11/102 AMo2).

Patients with SARI or ILI were defined as requiring hospitalisation (SARI) or attending a general practice (ILI) with a history of fever or measured temperature  $\geq 38$  °C, cough and onset within the past 7 days.

Hospitalised patients were recruited from individuals aged six months and older who were admitted to one of the four public hospitals covering all the population in the study catchment area in south, central and east Auckland. Community cases were identified from 16 sentinel general practices with 103,884 enrolled patients selected to be broadly representative of the population.

Data collection began on 28 April 2014. Analysis was restricted to the influenza season, which defined as being from the start of the first two consecutive weeks with two or more influenza cases (2 June 2014). The interim data collection was until 31 August 2014, based on the requirements to complete the analysis in time for the World Health Organization strain selection meeting in September.

Hospitalised patients were identified following screening by research nurses of all patients admitted with respiratory illness. Patients who gave verbal consent completed a case report form and provided a nasopharyngeal swab or aspirate for influenza virus testing.

All ILI patients presenting to one of the sentinel general practices were screened by the general practitioner or practice nurse, and data for all consenting patients were entered on an electronic form in the practice management system. A nasopharyngeal or throat swab was collected for influenza virus testing.

A confirmed case of influenza was defined as a patient with SARI or ILI with a positive laboratory result for any influenza virus detected by real-time reverse transcription polymerase chain reaction (rRT-PCR). Nasopharyngeal and throat swabs were tested using the United States Centers for Disease Control and Prevention (CDC) rRT-PCR protocol [5] or the AusDiagnostic PCR protocol [6]. The two assays perform very similarly [3]. rRT-PCR assays detected influenza virus types A and B and subtyped. A convenience sample was characterised antigenically using established methods [7].

For ILI cases, vaccination status was based on the presence or absence of documentation in the general practice electronic records of receiving one or more doses of the 2014 influenza vaccine, depending on age of the participant. Vaccination status in SARI patients before hospitalisation was determined by self-report of receipt of one or more doses of the 2014 seasonal influenza vaccine.

Patients excluded were infants less than 6 months of age who are not recommended to be vaccinated, those vaccinated less than 14 days before admission or presentation and those with symptom onset more than seven days before admission or presentation. For patients with multiple episodes, the first influenza virus-positive episode was used for the analysis or the

first illness episode if there was no influenza virus-positive episode.

For all patients, covariates included age, sex, ethnicity, current smoking status and chronic medical conditions. Further data collected on SARI patients included a patient- or caregiver-reported measure of dependence (classified as the requirement for assistance with normal activities or full dependency on nursing care), long-term use of oxygen, low income (using a small neighbourhood measure reflecting eight dimensions of deprivation [8]), a clinical judgement of obesity and a standard self-rated health item scored dichotomously as fair or poor versus good, very good or excellent overall health [9].

VE is presented for all influenza viruses and A(H1N1)pdm09. For the SARI dataset, less than 1% (3/519) of data were missing for any variable. The ILI dataset had no missing values. Interim VE estimates were calculated from all participants enrolled between 28 April and 31 August 2014. Standard logistic regression was used to compare the odds of vaccination among influenza-positive versus influenza-negative participants for both ILI and SARI, with VE estimated as  $100\% \times (1 - \text{odds ratio})$ . VE was also calculated adjusting for age and the week of the admission or presentation. As a sensitivity analysis for the SARI data, a more comprehensive adjustment was also carried out, similar to the previously reported analysis in 2013 [3]. For this adjustment, we used 2013 data to model the propensity to be vaccinated based on all potential confounders. The VE was then calculated adjusted for each individual's propensity to be vaccinated.

## Results

The number of ILI and SARI patients in this study are shown by influenza virus status in Figure 1.

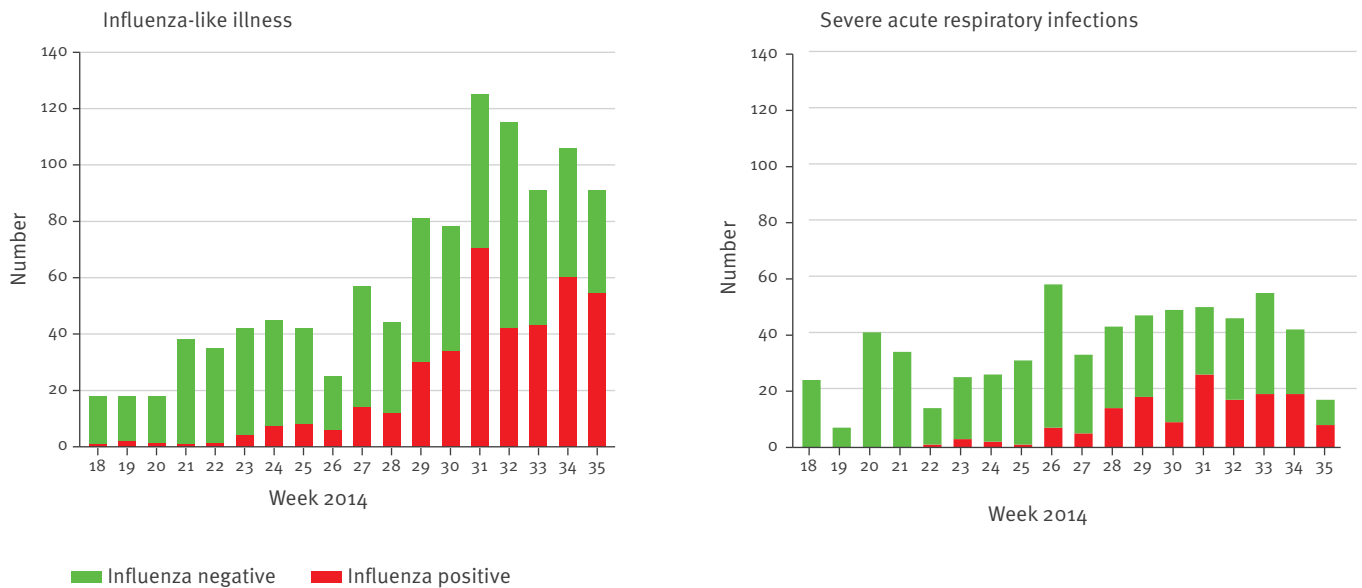
A total of 1,272 SARI patients were eligible: all were recruited and swabbed for influenza. A total of 1,226 ILI patients were recruited, of whom 1,221 were swabbed (99.6%). A total of 519 SARI and 919 ILI patients were included in the analysis, of whom 148 (29%) and 384 (42%) were influenza virus positive, respectively (Figure 2).

Of the 532 influenza cases detected in both SARI and ILI patients, 466 (88%) were type A, with 339 (64%) A(H1N1)pdm09, 32 (6%) A(H3N2) and 95 (18%) not subtyped (Table 1).

There were 66 (12%) type B detections. Among the 66 influenza B viruses, 48 were Yamagata lineage, one was Victoria lineage, and lineage was not determined in 17. Of the 48 Yamagata lineage, 25 were antigenically typed as B/Massachusetts/2/2012 oo-like viruses and 23 were not antigenically typed. The one B/Victoria lineage virus was antigenically typed as B/Brisbane/60/2008-like virus.

**FIGURE 1**

Study participants with influenza-like illness (n=1,069) and severe acute respiratory infections (n=642) who were influenza positive or negative, by week, New Zealand, 28 April–31 August 2014



The influenza season began on 2 June 2014 for both influenza-like illness and severe acute respiratory infections. During the season, 384 of 919 influenza-like illness and 148 of 519 severe acute respiratory infections tested influenza positive.

### Vaccine effectiveness

Of the 148 SARI patients who tested influenza virus positive, 35 (24%) were vaccinated, compared with 113 (30%) of the 371 who tested negative. Of the 384 ILI patients who tested influenza virus positive, 37 (10%) were vaccinated, compared with 116 (22%) of the 535 who tested negative (Figure 2).

The proportion vaccinated did not change throughout the season. For influenza-confirmed SARI, the crude VE for one or more vaccine doses against all circulating influenza virus strains was 34% (95% confidence interval (CI): -3 to 57) (Table 2).

After adjustment for age and week of admission, the estimated VE was 54% (95% CI: 19 to 74). The adjusted VE for the prevailing circulating subtype, influenza A(H1N1)pdm09, was 65% (95% CI: 33 to 81). VE was not calculated for other subtypes, or for individuals 6 months to 17 years of age because of sparse data. Adjusted VE against all influenza hospitalisation in the 18–49-year age group was 46% (95% CI: -42 to 80); in the 50–64 year-olds, 74% (95% CI: 23 to 91) and in the 65 and over age group, 58% (95% CI: -36 to 87). SARI influenza-positive cases were significantly more likely to be young (under five years of age) or old (65 years and older) and smokers than were SARI influenza-negative patients. There was no significant difference by chronic disease, sex, income, pregnancy or self-reported health status. In the SARI sensitivity analysis adjusted for the propensity to be vaccinated, the VE for all ages was 50% (95% CI: 19 to 69).

For influenza-confirmed ILI cases, the crude VE was 61% (95% CI: 43 to 74). After adjustment for age and week of presentation, the estimated VE was 67% (95% CI: 48 to 79). The adjusted VE for the prevailing circulating subtype, influenza A(H1N1)pdm09, was 73% (95% CI: 50 to 85). VE was not calculated for younger people or those aged 65 years and over because of sparse data. For the 18–49-year age group, the adjusted VE was 66% (95% CI: 30 to 84) and in the 50–64 year-olds, it was 57% (95% CI: -1 to 82).

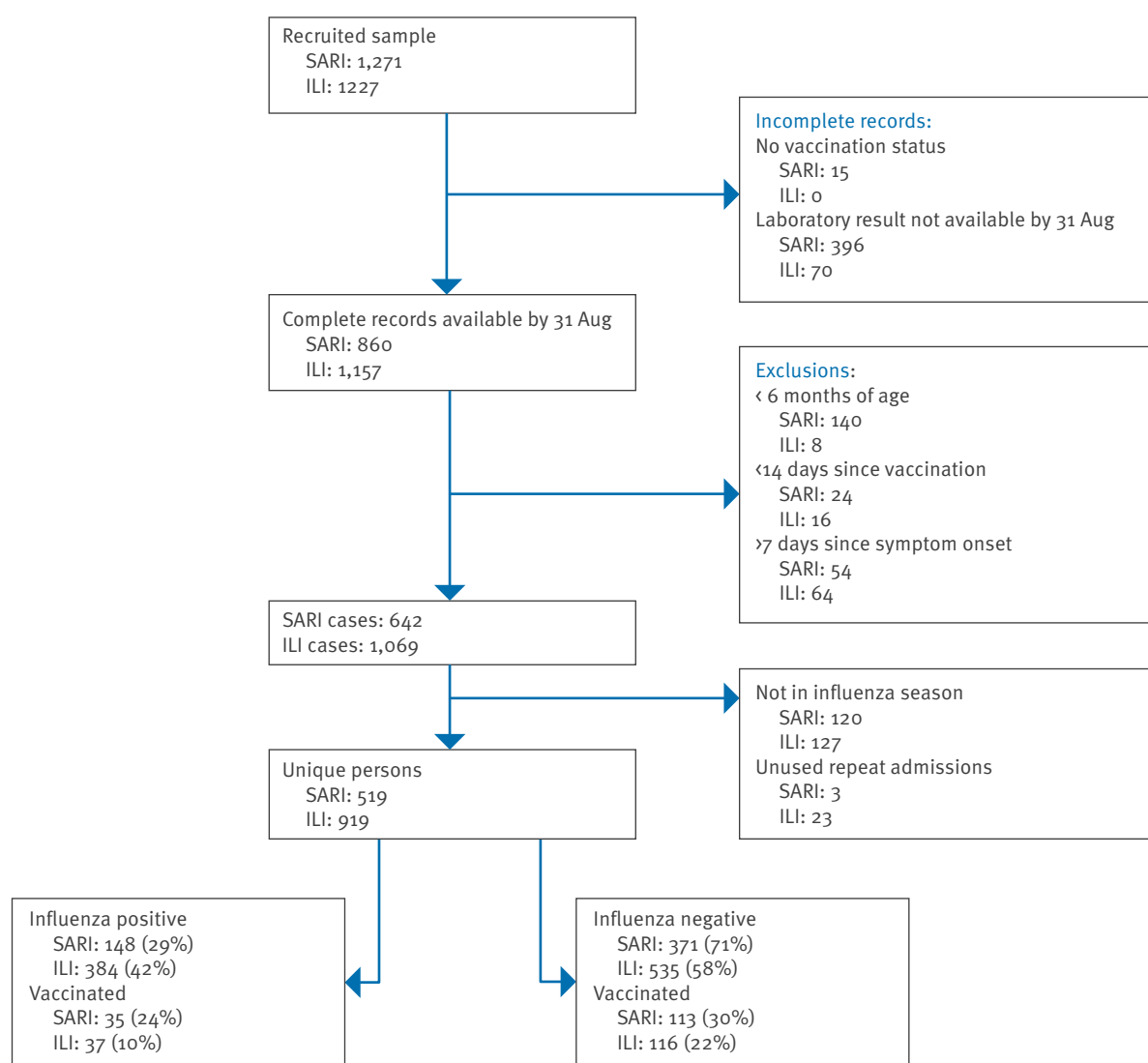
### Discussion

The SHIVERS study allows timely estimation of the protective effect of seasonal influenza vaccine in the southern hemisphere season. These preliminary results suggest that the 2014 vaccine was 54% effective in preventing hospitalisation for influenza and 67% effective against presentations to sentinel general practices. The 2014 season has been dominated to date by the influenza A(H1N1)pdm09 virus. VE was similar across adult age groups, although numbers were too small for accurate estimates in children and elderly people.

The New Zealand seasonal experience is very similar to interim VE estimates reported from Canada and the United States for the 2013/14 influenza season, when the dominant circulating virus was also A(H1N1)pdm09: the VE point estimate was 59% for preventing hospitalisation [10] and 74% for preventing medically attended influenza [11] in Canada, while in the United States, the interim VE was 61% against medically attended

**FIGURE 2**

Flowchart of all selected, recruited and tested patients with influenza-like illness and severe acute respiratory infection for interim influenza vaccine effectiveness analysis, New Zealand, 28 April–31 August 2014



ILI: influenza-like illness; SARI: severe acute respiratory infections.

**TABLE 1**

Vaccinated and unvaccinated influenza cases by virus type and subtype among hospital (n=519) and general practice participants (n=919), New Zealand, 2 June–31 August 2014

Influenza virus type	Hospitalised with severe acute respiratory infection		General practice visits for influenza-like illness	
	Number vaccinated (%)	Number unvaccinated (%)	Number vaccinated (%)	Number unvaccinated (%)
All	35 (100)	113 (100)	37 (100)	347 (100)
Any A <sup>a</sup>	30 (86)	108 (96)	30 (81)	298 (86)
A(H1N1)pdm09	22 (63)	97 (86)	14 (38)	206 (59)
A(H3N2)	7 (20)	7 (6)	4 (11)	14 (4)
All B <sup>a</sup>	5 (14)	5 (4)	7 (19)	49 (14)
B/Victoria <sup>b</sup>	0	0	0	1 (1)
B/Yamagata lineage	1 (3)	2 (2)	5 (14)	40 (12)

<sup>a</sup> Not all cases of influenza A and B were subtyped. The number of subtypes does not add up to the number of all influenza A viruses identified.

<sup>b</sup> B/Victoria = B/Victoria lineage-B/Brisbane/60/2008-like.

**TABLE 2**

Estimated influenza vaccine effectiveness, by participant age group and by influenza virus type and subtype: crude plus age- and time-adjusted models, New Zealand, 2 June–31 August 2014

Influenza type by age group	Influenza positive			Influenza negative			Vaccine effectiveness			
	Number vaccinated	Total	%	Number vaccinated	Total	%	Unadjusted		Adjusted <sup>a</sup>	
							%	95% CI	%	95% CI
<b>SARI</b>										
Overall	35	148	24	118	371	32	34	–3 to 57	54	19 to 74
6 months–17 years	4	42	10	15	193	8	NA	NA	NA	NA
18–49	9	58	16	13	52	25	45	–42 to 79	46	–42 to 80
50–64	10	29	34	29	51	57	60	–3 to 84	74	23 to 91
≥65	12	19	63	61	75	81	61	–18 to 87	58	–36 to 87
A(H1N1)pdm09	22	119	18	118	371	32	51	19 to 71	65	33 to 81
<b>ILI</b>										
Overall	37	384	10	116	535	22	61	43 to 74	67	48 to 79
6 months–17 years	2	143	1	26	226	12	NA	NA	NA	NA
18–49 years	12	168	7	32	195	16	61	21 to 81	66	30 to 84
50–64 years	12	60	20	26	75	35	53	–4 to 79	57	–1 to 82
≥65 years	11	13	85	32	39	82	NA	NA	NA	NA
A(H1N1)pdm09 all	14	220	6	116	535	22	75	56 to 86	73	50 to 85
A(H1N1)pdm09 ≥65years	1	2	50	32	39	82	NA	NA	NA	NA

CI: confidence interval; ILI: influenza-like illness; NA: not applicable, as there were insufficient data to report VE estimates, SARI: severe acute respiratory infections.

<sup>a</sup> Adjusted for six age groups: 6 months–5 years, 6–17, 18–44, 45–64, 65–79 and ≥80 years and week in the season.

influenza [12]. In contrast, the interim VE point estimate from Spain was 44% against all influenza strains, and even lower (33%) for the dominant circulating virus, A(H1N1)pdm09 [13].

Our interim report has several limitations. Similar to other interim VE reports [11], we relied on self-reported vaccination status for hospitalised patients. Not all laboratory results were available as of 31 August 2014 (70 ILI, 356 SARI). In addition, the analysis is adjusted for only two potential confounders (age and week of admission or presentation), although a propensity-adjusted sensitivity analysis for SARI patients produced a similar VE estimate. For this interim estimate, we were unable to estimate VE for young children with two doses of vaccine. We expect to be able to examine this and produce stratified VE estimates by age in our final season report.

This is the third year we have reported the effectiveness of trivalent seasonal influenza vaccine in the New Zealand setting. We have shown the continued predominance of circulating influenza A(H1N1)pdm09 virus and a continued moderate vaccine effectiveness against this strain, similar in magnitude to the North American estimates for the 2013/14 season. The 2014/15 northern hemisphere seasonal vaccine will contain the same components as the 2014 southern hemisphere vaccine [14]. These results may thus add useful information to consider in preparing for the upcoming northern

hemisphere influenza season and in selecting strains for the next southern hemisphere season.

#### **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

Nikki Turner: principal investigator, involved in study design, implementation, analysis, manuscript development. Nevil Piers: 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. Sarah Radke: involved in study design, data collection and analysis and manuscript development. Ange Bissielo: involved in data collection and analysis. 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.

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