The effectiveness of influenza vaccination against medically-attended illnesses in Hong Kong across three years with different degrees of vaccine match, 2014-17

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Keywords: Influenza, vaccine effectiveness, Hong Kong, vaccine match

Highlights: Overall vaccine effectiveness against medically-attended influenza was moderate in Hong Kong. The estimated vaccine effectiveness was generally lower against influenza A(H3N2) than influenza A(H1N1) and influenza B. Point estimates of vaccine effectiveness against influenza A(H3N2) were higher in young adults compared to other age groups. The overall protection provided by seasonal influenza vaccination among

different age groups and across different epidemics could be informed by routine monitoring in the community.

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ABSTRACT

Background: Influenza vaccination is the most effective intervention to prevent influenza virus infections. Vaccine effectiveness (VE) can vary due to factors such as matching between vaccine strains and prevailing strains, age and other characteristics of the vaccine recipients.

Objective: To evaluate influenza VE against medically-attended illness in different age groups and against specific influenza types/subtypes in Hong Kong.

Methods: A test-negative study was conducted from December 2014 through August 2017 in 20 outpatient clinics. Patients at least 6 months of age presenting with at least two symptoms of acute respiratory illness, ARI (fever ≥37.8°C, cough, sore throat, runny nose, headache, myalgia and phlegm) within 72 hours of onset were tested for influenza virus by reverse transcription polymerase chain reaction (PCR). Vaccination history was assessed by self-report or medical records at the clinics. VE against medically-attended illness was estimated using conditional logistic regression for influenza PCR result versus vaccination history, matching by calendar time and adjusting for age, age-squared, sex, and chronic medical illness. Additional analyses examined VE by age group and by influenza type/subtype.

Results: We enrolled 2566 patients, of whom 1118 (43.6%) tested positive for influenza A or B virus by PCR. Test-positive subjects were generally older, more likely to present with one of the symptoms of ARI, and less likely to receive vaccination against influenza. VE estimates for influenza A(H1N1), A(H3N2), B/Yamagata and B/Victoria were 61.6% (95% confidence interval, CI: 21.8%, 81.1%), 26.4% (95% CI: -1.3%, 46.6%), 67.0% (95% CI: 25.9%, 85.3%), 60.4% (95% CI: 0.3%, 84.3%), respectively. Estimates of VE

by age group were generally higher in adults aged 50-64 and lower among children and older adults.

Conclusions: VE against medically-attended influenza was moderate in Hong Kong, confirming the impact of influenza vaccination in reducing disease burden. The reduced VE for influenza A(H3N2) is a continuing concern.

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Conclusions: VE against medically-attended influenza was moderate in Hong Kong, confirming the impact of influenza vaccination in reducing disease burden. The reduced VE for influenza A(H3N2) is a continuing concern.

INTRODUCTION

Influenza virus infections are associated with a substantial burden of morbidity and mortality worldwide.[1] In Hong Kong, a subtropical city with a population of 7.3 million, it has been estimated that influenza causes an average of 430 respiratory deaths and 12,700 respiratory hospitalisations each year.[2] Vaccination is generally recognised as the most effective intervention to prevent influenza virus infections. In Hong Kong, influenza circulates for most of the year with epidemics almost every winter, as well as spring or summer epidemics in many years.[2] Hong Kong uses the northern hemisphere formulation and conducts annual influenza vaccination campaigns each year in October through December, covering around 10% of the population in recent years.[3] The local government provides subsidized or free influenza vaccination for target groups including children aged 6 months to 5 years (extended to 11 years since 2016/17), pregnant women, persons with chronic medical conditions, people aged 65 years or above, and long-stay residents of institutions for persons with disability.[4]

Influenza vaccine effectiveness (VE) may vary from year to year and in different settings. Important factors that can affect VE include age and medical conditions of the vaccine recipients, and the degree of matching between vaccine strains and prevailing strains in the community.[5-8] Continuous monitoring of influenza VE can provide evidence to support vaccination policy. Locally, we have monitored influenza VE against hospitalization in children for almost 10 years,[9-12] but there are no available data on VE against medically-attended illnesses in children outpatients, or illness of any severity in adults in Hong Kong. We therefore established a test-negative study in local private

outpatient clinics from December 2014 to August 2017 to estimate influenza VE against medically-attended illness for children and adults.

METHODS

Study Design

We conducted this study in 20 private outpatient clinics in Hong Kong Island, Kowloon and the New Territories, i.e. spread geographically across the whole of Hong Kong. We enrolled patients ≥6 months of age who presented with at least two symptoms of acute respiratory illness (ARI) including fever ≥37.8°C, cough, sore throat, runny nose, headache, myalgia and phlegm, within 72 hours of illness onset. A nasal swab and a throat swab were obtained from each patient and maintained at 4-8°C before delivery to a central laboratory within 24 hours of collection. Specimens were preserved at -80°C on receipt at the laboratory, and later thawed for testing in batches. Information regarding demographics, clinical signs and symptoms, influenza vaccination history, and history of chronic medical conditions were also collected in a structured interview.

Ethical Approval

The study received ethical approval from the Institutional Review Board of Hong Kong University. Written informed consent was obtained from all patients aged 18 years and older, and proxy written informed consent was obtained from parents or legal guardians for their children before enrollment.

Ascertainment of vaccination history

Information on seasonal influenza vaccination, including the date and type of vaccination received for the previous and current year, was reported by all patients or by their parents or legal guardians, or obtained from patients' medical records at the clinics if available. Patients who received vaccination for the year of participation and with the last dose more than 2 weeks before participation were considered as vaccinated, or otherwise were classified as unvaccinated.

Laboratory testing

For patients enrolled between 22 December 2014 and 31 March 2017, nose and throat swabs were tested separately for influenza A and B by PCR, and a positive result on either specimen was taken as evidence of influenza virus infection. For patients enrolled after 31 March 2017, nose and throat swabs were pooled prior to testing by PCR. We used EasyMag (Biomerieux) for total nucleic acid extraction and tested for the presence of influenza A and influenza B viral RNA using one-step reverse transcription-quantitative polymerase chain reaction (RT-qPCR) assays targeting the conserved region in matrix gene of influenza A and influenza B viruses. All influenza A and B positives detected were then subtyped for A(H1), A(H3), B/Yamagta and B/Victoria. Screening and subtyping RT-qPCR assays were performed according to the WHO protocol and influenza B M gene assay was performed according to our earlier study.[13, 14]

Statistical analysis

We used conditional logistic regression to compare the odds of influenza vaccination for the present season among patients with PCR-confirmed influenza overall and by influenza type/subtype versus those who tested negative for influenza, matched by calendar time (two-week interval) of the illness onset date, and adjusted for age, age-squared, sex, and presence of chronic medical illness. VE against medically-attended illness was then estimated as 100% multiplied by (one minus the adjusted conditional odds ratio). In further analyses, we stratified VE estimates by age group. VE estimates were regarded as "not available" for reporting when the 95% confidence interval of estimated VE is wider than 100%. All statistical analyses were performed using R version 3.3.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Six influenza epidemics were captured during the study period. Figure 1 shows the timeline of subject recruitment in this study and a comparison with the local influenza virus activity from the Centre for Health Protection. A total of 2,566 patients were recruited from 22 December 2014 through 31 August 2017, with patients recruited throughout the year and influenza detections almost year-round (Figure 1). 1118 (43.6%) of the patients tested positive for influenza A or B by PCR. Patients testing positive were older, more likely to present within a shorter interval since illness onset, and to present with one of the symptoms of fever ≥37.8°C, cough, sore throat, runny nose, headache, myalgia and phlegm than patients testing negative. All the influenza vaccinations that the patients received for the seasons of participation were inactivated, with 197 (54.6%) of

the patients known to have received quadrivalent vaccine and 71 (19.7%) received trivalent vaccine. Influenza vaccination uptake was higher in older adults and among test-negative patients. A detailed comparison of characteristics between test-positive and test-negative patients is shown in Table 1. Among the 2,566 patients, 14 (0.5%) who had uncertain vaccination status were excluded from further analysis. Therefore, 2552 patients (99.5%) were retained in the analyses for VE.

Over the entire study period, the overall VE against influenza A and B combined was estimated to be 37.9% (95% CI: 19.3%, 52.2%). The VE estimates for influenza A(H1N1), A(H3N2), B/Yamagata and B/Victoria were 61.6% (95% CI: 21.8%, 81.1%), 26.4% (-1.3%, 46.6%), 67.0% (25.9%, 85.3%), 60.4% (0.3%, 84.3%), respectively (Table 2). For A(H3N2), the subtype-specific VE were generally higher for the years 2015-2016 (39.9%, 95% CI: -50.6, 76.0) and 2016-2017 (27.9%, 95%CI: -11.0, 53.2) comparing with 2014-2015 (18.0%, 95%CI: -46.4, 54.0). By comparing the epidemic strains in northern hemisphere reported in literature with the influenza vaccine strains recommended by the WHO for northern hemisphere each year, the vaccine strains generally matched with the epidemic strains, except when there was a major mismatch between the recommended vaccine strain and the prevailing epidemic strain, causing a large local epidemic between January and March in 2015 (Table 3). Influenza vaccine recommended for southern hemisphere summer in 2015 was provided to local older adults aged 75 or above in May and June 2015,[15] but only 16 patients in our study

reported receipt of this vaccine. The age-related pattern of VE for each influenza type and subtype is shown in Table 4.. The age-stratified point estimates suggested that VE was generally higher among adults aged 50 to 64 years (68.5%) but lower among other younger age groups (35.5% - 38.6%) and older adults (22.1%) overall. In particular, higher VEs were observed among children aged 6 months to 5 years against influenza A(H1N1) (67%), and among younger adults aged 18 to 49 years had higher VE against influenza B (77.4%). However, age-specific VE estimates against influenza types and subtypes were not available for all age groups and influenza subtypes, particularly for older adults, due either to insufficient test-positive patients or wide 95% CIs, making direct comparison between subtypes not always possible.

DISCUSSION

Our study estimated VE against medically-attended influenza in Hong Kong over 2.5 years, covering six periods of influenza activity. Our estimate of overall VE against influenza A and B was 37.9% (95% CI: 19.3%, 52.2%), closest to the VE estimate for influenza A(H3N2), which constituted the most frequent type/subtype encountered in our study (Table 2). Our estimates are substantially higher than the estimates from some countries, including Israel and China,[16, 17] but generally comparable with the estimates reported in many other countries, including US, Canada and Europe and Japan.[18-23] In 2014-2015, the US and Europe reported the VE of 11.0 (95% CI: -1.0%, 21.0%) and 14.4% (95% CI: -6.3%, 31.0%) against the predominant strain influenza A(H3N2) respectively.[19, 21] Both influenza A(H1N1) and influenza B predominated in 2015-2016 and the reported VE were 39.4% and 45% against A(H1N1) and 47% and 49-

57% against B from the US and Europe.[18, 22] Last but not least, the dominant circulation of influenza A(H3N2) in 2016-2017 was associated with a VE of 42% (95% CI: 18.0%, 59.0%) in Canada and 43% (95% CI: 29.0%, 54.0%) in the US.[20, 24]

The overall vaccine coverage of 16.0% in the test-negative controls (Table 1) was largely consistent with what would be expected based on local influenza vaccination coverage, with around 700,000 doses administered in a population size of 7.3 million in 2017.[3] The vaccination uptake was significantly higher among test-negative patients. Compared to test-positive patients, age-specific uptake was higher among participants aged 6 months to 5 years, 18 to 49 years, and 50 to 64 years. This demonstrates the potential for higher vaccination coverage to further reduce the disease burden of influenza in the community.

The VE across different influenza seasons varied with different influenza types/subtypes, with low VE in periods when the vaccine strains did not match the epidemic strains. It was prominent in 2015 summer when the influenza A/Texas/50/2012 (H3N2)-like strain in the vaccine for 2014/15 winter season was not matching with the circulating influenza A/Switzerland/9715293/2013 (H3N2)-like virus, leading to a particularly low VE of 18.0% against influenza A (H3N2) in 2014-15 (Table 2). Similar figures of suboptimal VE were reported by other studies when there was a mismatch between the vaccine and circulating strains, with the estimated VE reported in the range of -3 to 20%.[19, 21, 25, 26] In the 2015/16 winter when the circulating strains of influenza A(H1N1) and influenza B were generally matching with the vaccine strains, type/subtype specific VEs

were estimated to be higher at 59.7% and 66.2% respectively, comparable with similar estimates from other regions.[18, 22] On the other hand, the VE estimates were reduced in the 2016-17 when influenza A(H3N2) predominating the northern hemisphere epidemic in winter time in the US and Europe but was mild in Hong Kong winter until it contributed to a high summer peak in 2017. The VE estimates reported in Canada and the US were 42% and 43% in 2016-2017, while the local VE estimated by this study was only 27.9% against influenza A(H3N2).[20, 24] Although there was no significant antigenic difference between the recommended vaccine strain and circulating strain of A(H3N2) in 2016-2017, the emergence of the viruses with hemagglutinin N121K substitution locally may explain the unexpectedly low VE for the season.[27] The emerging variants were also detected in Canada and the US,[20, 24] but these countries were affected not until the 2017-2018 season. Interim reports showed the VE estimates to be 25% in the US and even below 8% in Europe.[28, 29] A study in Denmark had demonstrated that different VEs were associated with genetically drifted A(H3N2) virus with different amino acid substitutions in N121K in the 2016/17 season in patients above 65 years.[30]

Apart from the degree of matching between vaccine strains and epidemic strains, we noted that age might be an individual factor associated with lower VE, as reported in some studies on influenza vaccine effectiveness involving diverse age groups,[31, 32, 34] but some other studies suggested VE between younger and older adults were not significantly different except in seasons predominated by influenza A(H3N2).[5, 33] The overall VE was relatively poor among older adults aged 65 or above, although they only

represented a minor proportion of sample in the study and no more precise strain-specific VE estimate could be made. The reason of lower VE in extreme age groups against A(H3N2) was postulated to be due to infection-naïve immune system, presence of underlying medical conditions or immunosenescence,[35] although the presence of chronic medical illness was not shown to be significantly associated with influenza infection in our study, probably because the majority of subjects were healthy young adults. Nevertheless, their higher risk to complication after influenza infection warranted special consideration on vaccination strategy when A(H3N2) epidemic season is anticipated.

The overall suboptimal vaccine uptake rate highlights the importance to consider potential strategies for further improving influenza vaccine coverage in Hong Kong, especially among subgroups with a higher risk of more serious disease. While routine monitoring of influenza VE should help to inform the level of protection provided by influenza vaccination across seasons, the differential age-stratified VE against different strains of influenza viruses highlighted the necessity of having a sufficient sample size on a rolling basis to allow for robust and precise VE estimation. Our experience from this study suggested that this is achievable if the wide-scale recruitment infrastructure we established, or a similar infrastructure can be maintained by a sustainable source of funding. This would serve to inform public health planning and action in a continuous and timely manner and to address any ungrounded scepticism in the community about VE in an evidence-based manner.

There are some potential limitations in our study. First, as there is no vaccination registry in Hong Kong, vaccination history could only be self-reported or checked with medical record at the clinics. It was challenging to verify vaccination history in most patients, as only some patients had received influenza vaccination in the same clinic that they subsequently attended for medical consultation with an acute respiratory illness, and thus no exact source of information of vaccination history was recorded. Second, test-positive subjects tended to be older adults, present earlier and with more ARI symptoms. We adjusted for age differences in our analysis and reduce over-representation of influenza, which can naturally present with slightly more severe symptoms than other "common cold" viruses, by setting broad eligibility criteria. Third, not each influenza type and subtype could have the corresponding VE estimated in each year, because there was insufficient number of subjects tested positive for the strain not predominating in a given influenza season. Although it would make direct comparison of type-specific VE difficult across years, in real life practice it is most important to have VE estimates against the predominant strain as these have the practical value of timely monitoring of the most relevant VE and advising the public. Finally, although history of influenza vaccination in previous years may affect VE of the present season [36-38], there was no comprehensive immunization information system that recorded all vaccination received by the patients in both public and private healthcare sectors.

In conclusion, VE against medically-attended illness was moderate overall in the years studied. The estimated VE was generally lower against influenza A(H3N2), partly due to the mismatch between vaccine strains and epidemic strains in 2014/15. There were higher

point estimates of VE in adults aged 50 to 64 years compared to other age groups noted. The point estimates of VE were lower among young children and older adults against influenza A(H3N2). Routine monitoring of influenza VE could inform the community the overall protection provided by seasonal influenza vaccination among different age groups and across different epidemics.

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POTENTIAL CONFLICTS OF INTEREST

BJC has received research funding from Sanofi for a study of influenza vaccine effectiveness in China, and honoraria from Sanofi and Roche. The authors report no other potential conflicts of interest.

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FIGURE LEGEND

Figure 1. (A) Timeline of recruitment of patients testing positive or negative for influenza virus. (B) Local influenza activity in Hong Kong obtained by multiplying together local surveillance data on consultation rates of influenza like illnesses with rates of laboratory detections of influenza by type/subtype.

Table 1. Comparison of participants who tested positive or negative for influenza viruses A and B virus infection by PCR.

Characteristics	**Test-positive (n=1118)**		**Test-negative (n=1448)**		**p-value** [a]
	N	**(%)**	**N**	**(%)**	
Age group, years					
0.5-5	97	(8.7)	188	(13.0)	<0.01
6-17	229	(20.5)	201	(13.9)	
18-49	473	(42.3)	718	(49.6)	
50-64	211	(18.9)	209	(14.4)	
≥65	108	(9.7)	132	(9.1)	
Male	540	(48.3)	713	(49.2)	0.67
Time of first symptom onset (hours)[†]					
<24	792	(70.8)	913	(63.1)	<0.01
24 to 48	278	(24.9)	423	(29.2)	
>48	34	(3.0)	98	(6.8)	
Presented symptoms					
Fever	986	(88.2)	832	(57.5)	<0.01
Cough	1040	(93.0)	1133	(78.2)	<0.01
Runny nose	957	(85.6)	1140	(78.7)	<0.01
Sore throat	823	(73.6)	1055	(72.9)	0.57
Headache	852	(76.2)	982	(67.8)	<0.01
Myalgia	873	(78.1)	985	(68.0)	<0.01
Phlegm	844	(75.5)	959	(66.2)	<0.01

Receipt of influenza vaccination for the season of participation at least 2 weeks before[†]					
All age group (years)	129	(11.5)	232	(16.0)	<0.01
0.5-5	13	(13.4)*	33	(17.6)*	0.50
6-17	27	(11.8)*	34	(16.9)*	0.16
18-49	30	(6.3)*	71	(9.9)*	0.04
50-64	11	(5.2)*	32	(15.3)*	<0.01
≥65	48	(44.4)*	62	(47.0)*	0.79
Type of influenza vaccination received for the season of participation[§]					
Quadrivalent	78	(60.5)	119	(51.3)	0.06
Trivalent	17	(13.2)	54	(23.3)	
Uncertain	34	(26.3)	59	(25.4)	
With chronic medical illness[†]	88	(7.9)	129	(8.9)	0.40
Cardiac disease	38	(3.4)	39	(2.7)	0.35
Respiratory disease	20	(1.8)	43	(3.0)	0.08
Hepatic disease	12	(1.1)	10	(0.7)	0.40
Renal disease	7	(0.6)	7	(0.5)	0.82
Haematological / Immunological disease	8	(0.7)	11	(0.8)	1
Smoking status[†]					
Current smoker	131	(11.7)	184	(12.7)	<0.01
Ex-smoker	39	(3.5)	90	(6.2)	
Non-smoker	940	(84.1)	1168	(80.7)	

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

† 2538 (98.9%) participants reported the time of first symptom onset; 2552 (99.5%) participants reported their vaccination status; 2555 (99.6%) participants reported whether they had chronic medical illnesses; and 2552 (99.5%) participants reported their smoking status

* Percentage was calculated by the numbers of subjects in each age group as the corresponding denominator

§ Percentage was calculated using the total number of vaccinated subjects in each test-positive (n=129) and negative group (n=232) as the corresponding denominators

Table 2. Estimated vaccine effectiveness (VE) in each study year against medically-attended PCR-confirmed influenza virus infection, overall and by influenza type and subtype

Year	Overall	2014-2015	2015-2016	2016-2017
No. of test-positive/Total	1112/2552	233/510	427/1035	452/1007
Virus	VE% [a] (95% CI)	VE% (95% CI)	VE% (95% CI)	VE% (95% CI)
Any influenza	37.9 (19.3, 52.2)	29.9 (-22.3, 59.8)	51.7 (24.8, 69.0)	28.1 (-8.2, 52.2)
Influenza A	29.1 (6.2, 46.4)	17.4 (-45.9, 53.3)	38.2 (-3.9, 63.2)	29.1 (-7.7, 53.3)
A(H1N1)	61.6 (21.8, 81.1)	Not available[b]	59.7 (9.8, 82.0)	64.3 (-71.3, 92.5)
A(H3N2)	26.4 (-1.3, 46.6)	18.0 (-46.4, 54.0)	39.9 (-50.6, 76.0)	27.9 (-11.0, 53.2)
Influenza B	64.9 (36.1, 80.7)	Not available[b]	66.2 (32.7, 83.0)	Not available[b]
B/Yamagata	67.0 (25.9, 85.3)	Not available[b]	64.5 (6.8, 86.5)	Not available[b]
B/Victoria	60.4 (0.3, 84.3)	Not available[b]	66.9 (9.8, 87.8)	Not available[b]

[a] Vaccine effectiveness = 100*(one minus adjusted odds ratio [the odds of vaccination among influenza-positive cases versus influenza-negative cases]) using conditional logistic regression, matched by calendar time (two-week interval) and adjusted for age, age squared, sex, and presence of chronic medical illness.

[b] VE estimate not presented due to wide 95% confidence interval

Table 3. Comparison of the northern hemisphere influenza vaccine strains recommended by the World Health Organization and the epidemic strains circulating during the influenza seasons in the study period.

2014-2015 [38, 39]

Influenza strain	WHO recommended northern hemisphere vaccine strain	Epidemic strain
A(H1N1)	A/California/7/2009 (H1N1)pdm09-like virus (clade 6)	A/California/7/2009
A(H3N2)	A/Texas/50/2012 (H3N2)-like strain (clade 3C.1)	A/Switzerland/9715293/2013
B/Yamagata	B/Massachusetts/2/2012-like strain (clade 2)	B/Massachusetts/2/2012-like
B/Victoria	B/Brisbane/60/2008-like virus (clade subgroup 1A)	B/Brisbane/60/2008-like

2015-2016 [38, 40]

Influenza strain	WHO recommended northern hemisphere vaccine strain	Epidemic strain
A(H1N1)	A/California/7/2009 (H1N1)pdm09-like virus (clade 6B)	A/California/7/2009
A(H3N2)	A/Switzerland/9715293/2013 (H3N2)-like virus (subclade 3C.3a)	A/Switzerland/9715293/2013
B/Yamagata	B/Phuket/3073/2013-like virus (clade 3)	B/Phuket/3073/2013
B/Victoria	B/Brisbane/60/2008-like virus (clade 1A)	B/Brisbane/60/2008

2016-2017 [38, 41]

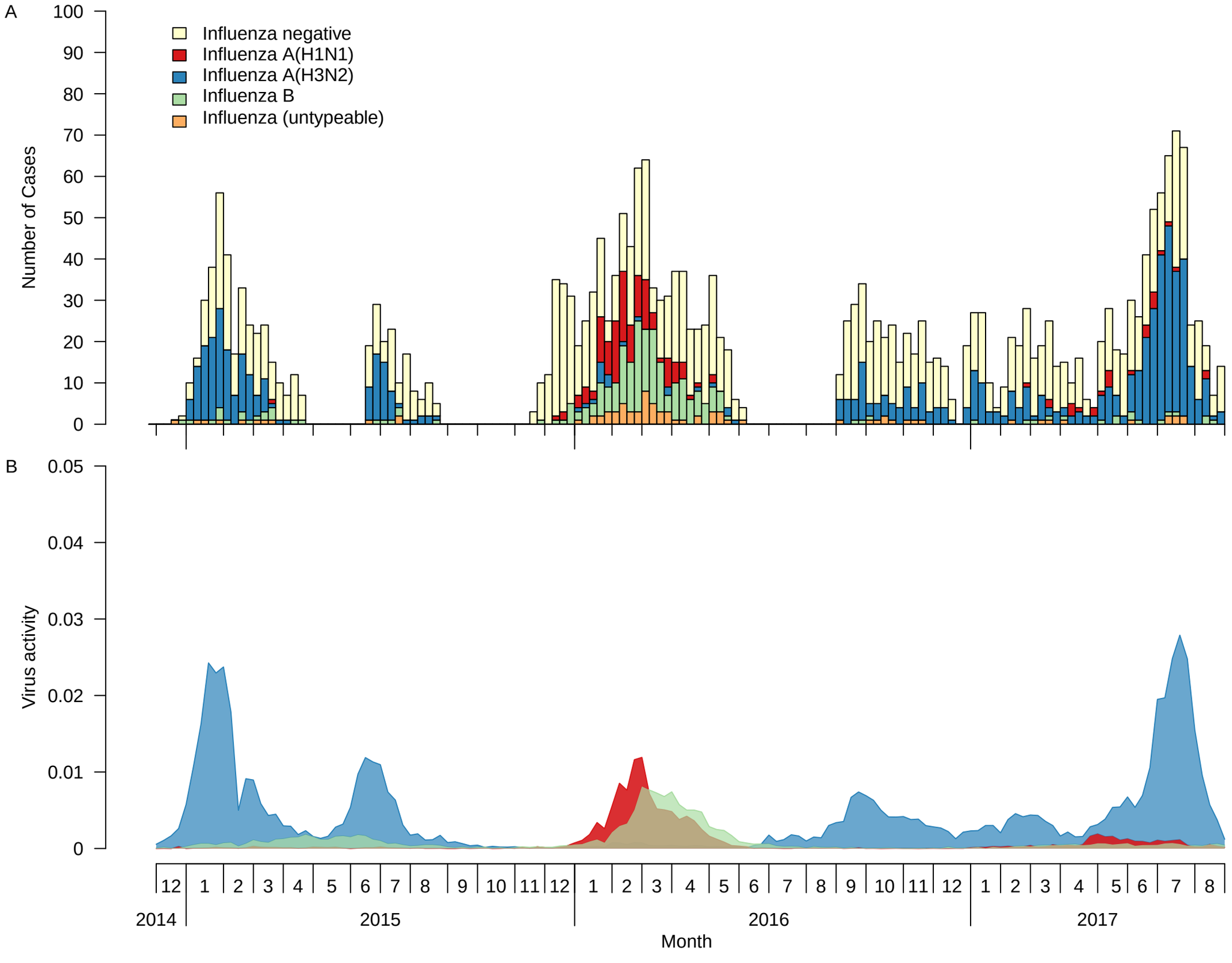
Influenza strain	WHO recommended northern hemisphere vaccine strain	Epidemic strain
A(H1N1)	A/California/7/2009 (H1N1)pdm09-like virus (subclade 6B.1)	A/California/7/2009-like
A(H3N2)	A/Hong Kong/4801/2014 (H3N2)-like virus (clade 3C.2a)	A/Hong Kong/4801/2014-like
B/Yamagata	B/Phuket/3073/2013-like virus (clade 3)	B/Phuket/3073/2013-like
B/Victoria	B/Brisbane/60/2008-like virus (clade 1A)	B/Brisbane/60/2008-like

Table 4. Estimated vaccine effectiveness (VE) in each age group against PCR-confirmed influenza virus infection by influenza type and subtype.

Virus	Any influenza	Influenza A	A(H1N1)	A(H3N2)	Influenza B	B/Yamagata	B/Victoria
No. of test-positive/Total	1112/2552	870/2310	147/1587	654/2094	224/1664	119/1559	94/1534
Age (years)	VE% [a] (95% CI)	VE% (95% CI)	VE% (95% CI)	VE% (95% CI)	VE% (95% CI)	VE% (95% CI)	VE% (95% CI)
0.5-5	35.5 (-46.9, 71.7)	34.6 (-65.5, 74.1)	67.0 (-71.3, 93.6)	Not available[b]	Not available[b]	Not available[b]	Not available[b]
6-17	35.8 (-21.5, 66.0)	37.9 (-27.6, 69.8)	Not available[b]	36.9 (-42.1, 72.0)	42.0 (-81.3, 81.4)	Not available[b]	Not available[b]
18-49	38.6 (0.6, 62.1)	26.3 (-21.7, 55.4)	48.2 (-44.8, 81.5)	25.6 (-38.3, 60.0)	77.4 (1.9, 94.8)	79.9 (-52.2, 97.3)	Not available[b]
50-64	68.5 (27.5, 86.3)	56.3 (-4.1, 81.7)	Not available[b]	46.9 (-31.1, 78.5)	Not available[b]	Not available[b]	Not available[b]
≥65	22.1 (-51.4, 59.9)	Not available[b]	Not available[b]	Not available[b]	Not available[b]	Not available[b]	Not available[b]

[a] Vaccine effectiveness = 100*(one minus adjusted odds ratio [the odds of vaccination among influenza-positive cases versus influenza-negative cases]) using conditional logistic regression, matched by calendar time (two-week interval) and adjusted for age, age squared, sex, and presence of chronic medical illness.

[b] VE estimate not presented due to wide 95% confidence interval


A
B
Influenza negative
Influenza A(H1N1)
Influenza A(H3N2)
Influenza B
Influenza (untypeable)
Number of Cases
Virus activity
0
10
20
30
40
50
60
70
80
90
100
0.01
0.02
0.03
0.04
0.05
12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8 9 10 11 12 1 2 3 4 5 6 7 8
2014
2015
2016
2017
Month