

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

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25 **Highlights**

26

- 27 1. Influenza vaccination coverage was 11.9% and 12.6% in the case and control
28 groups respectively.
- 29 2. The overall estimates of vaccine effectiveness were 46.9% (95% CI: -20.4%,
30 76.6%) for the 2013-14 season and 5.0% (95% CI: -53.0%, 41.0%) for the 2014-
31 15 season.
- 32 3. This study demonstrated the feasibility of routine assessment of influenza vaccine
33 effectiveness using the test-negative design in Beijing.

34

35

36

37 **ABSTRACT**

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

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

49 **Results:** A total of 2368 inpatients were recruited during the study period with a
50 vaccination coverage in the control group of 12.8%. The overall estimate of influenza VE
51 was 46.9% (95% CI: -20.4%, 76.6%) for the 2013-14 season and 5.0% (95% CI: -53.0%,
52 41.0%) for the 2014-15 season. Estimates of VE were relatively higher in children aged
53 6-17 years than older persons across two influenza seasons while estimates of VE for
54 both adults and elderly were relatively low.

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

58

59 **INTRODUCTION**

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

66

67 China is an upper middle income country in the northern hemisphere with a population of
68 1.3 billion. The capital city Beijing in the northeast of China has a typical temperate
69 climate with a population of 20 million. Sentinel surveillance data indicates that influenza
70 viruses circulate every year in Beijing from late autumn through to spring of the next year.
71 The municipal government of Beijing provided free influenza vaccination for adult
72 residents ≥ 60 y and subsidized influenza vaccination for elementary and high school
73 students 6-17 years of age from 2007 to 2008, and provided free influenza vaccination to
74 these two groups since 2009 [9]. However, few studies have evaluated influenza VE in
75 Beijing or elsewhere in China [10]. In 2013-14, the influenza vaccine strains matched the
76 circulating strains in China while most circulating A(H3N2) viruses in the 2014-15
77 season were low reactors to the A/Texas/50/2012 (H3N2)-like virus used for the
78 influenza vaccine in that season. As part of a global surveillance network with a unified
79 core protocol [11, 12], we implemented a test-negative study based in hospitals to
80 estimate VE in Beijing in the winter influenza seasons of 2013-14 and 2014-15.

81

82 **METHODS**

83 *Study setting and subjects*

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

91

92 We aimed to include inpatients whose disease episode was potentially associated with
93 infection of influenza virus in the study. Given the potential variation in clinical
94 presentation, we adopted different inclusion criteria for patients younger than 5 years and
95 those at age of 5 years and older. All patients 0-4y who were diagnosed any of the
96 diseases listed in Appendix Table 1 met the diagnostic criterion for inclusion. For patients
97 $\geq 5y$, the patient who was diagnosed as one of the diseases listed in Appendix Table 2 and
98 at the same time met the influenza like-illness (ILI) definition was eligible for further
99 screening. We adopted the ILI definition proposed by the European Centre for Diseases
100 Control that an ILI patient should present any of four systemic symptoms (fever or
101 feverishness, headache, myalgia or malaise) plus any of the three respiratory symptoms
102 (cough, sore throat or shortness of breath). In our study, patients' onset of ILI symptoms
103 had to be within the 7 days prior to admission, and all recruited patients were admitted
104 within the previous 24-48 hours. Only routine residents (living in the city for ≥ 6 months)

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

107

108 Two pharyngeal swabs were collected from each eligible patient and tested for influenza
109 A (H1N1pdm09 and H3N2) and influenza B (B/Yamagata, B/Victoria) by RT-PCR.

110 Demographic and related clinical information was obtained through face-to-face
111 interview or review of clinical records, including age, sex, smoking habit of the patient
112 (for adults) or parents (for children), pregnancy status, chronic conditions, influenza
113 vaccination status in the current and the previous seasons.

114

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

117

118 *Definition of vaccination status*

119 Influenza vaccination status of recruited patients was determined by vaccination record
120 registered in the Beijing Expanded Program on Immunization Information Management
121 System. Vaccination was defined as patients who had received trivalent inactivated
122 influenza vaccine (TIV) in the corresponding influenza season more than 2 weeks before
123 hospitalization. Patients who had a contra-indication to influenza vaccination or received
124 TIV less than 2 weeks before enrolment were excluded from the study. Vaccination
125 schedules generally followed the recommendations from the World Health Organization
126 [13]. Recruited patients who received at least one dose of influenza vaccine were
127 identified as vaccinated. The 2013-14 influenza TIV was composed of

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

132

133 ***Laboratory testing***

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

146

147 ***Statistical analysis***

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

151 models where the outcome was the specimen testing result, either positive or negative to
152 a certain type/subtype of influenza viruses, and the covariate of interest was vaccination
153 status, matching by calendar week of admission to account for variation in vaccination
154 coverage over time. Potential confounders such as age group (6m-5y, 6-17y, 18-59y,
155 $\geq 60y$), sex and chronic conditions were also included in the model. VE was defined as
156 one minus the adjusted odds ratio. VE analysis was performed for influenza overall and
157 by type/subtype, age and season.

158

159 **RESULTS**

160 Between December 9, 2013 and May 15, 2015, a total of 2368 patients presenting to the
161 selected hospitals were recruited. Patients who were institutionalized (n=7), who were
162 hospitalized within 30 days (n=15), who did not meet the ILI definition (n=45), and
163 whose symptoms started more than 7 days before admission (n=61) were excluded.

164 Among the remaining 2234 patients, children younger than 6 months were not eligible for
165 influenza vaccination and thus excluded (n=33). Patients who had contradictions to
166 vaccination were excluded (n=15), or vaccinated within 14 days of illness onset were
167 excluded (n=7). Therefore 2179 patients meeting the inclusion criteria were enrolled
168 during the study period and provided specimens for laboratory testing. The timeline of
169 patient recruitment was shown in Figure 1. The winter 2013-14 influenza season started
170 late in January 2014, and had influenza A(H1N1) (22.9%), A(H3N2) (22.9%) and B
171 (54.2%) co-circulating throughout the season while the winter 2014-15 influenza season
172 starting early in November 2014 was predominated by A(H3N2) (51.2%) at the

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

175

176 We restricted VE analysis to the two influenza seasons occurring during our study period
177 which were the time periods from 05 Jan 2014 to 19 Apr 2014 and from 16 Nov 2014 to
178 09 May 2015 respectively. A total of 1725 of the 2179 patients were enrolled during the
179 two seasons, including 353 who were test-positive for either influenza A or B virus, while
180 1372 were test-negative for any type/subtype of influenza virus (Table 1). Test-positive
181 cases were most frequently young children (n=131, 37.1%) and elderly (n=103, 29.2%),
182 and the age distribution was similar in the control group.

183

184 Influenza vaccination coverage was generally low, at 12.6% overall among the controls,
185 and varied substantially by age in the control group: it was 2.4% in children aged 6
186 months to 5 years, 31.2% in children 6-17y, 1.3% in adults 18-59y and 23.9% among
187 adults ≥ 60 y. The overall adjusted VE was 18.6% (95% confidence interval, CI: -22.0%,
188 45.7%) against influenza A and B combined in the two influenza seasons (Table 2).

189 Overall VE was modest (46.9%; 95% CI: -20.4%, 76.6%) for the 2013-14 season and low
190 (5.0%; 95% CI: -53.0%, 41.0%) for the 2014-15 season. Influenza VE was estimated to
191 be 59.5% (95% CI: -49.4%, 89.0%) for influenza A and 42.4% (95% CI: -59.7%, 79.2%)
192 for influenza B in the 2013-14 season. However, the VE against influenza A(H3N2) and
193 influenza B infection was 27.9% (95% CI: -41.5%, 63.3%) and -31.5% (95% CI: -153.9%,
194 31.9%) in the 2014-15 season (Table 2).

195

196 Stratified estimates by season and age group are shown in Table 3. In season-specific and
197 season-combined estimates of VE, we observed a declining trend of VE with increasing
198 age. Since no children aged 6 months to 5 years testing positive for influenza in the 2013-
199 14 season had been vaccinated in our data, point VE estimates for this age group against
200 all influenza virus infections was 100% for that season (Table 3). The overall VE
201 estimate for children aged 6-17 years was 52.0% (95% CI: -9.0%, 78.9%), similar across
202 two influenza seasons. However, VE estimates for both adults and elderly were relatively
203 low, with estimates of -9.7% (95% CI: -1207.8%, 90.8%) and -33.2% (95% CI: -127.1%,
204 21.9%) respectively (Table 3).

205

206 **DISCUSSION**

207 We used a hospital-based study to estimate influenza VE in Beijing in the 2013-14 and
208 2014-15 winter influenza seasons. Since 2009, the Beijing municipal government has
209 provided free influenza vaccination to school-age children 6-17y of age and adults ≥ 60 y
210 of age. Despite the free vaccination program, vaccine coverage was relatively low in the
211 control groups of our study in those two age groups: 30% in children 6-17y and 20% in
212 adults ≥ 60 y of age. Vaccination coverage in the control group was generally lower than
213 the coverage in the underlying population in Beijing, possibly because these newly
214 admitted patients with ILI symptoms had relatively lower health awareness and therefore
215 a lower probability to be vaccinated. The Beijing CDC recorded that around 1.5 million
216 doses were administered each year in the city for the 2013-14 and 2014-15 seasons.
217 Previously studies suggested that influenza vaccination covered around 70% of primary
218 and middle school students (6-17y) and 40% of adults (≥ 60 y) in Beijing [15, 16]. A

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

224

225 In the winter 2013-14 influenza season, we estimated an overall VE at 46.9% (95% CI: -
226 20.4%, 76.6%). This is comparable to other estimates of VE in the northern hemisphere
227 and consistent with moderate VE [17, 18]. A study conducted in Greece where the
228 influenza vaccination coverage was similar to Beijing estimated that the influenza
229 vaccination was 34.5% (4.1%, 55.3%) effective against inpatient and outpatient
230 infections [17]. Our estimate was lower than those reported from the United States (61%,
231 95% CI: 52%, 68%) [19] and Canada (58.5%, 95% CI: 43.9%, 69.3%) [20], which could
232 attribute to different circulating viruses in the two regions. In the 2013-14 season,
233 influenza H1N1, H3N2 and B viruses were co-circulating in Beijing while in Canada and
234 the United States it was predominated by H1N1 virus. Another potential explanation for
235 poorer VE is the potential for waning immunity between administration of vaccines in
236 October and November 2013 and the late peak of the 2013-14 influenza season in late
237 January-March in Beijing 2014.

238

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

242 season of influenza in the United States estimated a VE of 23% (8%, 36%) against
243 medically attended acute respiratory infections [21]. Similarly, a mid-season study in the
244 United Kingdom estimated a VE of 3.4% (-44.8%, 35.5%) against influenza overall and
245 -2.3% (-56.2%, 33.0%) against H3N2 among patients presenting acute ILI symptoms for
246 ambulatory care [22]. Interim VE estimates of the 2014-15 season in Canada were -16.8%
247 (-4.9%, 8.3%) overall against hospitalizations among all ages, and -25.4% (-65.0%, 4.6%)
248 for the elderly aged 65 years or above [20] while a similar study in Spain estimated a
249 moderate influenza VE of 33% (6%, 53%) and 40% (13%, 59%) in all age groups and the
250 elderly, respectively [23]. The lack of effectiveness of influenza vaccination might be
251 attributable to the mismatch in the H3N2 component. In addition there was a late
252 influenza B epidemic in Beijing in March and April 2015, and protective immunity from
253 pre-winter vaccinations may have waned by this time.

254

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

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

270

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

275

276

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284

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297

298 **POTENTIAL CONFLICTS OF INTEREST**

299 BJC has received research funding from Sanofi Pasteur and MedImmune Inc., and
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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.

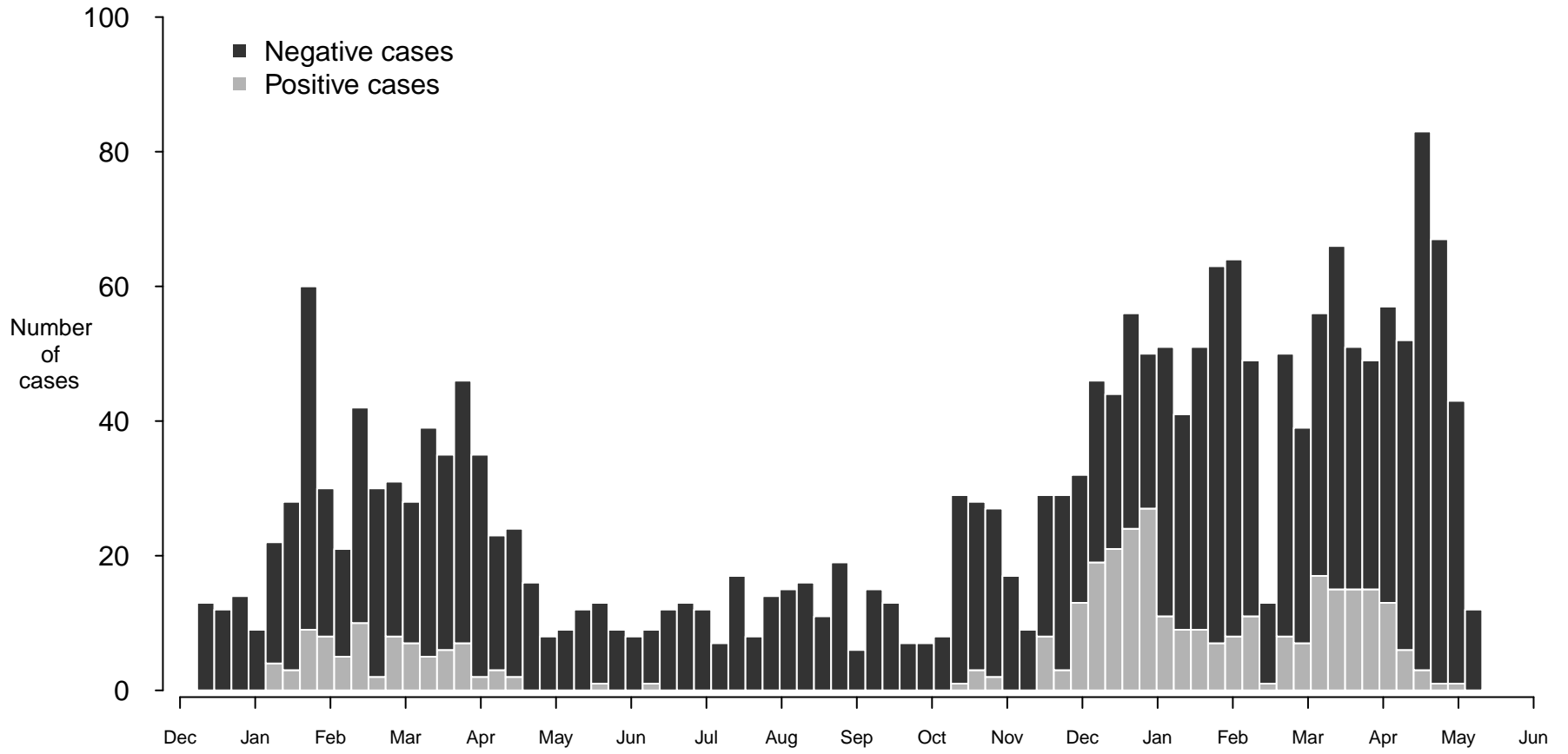
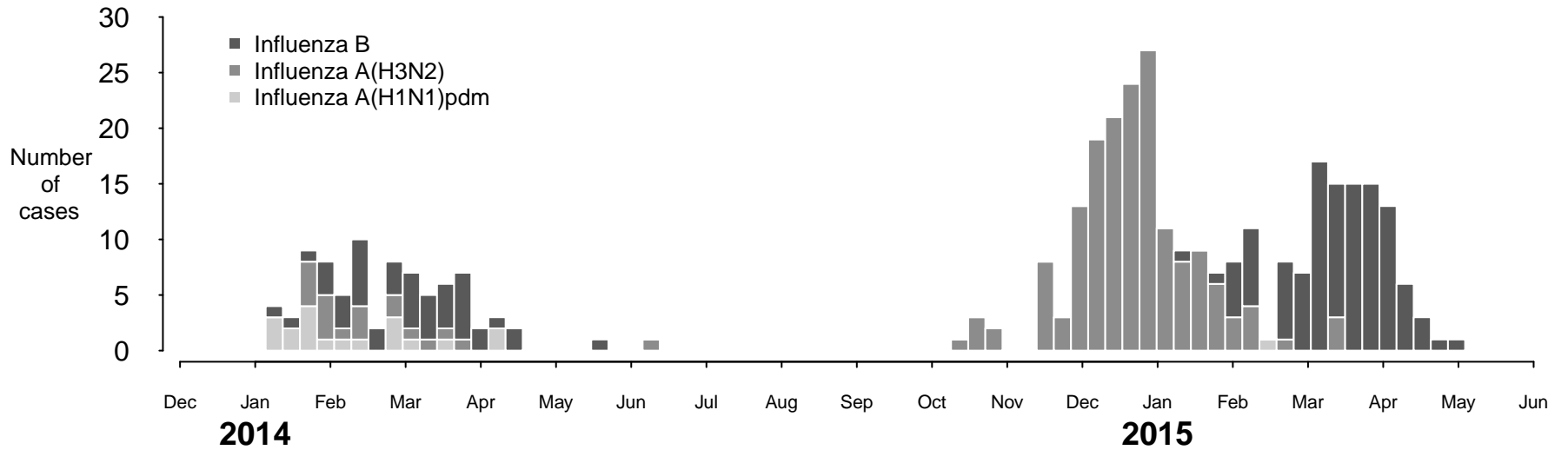
Table 3. Estimates of vaccine effectiveness of trivalent influenza vaccines against laboratory-confirmed influenza hospitalization in different age groups during 2013-14 and 2014-15 winter influenza seasons.

	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**B**

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