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Influenza vaccine effectiveness in preventing hospitalization among Beijing residents in China, 2013-15

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Highlights

1. Influenza vaccination coverage was 11.9% and 12.6% in the case and control groups respectively.
2. The overall estimates of vaccine effectiveness were 46.9% (95% CI: -20.4%, 76.6%) for the 2013-14 season and 5.0% (95% CI: -53.0%, 41.0%) for the 2014-15 season.
3. This study demonstrated the feasibility of routine assessment of influenza vaccine effectiveness using the test-negative design in Beijing.

ABSTRACT

Background: Estimates of influenza vaccination effectiveness (VE) are valuable for populations where the vaccine has been promoted in order to support vaccination policy and to permit evaluation of vaccination strategies. Such studies would be important for China due to limited data available during seasons when the vaccine strains matched or mismatched the circulating viruses.

Methods: We conducted a test-negative study in hospitals in Beijing. Patients admitted to five hospitals in the city were enrolled during the winter influenza seasons of 2013-14 and 2014-15. Influenza virus infections were determined by PCR, and influenza vaccination records were extracted from a centralized electronic immunization registry. Influenza VE was estimated by logistic regression adjusting for age group, sex and chronic conditions, and matched by calendar week.

Results: A total of 2368 inpatients were recruited during the study period with a vaccination coverage in the control group of 12.8%. The overall estimate of influenza VE was 46.9% (95% CI: -20.4%, 76.6%) for the 2013-14 season and 5.0% (95% CI: -53.0%, 41.0%) for the 2014-15 season. Estimates of VE were relatively higher in children aged 6-17 years than older persons across two influenza seasons while estimates of VE for both adults and elderly were relatively low.

Conclusions: Our findings were consistent with expected influenza vaccination effectiveness in seasons when the vaccine matched or mismatched circulating viruses. Strategies to increase influenza vaccine coverage could provide a public health benefit.

INTRODUCTION

Influenza vaccine effectiveness (VE) can vary from year to year, from location to location, and in persons of different ages, for a variety of reasons [1-5]. In populations where influenza vaccination is promoted, it can be valuable to have local estimates of VE to support policy and to permit evaluation of specific vaccination strategies [3, 6]. In recent years, a variant of the case-control study known as the test-negative design has become popular for routine estimation of influenza VE [7, 8].

China is an upper middle income country in the northern hemisphere with a population of 1.3 billion. The capital city Beijing in the northeast of China has a typical temperate climate with a population of 20 million. Sentinel surveillance data indicates that influenza viruses circulate every year in Beijing from late autumn through to spring of the next year. The municipal government of Beijing provided free influenza vaccination for adult residents ≥60y and subsidized influenza vaccination for elementary and high school students 6-17 years of age from 2007 to 2008, and provided free influenza vaccination to these two groups since 2009 [9]. However, few studies have evaluated influenza VE in Beijing or elsewhere in China [10]. In 2013-14, the influenza vaccine strains matched the circulating strains in China while most circulating A(H3N2) viruses in the 2014-15 season were low reactors to the A/Texas/50/2012 (H3N2)-like virus used for the influenza vaccine in that season. As part of a global surveillance network with a unified core protocol [11, 12], we implemented a test-negative study based in hospitals to estimate VE in Beijing in the winter influenza seasons of 2013-14 and 2014-15.

METHODS

Study setting and subjects

Our study was carried out in 2 general hospitals in Beijing in the 2013-14 influenza season, namely Changping District Hospital and The First Hospital of Huairou. The study was expanded to 5 hospitals in the 2014-15 season by including 3 additional general hospitals, namely Daxing District Hospital, Miyun County Hospital and Liangxiang Hospital. Patients admitted to the department of respiratory medicine, pediatrics and geriatrics and the intensive care unit (ICU) in each hospital were screened for eligibility for the study.

We aimed to include inpatients whose disease episode was potentially associated with infection of influenza virus in the study. Given the potential variation in clinical presentation, we adopted different inclusion criteria for patients younger than 5 years and those at age of 5 years and older. All patients 0-4y who were diagnosed any of the diseases listed in Appendix Table 1 met the diagnostic criterion for inclusion. For patients ≥5y, the patient who was diagnosed as one of the diseases listed in Appendix Table 2 and at the same time met the influenza like-illness (ILI) definition was eligible for further screening. We adopted the ILI definition proposed by the European Centre for Diseases Control that an ILI patient should present any of four systemic symptoms (fever or feverishness, headache, myalgia or malaise) plus any of the three respiratory symptoms (cough, sore throat or shortness of breath). In our study, patients' onset of ILI symptoms had to be within the 7 days prior to admission, and all recruited patients were admitted within the previous 24-48 hours. Only routine residents (living in the city for ≥6 months)

and non-institutionalized patients were eligible for this study. Patients who had been hospitalized in the previous 30 days were excluded.

Two pharyngeal swabs were collected from each eligible patient and tested for influenza A (H1N1pdm09 and H3N2) and influenza B (B/Yamagata, B/Victoria) by RT-PCR. Demographic and related clinical information was obtained through face-to-face interview or review of clinical records, including age, sex, smoking habit of the patient (for adults) or parents (for children), pregnancy status, chronic conditions, influenza vaccination status in the current and the previous seasons.

Ethical approval was obtained from the ethics committees in the participating hospitals. Participation was voluntary and informed verbal consent was obtained before enrollment.

Definition of vaccination status

Influenza vaccination status of recruited patients was determined by vaccination record registered in the Beijing Expanded Program on Immunization Information Management System. Vaccination was defined as patients who had received trivalent inactivated influenza vaccine (TIV) in the corresponding influenza season more than 2 weeks before hospitalization. Patients who had a contra-indication to influenza vaccination or received TIV less than 2 weeks before enrolment were excluded from the study. Vaccination schedules generally followed the recommendations from the World Health Organization [13]. Recruited patients who received at least one dose of influenza vaccine were identified as vaccinated. The 2013-14 influenza TIV was composed of

A/California/7/2009 (H1N1)pdm09-like virus, A/Victoria/361/2011 (H3N2) and B/Massachusetts/2/2012-like virus. The 2014-15 influenza TIV was composed of A/California/7/2009 (H1N1)pdm09-like virus, A/Texas/50/2012 (H3N2)-like virus and B/Massachusetts/2/2012-like virus.

Laboratory testing

All swab samples were kept at -20°C after collection and shipped to a local influenza reference laboratory within 48 hours. RNA extraction was performed from 140μL sampling solution using QIAamp Viral RNA Mini Kit (Qiagen, Denmark) according to the manufacturer's instruction. The yield RNA was finally eluted using 50μL RNase-free water. For influenza A and B detection, primers were designed basing on the sequence supplied by Chinese National Influenza Center for the matrix protein. The tests were performed by rRT-PCR using AgPath-ID One-Step RT-PCR kit (Applied Biosystems, USA) and 7500 Fast Real-Time PCR System (Applied Biosystems) using 5μL of RNA according to manufacturer's instruction and the WHO's protocol [14]. For influenza A-positive samples, a typing rRT-PCR assay was performed. For influenza B-positive samples, rRT-PCR was performed for the HA gene to distinguish B/Yamagata and B/Victoria lineages.

Statistical analysis

In our primary analysis, we restricted to two influenza seasons throughout the whole study period, which were defined as periods during which cases tested positive for influenza for two or more consecutive weeks. We used conditional logistic regression

models where the outcome was the specimen testing result, either positive or negative to a certain type/subtype of influenza viruses, and the covariate of interest was vaccination status, matching by calendar week of admission to account for variation in vaccination coverage over time. Potential confounders such as age group (6m-5y, 6-17y, 18-59y, ≥60y), sex and chronic conditions were also included in the model. VE was defined as one minus the adjusted odds ratio. VE analysis was performed for influenza overall and by type/subtype, age and season.

RESULTS

Between December 9, 2013 and May 15, 2015, a total of 2368 patients presenting to the selected hospitals were recruited. Patients who were institutionalized (n=7), who were hospitalized within 30 days (n=15), who did not meet the ILI definition (n=45), and whose symptoms started more than 7 days before admission (n=61) were excluded. Among the remaining 2234 patients, children younger than 6 months were not eligible for influenza vaccination and thus excluded (n=33). Patients who had contradictions to vaccination were excluded (n=15), or vaccinated within 14 days of illness onset were excluded (n=7). Therefore 2179 patients meeting the inclusion criteria were enrolled during the study period and provided specimens for laboratory testing. The timeline of patient recruitment was shown in Figure 1. The winter 2013-14 influenza season started late in January 2014, and had influenza A(H1N1) (22.9%), A(H3N2) (22.9%) and B (54.2%) co-circulating throughout the season while the winter 2014-15 influenza season starting early in November 2014 was predominated by A(H3N2) (51.2%) at the

beginning of the season and followed by a predominance of influenza B (43.2%) from March to April (Figure 1B).

We restricted VE analysis to the two influenza seasons occurring during our study period which were the time periods from 05 Jan 2014 to 19 Apr 2014 and from 16 Nov 2014 to 09 May 2015 respectively. A total of 1725 of the 2179 patients were enrolled during the two seasons, including 353 who were test-positive for either influenza A or B virus, while 1372 were test-negative for any type/subtype of influenza virus (Table 1). Test-positive cases were most frequently young children (n=131, 37.1%) and elderly (n=103, 29.2%), and the age distribution was similar in the control group.

Influenza vaccination coverage was generally low, at 12.6% overall among the controls, and varied substantially by age in the control group: it was 2.4% in children aged 6 months to 5 years, 31.2% in children 6-17y, 1.3% in adults 18-59y and 23.9% among adults ≥60y. The overall adjusted VE was 18.6% (95% confidence interval, CI: -22.0%, 45.7%) against influenza A and B combined in the two influenza seasons (Table 2). Overall VE was modest (46.9%; 95% CI: -20.4%, 76.6%) for the 2013-14 season and low (5.0%; 95% CI: -53.0%, 41.0%) for the 2014-15 season. Influenza VE was estimated to be 59.5% (95% CI: -49.4%, 89.0%) for influenza A and 42.4% (95% CI: -59.7%, 79.2%) for influenza B in the 2013-14 season. However, the VE against influenza A(H3N2) and influenza B infection was 27.9% (95% CI: -41.5%, 63.3%) and -31.5% (95% CI: -153.9%, 31.9%) in the 2014-15 season (Table 2).

Stratified estimates by season and age group are shown in Table 3. In season-specific and season-combined estimates of VE, we observed a declining trend of VE with increasing age. Since no children aged 6 months to 5 years testing positive for influenza in the 2013-14 season had been vaccinated in our data, point VE estimates for this age group against all influenza virus infections was 100% for that season (Table 3). The overall VE estimate for children aged 6-17 years was 52.0% (95% CI: -9.0%, 78.9%), similar across two influenza seasons. However, VE estimates for both adults and elderly were relatively low, with estimates of -9.7% (95% CI: -1207.8%, 90.8%) and -33.2% (95% CI: -127.1%, 21.9%) respectively (Table 3).

DISCUSSION

We used a hospital-based study to estimate influenza VE in Beijing in the 2013-14 and 2014-15 winter influenza seasons. Since 2009, the Beijing municipal government has provided free influenza vaccination to school-age children 6-17y of age and adults ≥60y of age. Despite the free vaccination program, vaccine coverage was relatively low in the control groups of our study in those two age groups: 30% in children 6-17y and 20% in adults ≥60y of age. Vaccination coverage in the control group was generally lower than the coverage in the underlying population in Beijing, possibly because these newly admitted patients with ILI symptoms had relatively lower health awareness and therefore a lower probability to be vaccinated. The Beijing CDC recorded that around 1.5 million doses were administered each year in the city for the 2013-14 and 2014-15 seasons. Previously studies suggested that influenza vaccination covered around 70% of primary and middle school students (6-17y) and 40% of adults (≥60y) in Beijing [15, 16]. A

perceived lack of effectiveness of the vaccine and low risk of influenza infection might be the main barriers to increasing influenza vaccination coverage in Beijing [15]. Further evidence from test-negative studies, like the present study, demonstrating that influenza does present a substantial disease burden and that influenza vaccination is effective could increase the public's willingness to receive free vaccination in Beijing.

In the winter 2013-14 influenza season, we estimated an overall VE at 46.9% (95% CI: -20.4%, 76.6%). This is comparable to other estimates of VE in the northern hemisphere and consistent with moderate VE [17, 18]. A study conducted in Greece where the influenza vaccination coverage was similar to Beijing estimated that the influenza vaccination was 34.5% (4.1%, 55.3%) effective against inpatient and outpatient infections [17]. Our estimate was lower than those reported from the United States (61%, 95% CI: 52%, 68%) [19] and Canada (58.5%, 95% CI: 43.9%, 69.3%) [20], which could attribute to different circulating viruses in the two regions. In the 2013-14 season, influenza H1N1, H3N2 and B viruses were co-circulating in Beijing while in Canada and the United States it was predominated by H1N1 virus. Another potential explanation for poorer VE is the potential for waning immunity between administration of vaccines in October and November 2013 and the late peak of the 2013-14 influenza season in late January-March in Beijing 2014.

However in the winter 2014-15 influenza season, we estimated an overall VE of 5.0% (95% CI: -53.0%, 41.0%) against hospitalization. The relatively low VE was also observed in other studies conducted in the Northern hemisphere. A study conducted in an early

season of influenza in the United States estimated a VE of 23% (8%, 36%) against medically attended acute respiratory infections [21]. Similarly, a mid-season study in the United Kingdom estimated a VE of 3.4% (−44.8%, 35.5%) against influenza overall and −2.3% (−56.2%, 33.0%) against H3N2 among patients presenting acute ILI symptoms for ambulatory care [22]. Interim VE estimates of the 2014-15 season in Canada were -16.8% (-4.9%, 8.3%) overall against hospitalizations among all ages, and -25.4% (-65.0%, 4.6%) for the elderly aged 65 years or above [20] while a similar study in Spain estimated a moderate influenza VE of 33% (6%, 53%) and 40% (13%, 59%) in all age groups and the elderly, respectively [23]. The lack of effectiveness of influenza vaccination might be attributable to the mismatch in the H3N2 component. In addition there was a late influenza B epidemic in Beijing in March and April 2015, and protective immunity from pre-winter vaccinations may have waned by this time.

Our study has several limitations. First, similar to other observational studies, our study could suffer bias from unidentified potential confounders although the common confounding factors including age and underlying medical conditions had been adjusted for in the analysis to minimize biases of VE estimates. Second, our estimates of VEs may not be directly comparable with those from previous studies because we applied a list of pre-defined hospital admission diagnoses to indicate influenza-associated diseases that might differ from outcomes used in other studies. Third, using influenza-associated hospitalization as the outcome in our study might lead to under-detection of influenza viruses since the patients were likely to have a longer delay from symptom onset therefore less likely to be tested positive for influenza, while our data suggested that most

patients were admitted within 4 days after symptom onset. Nevertheless, we have shown in a review that estimates from hospital-based test-negative studies tend to provide similar estimates of VE compared to estimates from test-negative studies in outpatient settings [REF]. Lastly, our study might have less power to obtain a reliable estimate of VE in some age groups given the small number of vaccinees observed in these groups.

In conclusion, our study provided estimates that were consistent with moderate influenza VE against laboratory-confirmed hospitalization in Beijing in the 2013-14 winter season, while the vaccine effectiveness was low in the 2014-15 season when vaccine components mismatched circulating virus strains.

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POTENTIAL CONFLICTS OF INTEREST

BJC has received research funding from Sanofi Pasteur and MedImmune Inc., and consults for Crucell NV. The authors report no other potential conflicts of interest.

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377

FIGURE LEGENDS

Figure 1. (A) Timeline of recruitment of patients testing positive or negative for influenza.

(B) Timeline of recruitment of patients testing positive for influenza by type/subtype.

Table 1. Descriptive analysis of patients recruited during 2013-14 and 2014-15 winter influenza seasons in Beijing, China.

Characteristics	**Test-positive (n=353) N (%)**	**Test-negative (n=1372) N (%)**	**p-value** [a]
Age group			
6m-5y	131 (37.1%)	534 (38.9%)	0.020
6-17y	67 (19.0%)	173 (12.6%)	
18-59y	52 (14.7%)	234 (17.1%)	
⩾60y	103 (29.2%)	431 (31.4%)	
Male	212 (60.1%)	826 (60.2%)	1.000
Chronic conditions [b]	111 (31.4%)	442 (32.2%)	0.831
Receipt of TIV in the current season	42 (11.9%)	173 (12.6%)	0.787

[a] p-values estimated by chi-squared tests.

[b] Chronic conditions included cardiovascular disease, chronic obstructive pulmonary disease, asthma, diabetes, immunodeficiency or organ transplant, renal impairment, rheumatologic disease, neuromuscular disease, cirrhosis or liver disease, neoplasm, autoimmune disease and hematological disease.

Table 2. Estimates of vaccine effectiveness of trivalent influenza vaccines against laboratory-confirmed influenza hospitalization during 2013-14 and 2014-15 winter influenza seasons.*

	All Influenza	Influenza A	Influenza A(H3N2)	Influenza B
Overall	18.6% (-22.0%, 45.7%)	32.9% (-20.3%, 62.6%)	31.6% (-26.8%, 63.1%)	0.2% (-71.4%, 41.9%)
Influenza season				
2013-14	46.9% (-20.4%, 76.6%)	59.5% (-49.4%, 89%)	59.5% (-110%, 92.2%)	42.4% (-59.7%, 79.2%)
2014-15	5.0% (-53.0%, 41.0%)	27.1% (-43.1%, 62.9%)	27.9% (-41.5%, 63.3%)	-31.5% (-153.9%, 31.9%)

* From conditional logistic regression models adjusting for age group, sex and chronic conditions, and matched by calendar week.

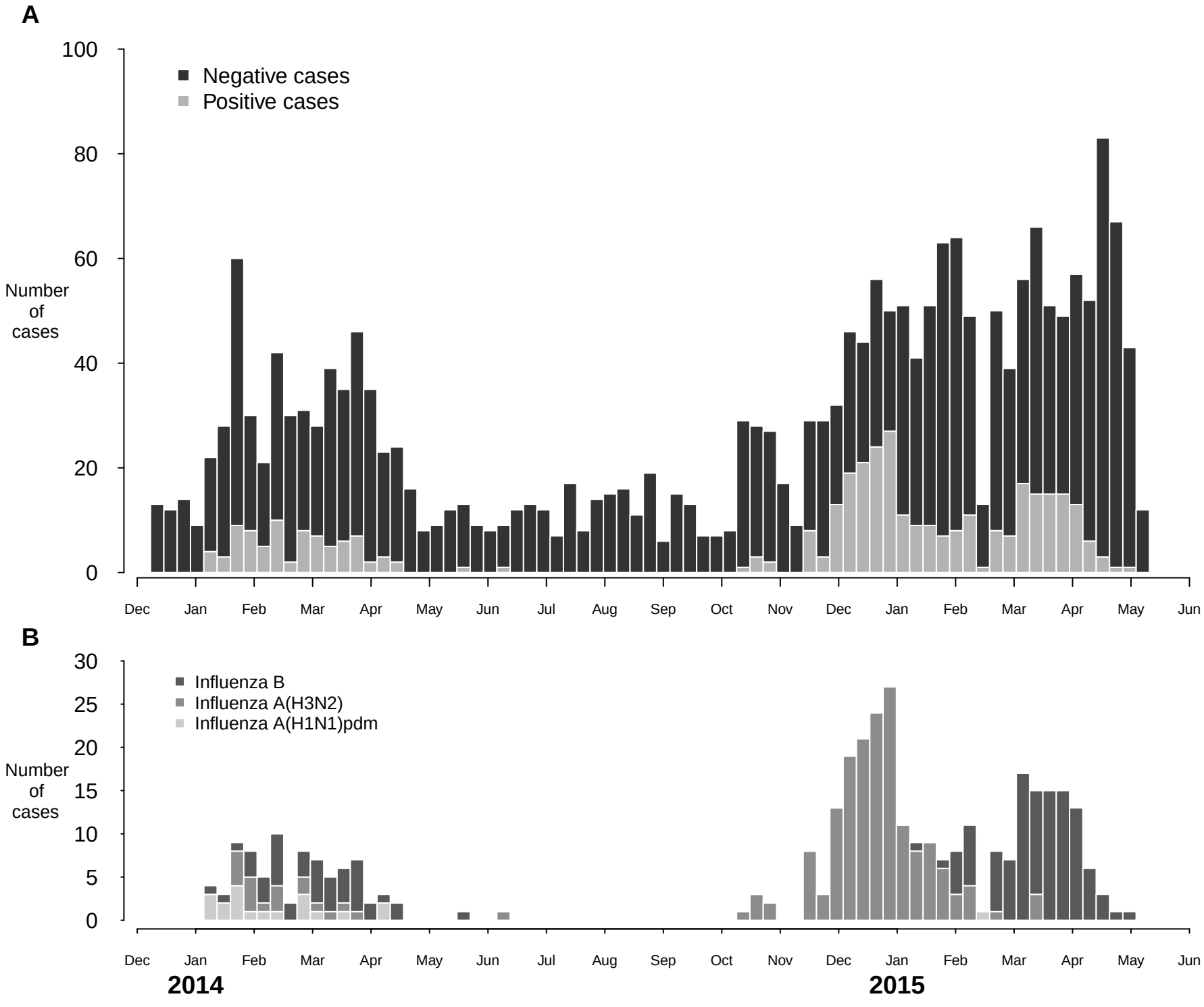
Table 3. Estimates of vaccine effectiveness of trivalent influenza vaccines against laboratory-confirmed influenza hospitalization in different age groups during 2013-14 and 2014-15 winter influenza seasons.

	Both seasons	**2013/14 season**	**2014/15 season**
Overall	18.6% (-22.0%, 45.7%)	46.9% (-20.4%, 76.6%)	5.0% (-53.0%, 41.0%)
Age group			
6m-5y	81.2% (-52.3%, 97.7%)	-[a, b]	70.6% (-163.2%, 96.7%)
6-17y	52.0% (-9.0%, 78.9%)	45.5% (-152.7%, 88.2%)[a]	56.1% (-17.5%, 83.6%)
18-59y	-9.7% (-1207.8%, 90.8%)	--	-13.0% (-1219.8%, 90.3%)
≥60y	-33.2% (-127.1%, 21.9%)	26.8% (-114.3%, 75.0%)	-66.7% (-211.9%, 10.9%)

Estimates of vaccine effectiveness from conditional logistic regression models adjusted for age group, sex, chronic conditions, and matched by calendar week, unless otherwise specified.

[a] Estimated from conditional logistic regression models adjusting for age group, sex, and matching by calendar week.

[b] The estimate was not provided because there were no vaccinated subjects in the group of cases testing positive for influenza, and a limited number of vaccinees in the corresponding control group during that season.


A
Negative cases
Positive cases
Number of cases
100
80
60
40
20
0
Dec
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Jan
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Apr
May
Jun
B
Influenza B
Influenza A(H3N2)
Influenza A(H1N1)pdm
Number of cases
30
25
20
15
10
5
0
Dec
Jan
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Jun
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2014
2015

Appendix Table 1. Admission diagnoses potentially associated with influenza infections for patients less than 5 years old.

Admission diagnoses	**ICD 10 Codes**
Acute upper or lower respiratory disease	J00-J06, J20-J22
Dyspnea, breathing anomaly, shortness of breath, tachypnea	R06.0, R06, R06.9, R06.3, R06.00, R06.09, R06.83, R06.02, R06.82, R06.2, R06.89
Asthma	J45.2-J45.22, J45.9-J45.998, J44-J44.9
Pneumonia and influenza	J09-J18
Heart failure	I50-I50.9; I51.4
Myalgia	M79.1
Altered consciousness, convulsions, febrile convulsions	R40.20, R40.4, R40.0, R40.1, R56.00, R56.01
Fever or fever unknown origin or non-specified	R50, R50.9
Cough	R05
Gastrointestinal manifestations	A09.0; A09.9
Sepsis, systemic inflammatory response syndrome	R65.10, R65.11, R65.20, A41.9

Appendix Table 2. Admission diagnoses potentially associated with influenza infections for patients 5 years or older.

Admission diagnoses	**ICD 10 Codes**
Acute respiratory infection	J00-J06, J20-J22, H66.90
Acute myocardial infarction or acute coronary syndrome	I20-I25.9
Asthma	J45.2-J45.22, J45.9-J45.998, J44-J44.9
Heart failure	I50-I50.9; I51.4
Pneumonia and influenza	J09-J18
Chronic Pulmonary Obstructive disease	J40-J44.9
Myalgia	M79.1
Malaise	R53.81
Metabolic failure (diabetic coma, renal dysfunction, acid-base disturbances, Altered consciousness, convulsions, febrile-convulsions	E11.9, E10.9, E11.65, E10.65, E10.11, E11.01, E10.641, E11.641, E10.69, E11.00, E10.10, E11.69, R40.20, R40.4, R40.0, R40.1, R56.00, R56.01
Dyspnea/respiratory abnormality	R06.0, R06-R06.9
Respiratory abnormality	R06.9
Shortness of breath	R06.02
Other respiratory abnormalities	R06.3, R06.00, R06.09, R06.83
Respiratory symptoms/chest symptoms	R06.89
Fever or fever unknown origin or non-specified	R50, R50.9
Cough	R05
Sepsis, Systemic inflammatory response syndrome	R65.10, R65.11, R65.20, A41.9