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The effectiveness of seasonal trivalent inactivated influenza vaccine in preventing laboratory confirmed influenza hospitalisations in Auckland, New Zealand in 2012

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Abstract

Background—Few studies report the effectiveness of trivalent inactivated influenza vaccine (TIV) in preventing hospitalisation for influenza-confirmed respiratory infections. Using a prospective surveillance platform, this study reports the first such estimate from a well-defined ethnically diverse population in New Zealand (NZ).

Methods—A case test-negative study was used to estimate propensity adjusted vaccine effectiveness. Patients with a severe acute respiratory infection (SARI), defined as a patient of any age requiring hospitalization with a history of a fever or a measured temperature ≥38°C and cough and onset within the past 7 days, admitted to public hospitals in Central, South and East Auckland were eligible for inclusion in the study. Cases were SARI patients who tested positive for influenza, while non-cases (controls) were SARI patients who tested negative. Results were adjusted for the propensity to be vaccinated and the timing of the influenza season

Results—The propensity and season adjusted vaccine effectiveness (VE) was estimated as 37% (95% CI 18;51). The VE point estimate against influenza A (H1N1) was higher than for influenza B or influenza A (H3N2) but confidence intervals were wide and overlapping. Estimated VE was 51% (95% CI 28;67) in patients aged 18-64 years but only 6% (95% CI -51;42) in those aged 65 years and above.

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Conclusion—Prospective surveillance for SARI has been successfully established in NZ . This study for the first year, the 2012 influenza season, has shown low to moderate protection by TIV against hospitalisation for laboratory-confirmed influenza.

Keywords

Influenza Vaccine; Vaccination; Immunization; Vaccine Effectiveness

Introduction

Influenza continues to cause a significant burden of illness in adults and children [1, 2] despite vaccines having been used internationally for more than 60 years and being recommended by the World Health Organization [3]. Estimates of efficacy (from trials) and effectiveness (from observational studies) for seasonal trivalent inactivated vaccine (TIV) have been variable. An umbrella review of meta-analyses of community studies from 2005 to 2011 concluded that protection against laboratory-confirmed influenza (largely mild disease) by TIV ranged from 59-65% with estimates being similar in working age adults and children aged 2 years and above [4]. There have been too few trials in children under 2 years for accurate estimates of efficacy in this age group [5, 6], although influenza vaccines are generally considered to be less effective in young influenza-naïve children and observational studies provide a range of effectiveness estimates from zero to approximately 60% protection [7-9]. While studies specifically of older adults are less common, vaccine effectiveness (VE) has been reported to be as high as 57% in adults over 70 years [6]. However significant variability by season is acknowledged [10] and increasing immunosenescence and the presence of comorbidities are likely to reduce effectiveness [6].

Results are more limited when reviewing protection against influenza-confirmed hospitalisation. No trials address this outcome. Estimates from observational studies include no protection by TIV against laboratory-confirmed influenza [11] to a protective range of 49% to 61% in adults [12-14]. Pooled European data for VE against A(H3N2) during 2011/2012 gave a point estimate for the target groups for vaccination of 29% with wide confidence intervals[15].

The antigenic composition of influenza vaccines is reviewed annually to predict the best match for a constantly evolving virus. The impact of vaccination is expected to be higher in the presence of a good antigenic match, although significant effectiveness has been shown even in seasons when the circulating strain is not a good match[16, 17].

In New Zealand (NZ) seasonal unadjuvanted TIV is offered annually free of charge to all adults aged 65 years and over, pregnant women and all those over 6 months of age with chronic medical conditions that are likely to increase severity of infection. The vaccines are also available from early March on the private market for all others over 6 months of age. The influenza season usually occurs between early May and late September.

Using a case test-negative design we aimed to estimate the effectiveness of seasonal TIVs in preventing hospitalised laboratory-confirmed influenza in persons aged at least 6 months who were admitted with a febrile respiratory illness to public hospitals in Central, South and

East Auckland between April 2012 and February 2013. The study reports results from the first year of a five year SHIVERS (Southern Hemisphere Influenza Vaccine Effectiveness, Research and Surveillance) project.

Methods

Ethics approval for the study was obtained from the Northern A Health and Disability Ethics Committee (NTX/11/11/102 AM02).

Study Design

We used the standard case test-negative design[18] and a similar analytic approach to a previous study of hospitalised patients, with adjustment for the propensity to be vaccinated [13]. From 30 April 2012 to 28th February 2013 we attempted to enrol all individuals aged 6 months and older who were hospitalized with a severe acute respiratory illness (SARI). Based on the World Health Organization definition, this was defined as a patient requiring hospitalization with a patient-reported history of a fever or a measured temperature ≥38°C, cough and onset within the past 7 days [19].

A confirmed case of hospitalised influenza was defined as a SARI patient with a positive laboratory result for any influenza virus detected by real time reverse transcription polymerase chain reaction (RT-PCR) or viral isolation, while non-cases (controls) were those who tested negative to all influenza viruses.

Eligible patients were those admitted to the public hospitals Middlemore, Kidz First Children's, Auckland City and Starship Children's which together serve a population catchment of approximately 838,000 people in Central, South and East Auckland. Recruitment was undertaken by trained research nurses. The nurses recruited patients during the day and screened all overnight admissions of febrile patients with respiratory symptoms daily from Monday to Saturday. Sunday admissions were captured on Mondays if the patients were still hospitalized.

All identified SARI cases who gave verbal consent completed a case report form, administered by a research nurse, and provided a nasopharyngeal swab or aspirate for influenza testing by RT-PCR and/or viral isolation.

Excluded from the analysis were patients transferred from another hospital, children under 6 months of age, patients who had not provided consent, patients with incomplete data for vaccination status or age, or patients who were swabbed more than 7 days after the onset of symptoms. At the end of the season, people with multiple SARI hospitalisations were excluded if their vaccination status differed between hospitalisations, otherwise the first influenza positive admission was used. Only the first hospital admission was used if a person had multiple admissions but no influenza positive admission.

Participant information

Demographic data on all cases and non-cases included age; sex; ethnicity (Māori , Pacific Islander, Asian, NZ, European or other); and income, with low income defined as a

household that received either a government benefit or held a community services card. The age data were cross validated with hospital held electronic data. Clinical information was obtained from both the case report form and electronic data extraction from hospital databases. This included clinical symptoms and signs; influenza vaccination status recorded on the case report form; smoking status; body mass index based on either measured weight and height or a visual estimation by the research nurses using the categories obese, overweight, normal weight, underweight or unsure; a patient or caregiver reported measure of dependence, assessing requirement for assistance with normal activity or full dependency on nursing care; a simple frailty measure based on use of long term oxygen; a history of chronic medical conditions; and a self-defined health status score using the general health question from the SF36 [20] and combining fair or poor versus all others. The SF-36 is a generic measure using a multi-purpose, short-form health survey that measures a functional health and well-being score.

The presence of any chronic condition was defined as at least one of the following: asthma, with the need for preventative therapy; diabetes; chronic pulmonary disease (COPD); other chronic lung disease; cardiac disease; cerebrovascular disease; moderate to severe cognitive impairment; other chronic neurological disease; psychiatric disorder (psychotic or major affective disorder); current alcohol or drug dependence; active cancer (excluding non-invasive skin cancer); immune deficiency condition (including asplenia, HIV/AIDS); immune suppressive treatment; chronic renal disease; or chronic liver disease (including cirrhosis, chronic hepatitis, transplant). The covariate for co-morbidity was a binary variable coded as yes/no.

Vaccination status was recorded as fully vaccinated if the patient or caregiver reported influenza vaccination given during the current season at least 14 days prior to the onset of symptoms for which they were hospitalised. All children less than 9 years of age were recorded as fully vaccinated if they had received a vaccination in the season at least 14 days prior to onset of symptoms, and had ever received an earlier vaccine at least one month prior to the current vaccine. Children under 9 years of age who had received only one dose of vaccine in the season and no previous vaccine were considered partially vaccinated but were analysed as nonvaccinated.

Two commercial vaccine products were available on the NZ market in 2012: Fluarix® (GlaxoSmithKline) approved for used in people 6 months and over, and Fluvax® (bioCSL) approved for use in people aged 5 years and over, but recommended to be used with caution in children aged 5-8 years. Both vaccines contained A/California/7/2009 (H1N1)-like strain, A/Perth/16/2009 (H3N2)-like strain and B/Brisbane/60/2008-like strain.

Laboratory Methods

Nasopharyngeal swabs were collected with a COPAN flocked swab and transported in viral transport medium (VTM) at 4°C. Nasopharyngeal aspirates and other respiratory samples were collected according to hospital standard operational procedures. Respiratory samples were tested using the United States Center for Disease Control and Prevention real time RT-PCR protocol [21] at Auckland District Health Board Laboratory and the AusDiagnostic

PCR protocol at the South Auckland District Health Board laboratory [22]. All influenza positive PCR cases were forwarded to the National Influenza Centre on a weekly basis for antigenic typing. RT-PCR assays detected influenza virus types A and B and subtyping was performed for A subtypes. A small proportion of cases (8.5%) were subjected to viral isolation by inoculation into Madin-Darby canine kidney (MDCK) cells.

Statistical analysis

Characteristics of patients who were influenza positive and negative were compared using univariate χ^2-tests. Patients at higher risk of an adverse outcome from influenza infection, and for whom the vaccine is provided at no charge, may be more likely to be vaccinated. We allowed for this by using a multivariate logistic model to calculate the propensity to get vaccinated, given the range of patient characteristics listed in Table 1. The results from the propensity model are presented as odds ratios (OR) and were used to adjust the VE estimate.

In the primary analysis VE was defined as 1-OR with the OR derived from logistic regression models where influenza was the outcome variable. We calculated the crude VE adjusting only for the timing of the admission relative to the influenza season and the adjusted VE which included both the timing of the admission and a term derived from a cubic spline of the fitted values of the propensity model. A cubic spline was used as propensity was not linear with respect to influenza status. This approach has previously been used by Talbot et al. [13].

The season was defined to include continuous weeks with at least two laboratory-confirmed influenza cases. It began on week 5 of the study (May 29, 2012) and ended on week 24 (October 22, 2012). We present a summary VE estimate against all influenza infections and separate stratified estimates for three age ranges (0 to 17, 18 to 64 and 65 and over) and influenza A(H1N1)pdm09, A(H3N2) and influenza B. VE estimates for types and subtypes used cases positive for the specific type or subtype compared with influenza negative non-cases.

For all patient characteristics, other than age and vaccination status, missing values were imputed as the modal baseline case of non-Māori, non-Pacific ethnicity, female, not low income, not pregnant, non-smoker, without chronic disease, not obese, with self-rated health average or better, not on long term oxygen use and living without assistance. Sensitivity analyses were performed excluding individuals with missing data and samples tested only by viral isolation. We also compared results from the propensity adjusted model with an epidemiological model where the same covariates were forced into a logistic regression model with influenza as the outcome and vaccination as the primary exposure variable. We further constructed a statistical model where only the variables in the epidemiological model that were significant at the level of $p<0.05$ in univariate analysis were included in the logistic regression model. Assuming VE was 50% and vaccine coverage in the controls was 20%, we estimated 207 cases gave 80% power to detect a significant protection due to vaccine.

Results

Case selection and exclusion/inclusion criteria are shown in Figure 1. Of the 6373 admissions screened, 2682 (42%) met the definition of SARI. After exclusions for lack of consent (n=224), no record of vaccination history (n=300), no recorded date of birth (n=1), aged less then 6 months (n=226) or no laboratory results available (n=88), a total of 1843 admissions remained, of whom 382 (21%) were influenza positive (Figure 2) . Excluding multiple admissions, 1773 SARI patients were included in this analysis. Of the 379 (21%) who were inflenza positive, 123 (32%) were vaccinated and, of the 1394 who tested negative for influenza, 534 (38%) were vaccinated (Figure 1). There were 88 samples where no laboratory results were available because we were unable to obtain or analyse the sample. Most (n=49) were unvaccinated children under the age of 5 years and, of the remaining 39 more than five years of age, 14 (36%) were vaccinated.

The 379 influenza positive case and 1394 influenza negative non-cases were compared across a range of patient characteristics. Patients who were. Influenza positive were more likely to be unvaccinated, younger, of Pacific ethnicity, not on long term oxygen, to require assistance with daily living and to be admitted during the influenza season. There were no statistically significant differences by gender, income, pregnancy, smoking, presence of a chronic disease, obesity or self-rated health (Table 1). The adjusted odds ratios for the association of various patient characteristics with likelihood of vaccination showed that older age groups, those with chronic diseases or on long term oxygen were more likely, and smokers were less likely, to be vaccinated (Table 2). In contrast, there was no statistically significant difference in the likelihood of vaccination by ethnicity, gender, income, pregnancy, obesity, self-rated health, assisted living or the timing of the admission relative to the influenza season (Table 2).

Vaccine Effectiveness

The VE against any influenza infection and adjusted only for season was 25% (95% confidence interval 4;41). After adjusting for the propensity to be vaccinated the estimated VE was 37% (18;51). In the sensitivity analysis, the VE against any influenza infection estimated from the epidemiological model was 40% (19;55) and from the statistical model was 41% (22;56). There was no significant change to these estimates when ommitting patients with missing values or for whom influenza was tested only by viral isolation (data not shown). VE for patients aged 18-64 years was 51% (28;67) with a point estimate of 69% in patients aged 0-17 years but only 6% in patients aged at least 65 years . The VE estimate against influenza A (H1N1) was higher than the point estimates for influenza B and influenza A (H3N2) but confidence intervals were wide and overlapping (Table 3). With 27 cases and 278 non-cases in patients aged at least 65 years, the propensity adjusted VE against influenza A(H3N2) was 35% (−49; 72).

The vaccine formulations used in New Zealand in 2012 included a strain that matched the circulating 2009 A(H1N1)pdm09 strain which represented 10% (247/2425) of all viruses detected in NZ in 2012. VE against this strain was 52% (23;71). Influenza B virus represented 13% (306/2425) of all viruses detected with both B lineages co-circulating. The

2012 vaccine strain was a B/Victoria lineage. More B/Yamagata lineage viruses (84%, 99/118) than B/Victoria lineage viruses (16%, 19/118) were detected. VE against influenza B was 45% (9;66). There were too few data to calculate B lineage specific VE estimates Influenza A(H3N2) viruses represented 65% of all viruses detected. Most A(H3N2) viruses had drifted away from the A/Perth/16/2009 vaccine strain (data not shown). VE against A(H3N2) was 25% (−8;48).

Discussion

This study has four important findings. Firstly, we found that 21% of SARI admissions in Auckland during the study period were due to influenza. Secondly, VE against hospitalisation for the 2012 season was relatively low with a point estimate of 37%. Thirdly, while underpowered to show age effect, vaccination appeared less effective in patients aged at least 65 years although this may be an effect of response to the circulating influenza type rather than an age effect, and lastly VE varied by influenza type and subtype. Specifically, older people did not appear to be significantly protected against hospitalisation for infection with influenza A(H3N2). Studies of hospitalised patients using a laboratory-confirmed endpoint have reported a wide range of results for VE. Our point estimate of 37% is within this range. Using a test negative design over two seasons, Puig-Barbera and colleagues were unable to show a significant protective effect from seasonal vaccine for adults, although adjusted VE for monovalent A(H1N1) pandemic provided high protection [11]. Talbot et al studied adults 50 years and older hospitalised in the US and found a VE estimate of 61% (18;82) [13]. A test negative case-control in the 2010/2011 season in Spain showed VE of 58% (20;89) against hospitalised laboratory-confirmed influenza in adults aged between 52 and 84 years, although VE rose to 68% (13;77) for those who had received both the seasonal and pandemic A(H1N1) monovalent vaccine[23]. A more recent Spanish study of hospitalised patients using three different control groups showed similar vaccine effectiveness of 60% for all ages but higher effectiveness (89%) against severe cases[24]. In the southern hemisphere, Cheng et al reported VE against influenza hospitalisation of 49% (13;70) for adults aged 18 years and older in the 2010 Australian influenza season[14].

The lower VE results from our study are not dissimilar to a population-based study by Baxter et al to determine the association between hospitalization and prior vaccination over an 11 year period. The study examined VE within the season, compared to outside the season, using a “difference-in-differences” approach [25]. Estimated reduction in influenza-attributable hospitalisations from influenza vaccination were 28% (9;30) for adults 50-64 years and 48% (12;26%) for those 65 years and over.

Similar to our study findings low to moderate effectiveness and variations by age and type/subtype have been identified as challenges with seasonal influenza vaccines [26]. In the 2012 Danish influenza season no significant protection against influenza-confirmed hospitalisation for patients aged 65 years and older was seen for A(H3N2), whereas VE in the same age group for influenza B was 69% (26;87)[27].

Strengths and Limitations

The strengths of this study include the establishment of an effective influenza surveillance system in New Zealand, using RT-PCR-confirmed hospitalised influenza as the outcome measure. Estimating VE against the serious outcome of hospitalisation may have more relevance for public health policy than estimation of protection against milder disease that is managed in the community. The recruitment process selected potential SARI cases from a full range of respiratory illness categories including both acute and chronic illnesses. However we would not have captured influenza related hospitalisations that presented as a non-respiratory illness such as patients with exacerbation of cardiovascular disease.

We collected a large range of variables that could be included in the statistical model. However adjustment for the differences between vaccinated and unvaccinated study participants may have differed in ways that had not been considered or were difficult to measure. Furthermore, little is known about the 220 individuals with SARI who did not give informed consent. This was mostly due to language barriers. It is possible that people for whom English is not a first language may have greater challenges in accessing health care services and therefore more likely to be under-vaccinated. A further study weakness was the record of vaccination status, based only on patient recall. However self-report has been shown to be generally accurate in hospitalised elderly[28]. Future studies will use verified vaccinations based on provider records. The influenza laboratory test has some limitations. The clinical sensitivity for all targets (influenza A, influenza B, A(H1N1)pdm09 and A(H3N2) is greater than 93% and the clinical specificity for all targets is greater than 90% [29]. Any resulting misclassification can be expected to have biased our estimates towards the null [30] and this could be more likely in hospitalised patients where an upper respiratory tract specimen is used to diagnose lower respiratory tract disease.

In summary, we have established prospective surveillance for SARI in New Zealand and have shown low to moderate protection from TIV in influenza-positive SARI patients in the 2012 influenza season. In future years, surveillance will include patients seen in sentinel general practices as well as those admitted to hospital and we will be able to provide a more complete picture of the burden of influenza in a well-defined ethnically diverse community. We will also be able to compare the effectiveness of influenza vaccines in preventing attendance at a general practitioner for laboratory-confirmed influenza with effectiveness against the, possibly more policy relevant, outcome of admission to hospital.

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Highlights

- This study adds to the limited research on VE to influenza from the southern hemisphere
- TIV vaccines show low to moderate protection against hospitalisation for laboratory confirmed influenza in 2012.
- VE varied by influenza type and subtype
- Vaccination appeared to be less effective in patients aged 65 years and older
- Older people did not appear to be significantly protected against infection with influenza A(H3N2)

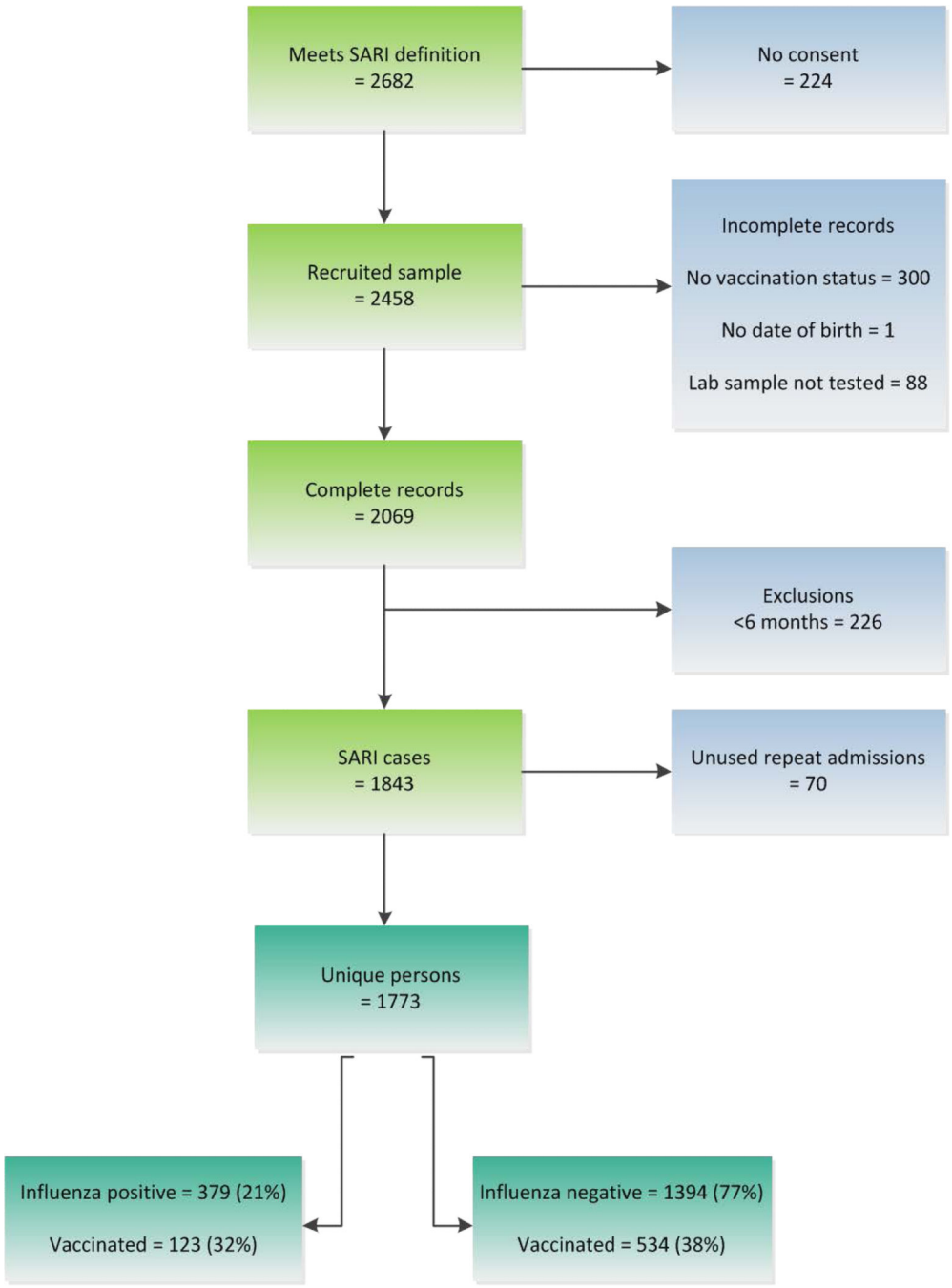
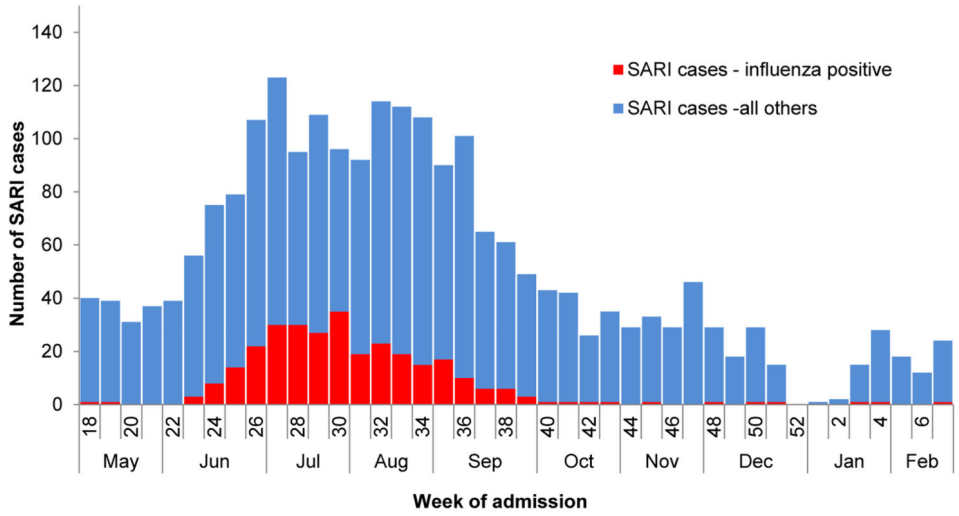


Figure 1.
Flowchart of all selected, recruited, eligible, complete and unique admissions for VE analysis



NB Pre-season is before week 5; 29 May2012
Post season is after week 24; 22 October2012

Figure 2.

Weekly SARI cases including influenza PCR positive cases during 30 April 2012 to 28 February 2013

Table 1

Patient characteristics and their association with influenza status

	Influenza Positive n=379	Influenza Negative n= 1394	P Value
Vaccinated	123(32.5%)	534(38.3%)	0.04
Median Age	44 years	41 years	0.10
Age Group 0 to 5	67(17.7%)	376(27.0%)	<0.01
6 to 17	23(6.1%)	61(4.4%)	
18 to 45	94(24.8%)	264(18.9%)	
46 to 64	86(22.7%)	269(19.3%)	
65 to 79	66(17.5%)	278(19.9%)	
80+	43(11.4%)	146(10.5%)	
Male	177(46.7%)	693(49.7%)	0.33
Maori	53(14.0%)	253(16.9%)	<0.01
Pacific	138(36.4%)	377(27.0%)	
Other	188(49.6%)	764(56.1%)	
Low Income	219(57.8%)	830(59.5%)	0.58
Pregnant	8(2.1%)	13(0.9%)	0.11
Smoker	50(13.2%)	172(12.3%)	0.72
Chronic Disease	242(63.8%)	851(61.0%)	0.35
Obese	52(13.7%)	194(13.9%)	0.99
SF36- (poor or fair)	70(18.5%)	172(19.1%)	0.82
Long Term Oxygen use	3(0.8%)	37(2.6%)	0.05
Dependence	***271(71.5%)***	***792(56.8%)***	***<0.01***
Pre Season	***3(0.8%)***	***116(8.3%)***	***<0.01***
Peak Season	353(93.1%)	969(69.5%)	
Late Season	***23(6.1%)***	***309(22.2%)***	

Table 2

Patient characteristics and their association with influenza vaccination status*

	OR	95% lower confidence interval	95% upper confidence interval	P
Age 0 to 5	*0.16*	*0.09*	*0.28*	*<0.01*
Age 6 to 17	*0.36*	*0.19*	*0.69*	*<0.01*
Age 18 to 45	*0.5*	*0.35*	*0.7*	*<0.01*
Age 65 to 79	*2.26*	*1.64*	*3.13*	*<0.01*
Age 80	*2.37*	*1.58*	*3.54*	*<0.01*
Maori	0.87	0.61	1.23	0.43
Pacific	1.03	0.77	1.37	0.83
Male	0.98	0.77	1.23	0.85
Low income	1.2	0.93	1.54	0.16
Pregnant	0.77	0.25	2.43	0.66
Smoker	*0.7*	*0.5*	*0.99*	*0.04*
Chronic	*2.59*	*1.91*	*3.5*	*<0.01*
Obese	0.88	0.64	1.22	0.45
Sf36-	1.05	0.79	1.4	0.72
Long term oxygen use	*5.78*	*2.29*	*14.59*	*<0.01*
Dependence	1.33	0.89	1.99	0.16
Early Season	0.83	0.48	1.45	0.51
Late Season	0.89	0.65	1.2	0.44

*Adjusted odds ratio compared to referent group: female, aged 46 to 64 years, non-Māori non-Pacific ethnicity, not low income, not pregnant, non-smoker, without chronic disease, not obese, with self-rated health average or better, not on long term oxygen use, living without assistance and admitted to hospital for SARI during the influenza season.

Table 3

Estimated vaccine effectiveness, overall by age range and by sub-strain, for the crude and propensity adjusted models.

		Number Vaccinated		Number Unvaccinated		Crude Model			Propensity Adjusted Model		
		Flu+*	Flu−*	Flu+	Flu−	VE	LCL*	UCL*	VE	LCL	UCL
	Overall	123	534	256	860	25%	4%	41%	37%	18%	51%
Stratified by strain type	**H1N1**	26	534	77	860	48%	17%	67%	52%	23%	71%
	H3N2	56	534	95	860	8%	−31%	35%	25%	−8%	48%
	A	98	534	198	860	23%	−1%	41%	35%	14%	51%
	B	25	534	59	860	33%	−8%	59%	45%	9%	66%
Stratified by age group (years)	0 to 17	4	40	86	397	48%	−52%	82%	69%	2%	90%
	18 to 64	44	203	136	330	51%	27%	67%	51%	28%	67%
	65 +	75	291	34	133	11%	−41%	45%	6%	−51%	42%

*Flu+ = influenza detected Flu− = influenza not detected

*LCL = lower confidence limits UCL = upper confidence limits