MAJOR ARTICLE

Influenza vaccine effectiveness against influenza A(H3N2) hospitalizations in children in Hong Kong in a prolonged season, 2016/17

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BRIEF SUMMARY

We conducted a test-negative study in children in three hospitals in Hong Kong in 2016/17. We estimated that influenza vaccine effectiveness against hospitalization due to influenza A(H3N2) was 39.7% (95% CI: 14.7, 57.3%).

Abstract

Background: Influenza A(H3N2) viruses circulated for 12 consecutive months in Hong Kong in 2016-2017, peaking in late June and July 2017. The objective of our study was to estimate the effectiveness of influenza vaccination in preventing hospitalizations in children in Hong Kong.

Methods: We conducted a test-negative study between September 1 2016 and August 31 2017, enrolling children 6 months to 17 years of age hospitalized for an acute respiratory infection. Influenza was diagnosed by PCR on nasopharyngeal aspirates.

Results: We enrolled 5514 children, including 3608 children between 6 months to 2 years, 1600 children 3-5 years, and 1206 children 6-17 years of age. Influenza-associated hospitalizations occurred throughout the study year but time of vaccination of these children was also wide-spread, from September 2016 to May 2017. Influenza vaccine effectiveness (VE) was 39.7% (95% CI: 14.7, 57.3%) against laboratory-confirmed influenza A(H3N2). In analyses stratified by time since vaccination, the VE against influenza A(H3N2) was 52.8% (17.1%, 73.2%) within 3 months of vaccination, and 31.2% (−6.6%, 55.6%) 4-6 months after vaccination.

Conclusions: Influenza vaccination was effective in preventing hospitalizations in children in Hong Kong.

Background

Hong Kong is a subtropical city in the Northern Hemisphere, on the south coast of China. In Hong Kong, influenza viruses circulate for the majority of each year, with peaks in activity most winters, and in other seasons in some years [1, 2]. Influenza vaccination is effective in reducing the risk of influenza virus illness and hospitalization [3-5]. In Hong Kong, individuals 6 months or older are recommended to receive influenza vaccination each year, and an annual campaign takes place each autumn and winter, using the northern hemisphere vaccine formulation. Priority groups include children aged 6 months to 11 years, older adults, pregnant women, healthcare workers, and persons with chronic medical problems [6].

Influenza vaccine effectiveness (VE) can vary from year to year due to many factors including timing of season, change of circulating viruses and population characteristics [7, 8]. Previously we have documented influenza VE in preventing hospitalization in children in Hong Kong using the test negative design [1, 4, 9]. This study assessed the VE against influenza in preventing hospitalization in Hong Kong children for 2016-17 influenza season.

Methods

Study design

In this current study, we used the test-negative design [8, 10-12], and children were recruited when they were admitted to Queen Mary Hospital, Yan Chai Hospital and Princess Margaret Hospital between 1 September 2016 and 31 August 2017. All three hospitals shared the same study protocol. Children were enrolled if they were between

6 months and 17 years of age, and admitted to the general wards with fever ≥38°C and any respiratory symptom such as runny nose, cough or sore throat. We did not exclude children who were potentially at risk for severe diseases resulting from influenza infection. As previously described [1, 4, 9], nasopharyngeal aspirates were collected from all eligible children on admission and initially tested by direct immunofluorescence assay (DFA) and then subsequently tested by reverse transcription polymerase chain reaction (RT-PCR) for influenza A and B. The DFA testing was performed as part of patient management and infection control with a turnaround time of several hours, while the RT-PCR was the Gold Standard for infection with a turnaround time of several days. Patients who tested positive for influenza A or B by RT-PCR were considered as cases and those testing negative were considered as controls.

Research personnel obtained influenza vaccination history including the month and year of influenza vaccination, from the parents or caretakers using a standardized questionnaire. Clarification of information included checking vaccination record and contacting private practitioners who administered the vaccine. Children were considered vaccinated if they received the influenza vaccination since September 2016 (when the 2015/16 influenza vaccine became unavailable) with appropriate dosage according to the Advisory Committee on Immunization Practices two weeks prior to admission [13]. Those who had received vaccine less than 2 weeks of admission or had received only 1 dose out of 2 doses were considered as unvaccinated. The vaccines used during our study period were the Northern hemisphere formulation of trivalent and quadrivalent inactivated influenza vaccines.

Ethical approval

The study protocol was approved by the Institutional Review Board of the University of Hong Kong/Hospital Authority of Hong Kong West Cluster and that of the Kowloon West Cluster Research Ethics Committee.

Statistical analysis

We employed the same analytic methods used in our previous studies [1, 4, 9]. We used conditional logistic regression models for influenza infection compared to vaccination status, adjusted for age and age squared and matched by calendar week. VE was calculated as one minus the adjusted odds ratio of vaccination between cases and controls, multiplied by 100%. We estimated VE against influenza A or B overall, by type/subtype, for any ages, and stratified by 3 age groups (6m-2y, 3-5y and 6-17y).

To examine potential changes of VE with time, we further divided the whole study period into 2 and 3 phases and estimated VE for different phases. For the 2-phase analysis, the early phase was defined as 1st September 2016 to 28th February 2017, and the late phase defined as 1st March to 31st August 2017. For the 3-phase analysis, phase I was defined as 1st September to 31st December 2016, phase II was defined as 1st January to 30th April 2017 and phase III was defined as 1st May to 31st August 2017. We also performed separate VE analysis by intervals since vaccination, comparing VE for vaccinated ≥14 days (0.5 month) and ≤3 months verses VE for vaccinated ≥4 months and ≤6 months.

Results

Between 1st September 2016 and 31st August 2017, we recruited 5514 children hospitalized for an acute respiratory infection, 912 (16.5%) of them were for influenza A or B with 707 (77.5%) positive for influenza A(H3N2) (Table 1). Time of vaccination was wide-spread, from September 2016 to May 2017 (Supplementary Figure S1). Influenza-associated hospitalizations occurred throughout the study year, increasing after January 2017, continuing to rise in March through May, and peaking in late June and July (Figure 1). More influenza positive cases (53.9%) were observed in phase III ($p<0.001$) (Table 1). The vaccination coverage obtained from test-negative patients was 9.7%, higher than 5.3% among test-positive patients ($p<0.001$). Receipt of influenza vaccine among the test-negative group was consistently statistically significantly higher than that of the test-positive group except in phase III (Table 1).

VE was 46.8% (95% CI: 27.0%, 61.2%) against all influenza A or B hospitalization (Figure 2) and 39.7% (95% CI: 14.7%, 57.3%) influenza A(H3N2) associated amongst children of all ages (Figure 3A & B). Children between 3-5 years had a higher VE point estimate against influenza A(H3N2): 53.3% (95% CI:16.3%, 74.0%) (Figure 3A & B). VE against influenza A(H3N2) hospitalization decreased with calendar time for both overall influenza or influenza A (H3N2) regardless of how different phases were defined (Figure 3 A & B, Figure 4A & B). Point estimates of VE against influenza A or B hospitalization decreased from 84.3% (95% CI: -16.9%, 97.9%) in phase I to 50.5% (95% CI:24.0%, 67.8%) in phase II to 37.6% (95% CI: -2.2%, 61.9%) in phase III although the pattern was sustained among children aged 3-5 years (Figure 4B). Likewise, point estimates of VE against influenza A(H3N2) hospitalization decreased from 83.4% (95% CI: -23.5%, 97.8%) for phase I to 41.2% (95% CI: 4.9%, 63.7%) for

phase II and 32.4% (-14.9%, 60.2%) for phase III, (Figure 3B). The effect of vaccination interval on VE in different age groups was examined (Figure 5). Vaccination within 3 months was associated with better protection compared with vaccination between 4 to 6 months, consistently among age groups, albeit with overlapping confidence intervals.

Discussion

Influenza circulation in Hong Kong in 2016-17 was year-round, with the predominance of H3N2, leading to persistent paediatric hospitalization from autumn 2016 to summer 2017, peaking in late June and July. VE against hospitalization for influenza A(H3N2) was 39.7% (95% CI: 14.7%, 57.3%) and comparable to interim VE reported in the US where the estimates were 53% (95% CI: 16, 74%) and 23% (95% CI: -43%, 59%) for patients 6 months- 8 years and 9-17 years, respectively [14], and interim VE from Europe in outpatients 0-14 years was 44.1% (95% CI: -12.3%, 72.2%) [15]. As reported by a meta-analysis, pooled VE estimate against A(H3N2) was 56% (95% CI 28, 55%) for the paediatric age groups [7], higher than overall VE (39.7%; 95% CI: 14.7%, 57.3%) in our study but comparable to VE estimated for early phase (60.0%; 95% CI: 21.4%, 79.6%) (Figure 3A), although most other reports included outpatients whilst our subjects were inpatients. We noted that in a prolonged season VE may change depending on how the phases are defined (Figure 3A & B, Figure 4A & B) and early VE estimates may overestimate overall VE. When further stratified by age, we found fairly similar effectiveness by age with slightly higher point estimates in younger children (Figure 2, Figure 3). Despite a very prolonged season and late peaking in Hong Kong, the VEs estimated were comparable with that reported in other parts of the world. This might be because despite official recommendation for vaccination in the autumn, the

children received vaccination late throughout the season through to May 2017 (Supplementary Figure S1) as parents became concerned as the year progressed.

Waning of influenza VE especially with influenza A(H3N2) during the season have been reported from areas with one winter influenza season lasting up to 4 or 5 months [16-20]. An advantage of our study is the almost year-round activity of influenza plus vaccination throughout the year in the study year, allowing us to identify some evidence consistent with waning protection in a very prolonged and late peaking influenza season. Waning in VE has been reported elsewhere, for example a study in the US estimated that VE against influenza A(H3N2) decreased by around 7% per month with increasing time since vaccination, and was more pronounced among persons who had been vaccinated in prior years than in those who had not [17]. In Europe, a study reported VE for all ages declined from around 50% to close to 0% within around 4 months after vaccination [18]. VEs documented in an early or interim analysis would have overestimated the final overall VE in this year with prolonged and late peaking influenza A(H3N2) activity. There are two possible mechanisms for waning in VE. First, antibody titers rise within 2-4 weeks of vaccination and then gradually decline over time, and this decline is likely to be associated with gradually declining protection. Second, circulating viruses may drift antigenically as the season progresses. Genetically drifted H3N2 influenza A viruses, specifically the 3C.2a1 subclusters, have been reported over time during the 2016/17 season in Canada and Europe, and were associated with poorer protection from the 2016/17 NH vaccine strain [21, 22].

We did not perform variant analysis in this data. However, we observed that point estimates of VE were higher within 3 months of vaccination and decreased as time since

vaccination increased within the 6 months' time-frame (Figure 5). Waning of VE in the late phases of the season was least observed in the 3-5 year group (Figure 3 and Figure 4). However, some degree of waning was observed with longer interval since vaccination: the most significant protection seen at 14 days to 3 months after vaccination: and 52.8% (95% CI: 17.1%, 73.2%) for influenza A(H3N2) and reduced to 31.2% (-6.6%, 55.6%) in the 4 to 6 months after vaccination (Figure 5). Taken together, and noting that test-negative children in this age group had significantly higher vaccination rates than those who tested positive throughout all phases of the study, the observation of sustained VE during the whole study year in this age group was likely due to higher vaccination rate later in the year when influenza activity was highest. Decreased immunity therefore appeared to play an important role in decreased VE over time.

Our findings here add to the increasing discussion of the best timing for influenza vaccination and if more than one dose per year is needed to provide prolonged protection in a location with year-round activity and unpredictable timing of peaks in activity [1]. Vaccines that include a higher antigen content, adjuvanted, or are delivered intradermally are more immunogenic than traditional influenza vaccines, but it is not known if this will translate to more prolonged protection, and these enhanced vaccines are mostly used in older adults, not children [23].

Strengths of the study include our unique position to study VE during prolonged- and multi-season influenza circulation, ascertainment of month of vaccination in the history, and using molecular tests for influenza detection in all hospitalized children. Limitations include the lack of information on influenza vaccination in previous years

which may affect VE, and a lack of sequencing data to examine the issue of antigenic changes through the season.

In conclusion, we documented a modest VE for all influenza and influenza A(H3N2) with higher VE observed particularly in the early phase of the season and earlier after vaccination. We identified some evidence consistent with waning of VE within 6 months after vaccination. Decreased immunity appeared to play an important role in VE.

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Potential conflicts of interest

BJC has received research funding from Sanofi Pasteur for a study of influenza vaccine effectiveness. The authors report no other potential conflicts of interest.

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Table 1. Comparison of cases test-positive for any influenza virus and test-negative cases in Hong Kong, September 2016 to August 2017

Characteristic	Test-positive (n=912) N (%)	Test-negative (n=4602) N (%)	p-value [a]
Age group			
6m-2y	341 (37.4%)	2367 (51.4%)	<0.001
3-5y	298 (32.7%)	1302 (28.3%)	
6-17y	273 (29.9%)	933 (20.3%)	
Female	431 (47.3%)	2028 (44.1%)	0.083
By calendar time			
Phase I (Sep 2016 to Dec 2016)	131 (14.4%)	1349 (29.3%)	<0.001
Phase II (Jan 2017 to Apr 2017)	289 (31.7%)	1778 (38.6%)	
Phase III (May 2017 to Aug 2017)	492 (53.9%)	1475 (32.1%)	
Receipt of influenza vaccination [b]			
Overall	48 (5.3%)	447 (9.7%)	<0.001
By 3 phases			
Phase I	1 (0.8%)	63 (4.7%)	0.039
Phase II	26 (9.0%)	287 (16.1%)	0.001
Phase III	21 (4.3%)	97 (6.6%)	0.063
By age group			
6 months – 2 years	15 (4.4%)	169 (7.1%)	0.082
3 – 5 years	15 (5.0%)	188 (14.4%)	<0.001

6 – 17 years	18 (6.6%)	90 (9.6%)	0.148

[a] p-values estimated by chi-squared tests or Fisher's exact test whenever appropriate

[b] Receipt of influenza vaccination defined as receipt of an quadrivalent or trivalent inactivated influenza vaccine with an age-appropriate schedule within 6 months prior admission.

FIGURE LEGENDS

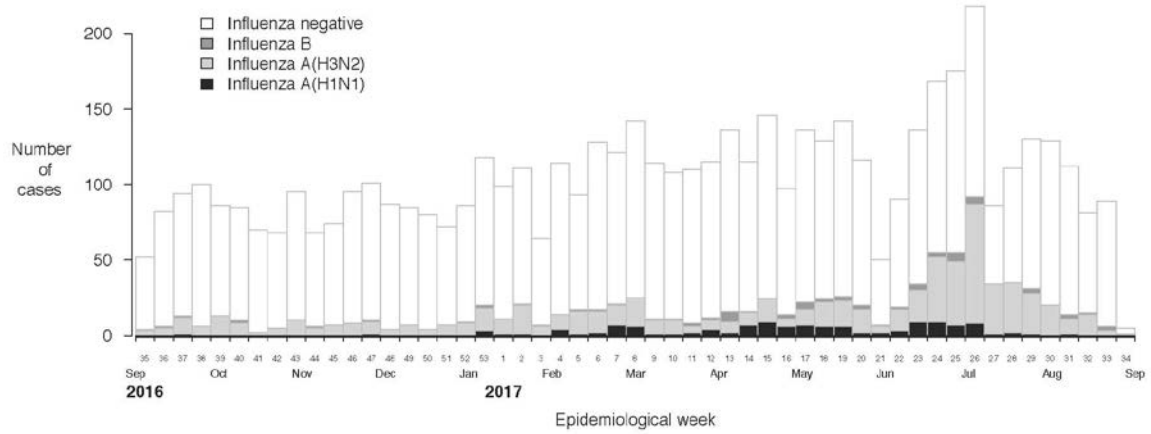

Figure 1. Timeline of recruitment of cases testing positive or negative for influenza virus by type/subtype in Hong Kong, September 2016 to August 2017.

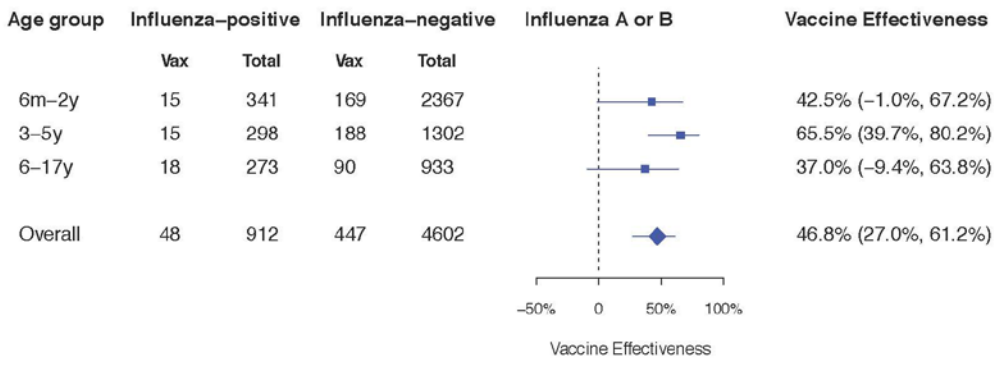

Figure 2. Estimated influenza vaccine effectiveness against influenza A or B among children in Hong Kong by age group, September 2016 to August 2017.

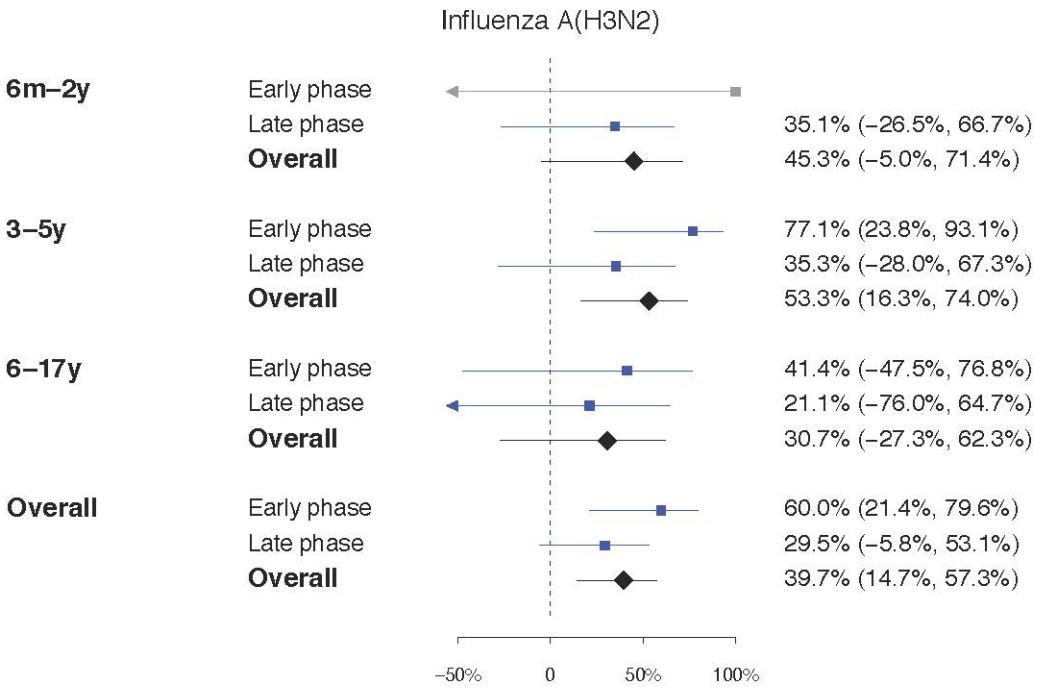

Figure 3A. Estimated influenza vaccine effectiveness against influenza A(H3N2) among children in Hong Kong by age group and phase of hospitalization), September 2016 to August 2017 (Early phase was defined as September 1st 2016 to February 28th 2017; Late phase was defined as March 1st to August 31st 2017).

Results for confidence intervals wider than 500% were not shown.

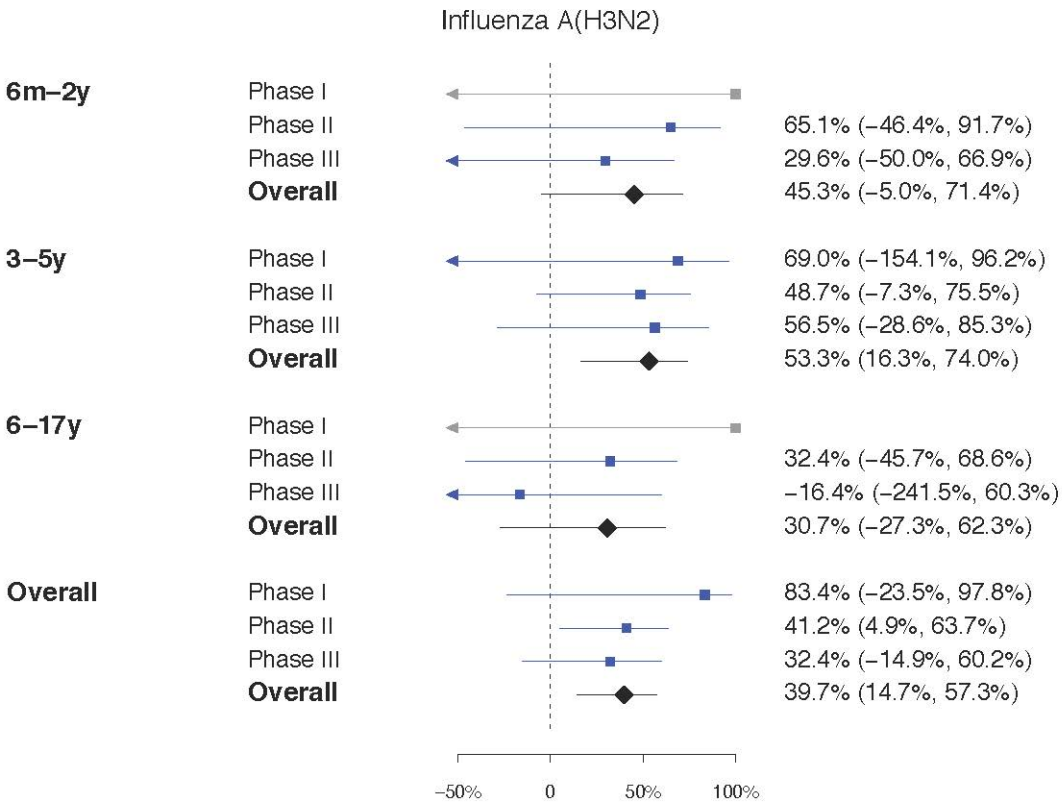

Figure 3B. Estimated influenza vaccine effectiveness against influenza A(H3N2) among children in Hong Kong by age group and phase of hospitalization, September 2016 to August 2017 (Phase I was defined as September 1st to December 31st 2016; Phase II was defined as January 1st to April 30th 2017; Phase III was defined as May 1st to August 31st 2017).

Results for confidence intervals wider than 500% were not shown.

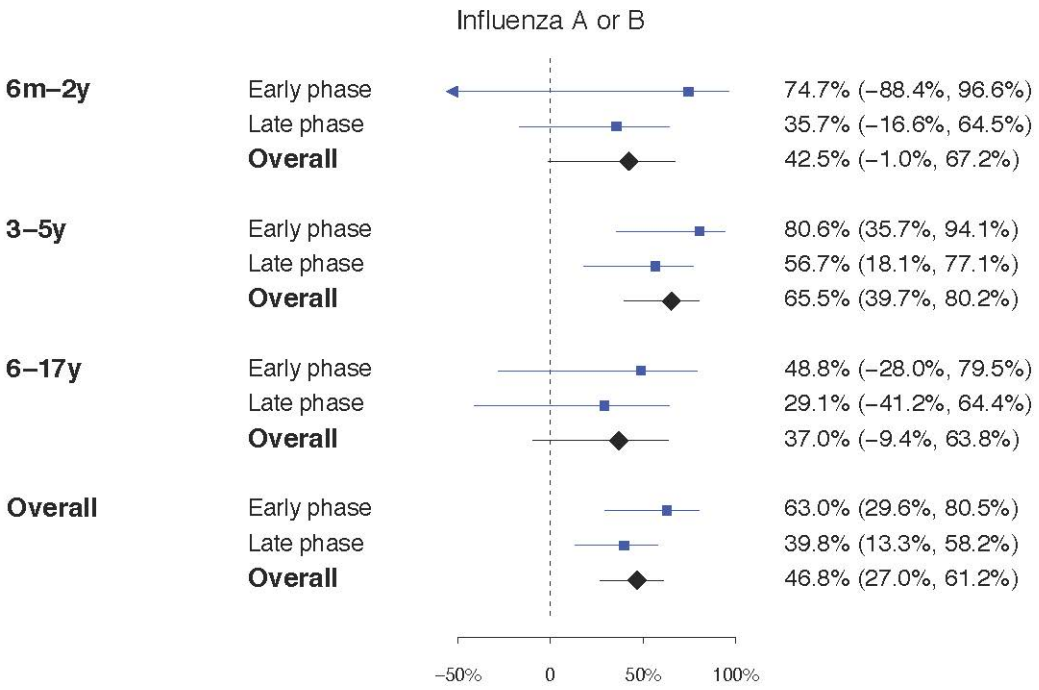

Figure 4A. Estimated influenza vaccine effectiveness against influenza A or B among children in Hong Kong by age group and phase of hospitalization), September 2016 to August 2017 (Early phase was defined as September 1st 2016 to February 28th 2017; Late phase was defined as March 1st to August 31st 2017).

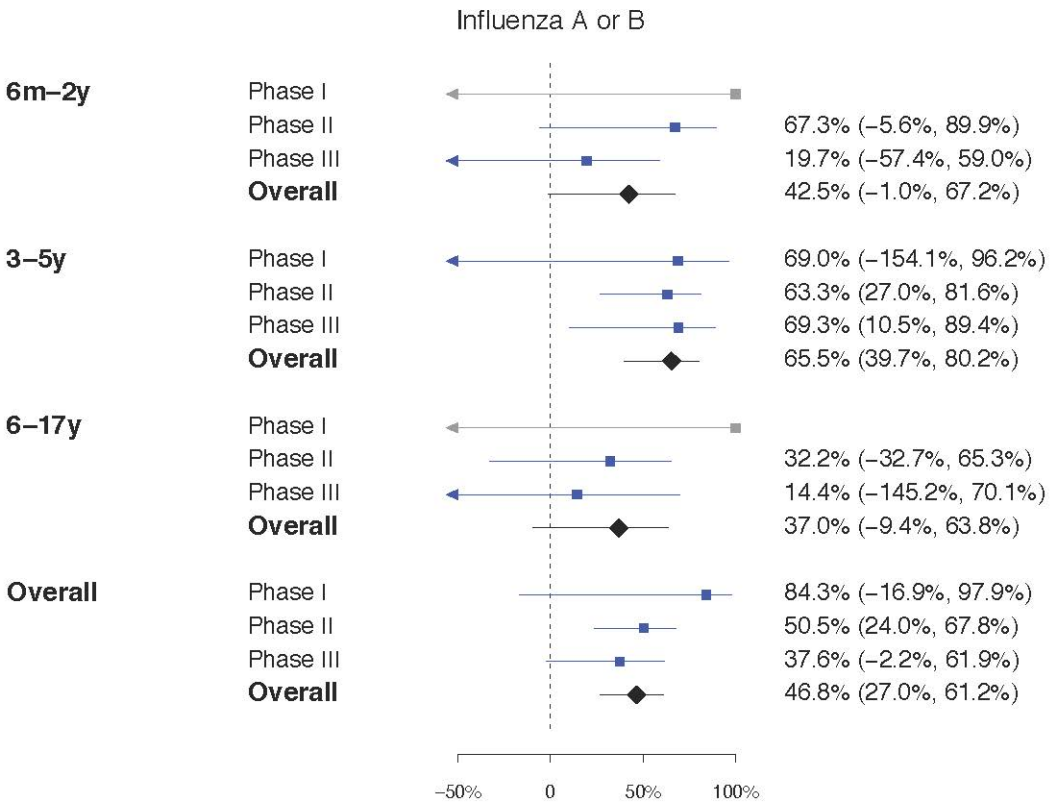

Figure 4B. Estimated influenza vaccine effectiveness against influenza A or B among children in Hong Kong by age group and phase of hospitalization, September 2016 to August 2017 (Phase I was defined as September 1st to December 31st 2016; Phase II was defined as January 1st to April 30th 2017; Phase III was defined as May 1st to August 31st 2017).

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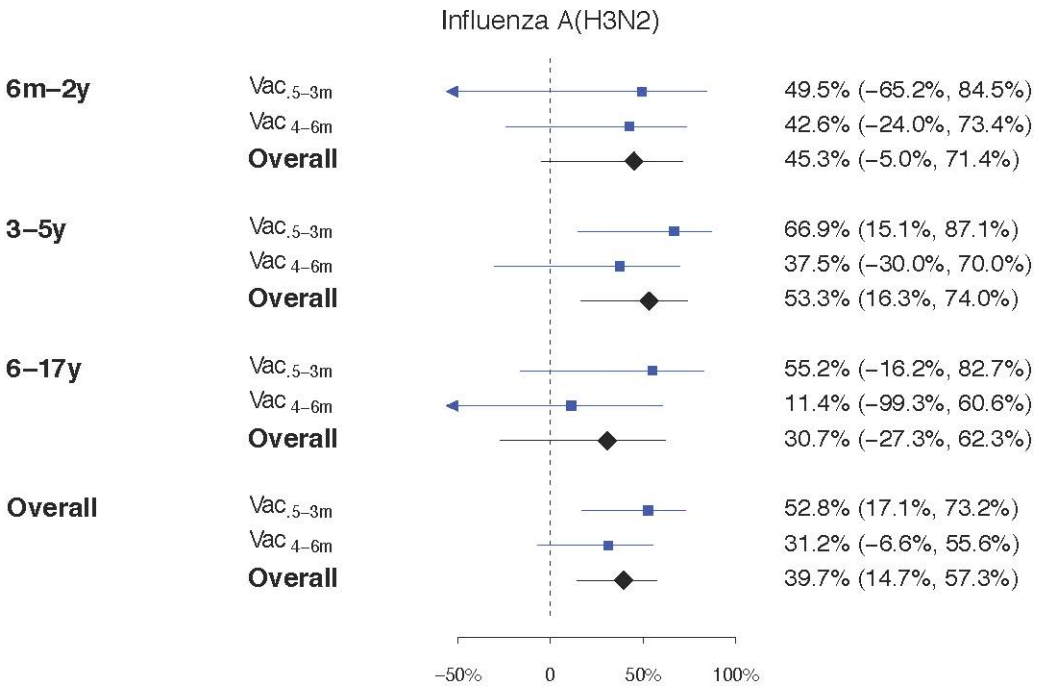
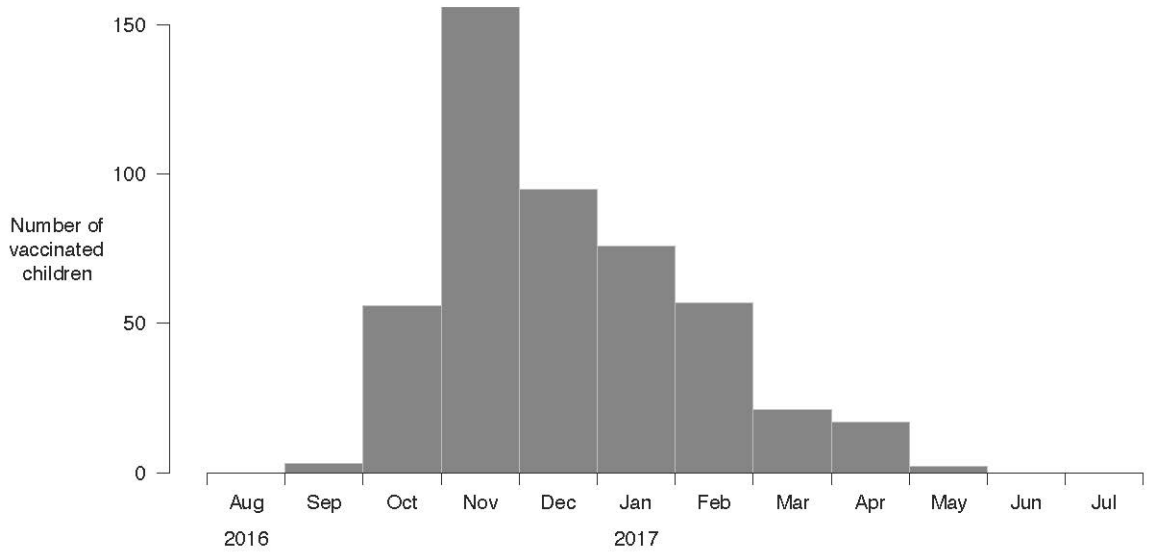


Figure 5. Estimated influenza vaccine effectiveness against influenza A(H3N2) among children in Hong Kong by age group and interval since vaccination (vaccinated from 14 days to 3 months versus 4 to 6 months), September 2016 to August 2017.



Supplementary Figure S1: Month and year of influenza vaccination in 495 children that were hospitalized for an acute respiratory infection between 1st September 2016 and 31st August 2017 and who had reported receipt of influenza vaccination.