Protective Efficacy Against Pandemic Influenza of Seasonal Influenza Vaccination in Children in Hong Kong: A Randomized Controlled Trial


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(See the Editorial Commentary by Monto and Ohmit, on pages 703–5.)

**Background.** The efficacy of seasonal influenza vaccination against 2009 pandemic influenza A(H1N1) remains unclear.

**Methods.** One child aged 6–17 years in each of 796 households was randomized to receive 2009–2010 seasonal trivalent inactivated influenza vaccine (TIV) or saline placebo between August 2009 and February 2010. Households were followed up with serology, symptom diaries, and collection of respiratory specimens during illnesses. The primary outcomes were influenza infection confirmed by reverse-transcription polymerase chain reaction (RT-PCR) or a ≥4-fold rise in serum antibody titer measured by hemagglutination inhibition assay.

**Results.** Receipt of TIV led to 8–13-fold mean geometric rises in antibody titers against seasonal A and B viruses, but only 1.5-fold mean geometric rises against the pandemic A(H1N1) virus that was not included in the vaccine. Children who received TIV had a reduced risk of seasonal influenza B confirmed by RT-PCR, with a vaccine efficacy estimate of 66% (95% confidence interval [CI], 31%–83%). Children who received TIV also had a reduced risk of pandemic influenza A(H1N1) indicated by serology, with a vaccine efficacy estimate of 47% (95% CI, 15%–67%).

**Conclusions.** Seasonal TIV prevented pandemic influenza A(H1N1) and influenza B infections in children. Pandemic A(H1N1) circulated at the time of vaccination and for a short time afterward with no substantial seasonal influenza activity during that period. The potential mechanism for seasonal TIV to provide protection, possibly short lived, for children against pandemic A(H1N1) infection despite poor cross-reactive serologic response deserves further investigation.

**Clinical Trials Registration.** NCT00792051.
marginally increased cross-reactive antibody to the pH1N1 virus [3]. It was therefore thought that seasonal influenza vaccination would have low effectiveness against pH1N1. Estimates of seasonal vaccine efficacy against pH1N1 have varied substantially [4–16]. A monovalent pH1N1 vaccine was distributed in Hong Kong only in January 2010 at the end of the first wave of infections, and uptake of the vaccine in the general community was <1% [17].

After a pilot study in 2008–2009 [18], we conducted a large community-based, randomized controlled trial in Hong Kong during the 2009–2010 influenza season. The aim of our study was to evaluate the efficacy of TIV for prevention of laboratory-confirmed influenza in children. The study was also designed to evaluate indirect benefits to household members, which will be reported separately.

METHODS

Recruitment and Follow-up of Participants
Invitation letters were distributed to participants of our previous studies, via schools, and to the families of members of a local birth cohort [19]. Eligible households included ≥1 child aged 6–17 years who did not have any contraindications against injection of TIV and was not immunocompromised. One eligible child from each household was randomized to receive either a single dose of TIV (0.5 mL of VAXIGRIP; Sanofi Pasteur) or placebo (0.5 mL of saline solution) intramuscularly. The 2009–2010 TIV used in our study included the strains A/Brisbane/59/2007(H1N1)-like, A/Brisbane/10/2007(H3N2)-like, and B/Brisbane/60/2008-like.

Serum specimens were collected from study subjects at baseline before vaccination (August 2009 through February 2010), 1 month after vaccination, after the winter/spring influenza season for 25% of subjects (“midstudy,” April–May 2010), and at the end of the follow-up period (August–December 2010), which would also capture influenza infections that occur during the summer in Hong Kong. Enrollment of subjects, vaccinations, and serum collections were performed by trained research staff at a study clinic. All subjects and their household contacts were instructed to record the presence of any systemic and respiratory symptoms in a symptom diary daily throughout the study. Telephone calls were made biweekly to monitor for any acute upper respiratory tract infections (URTIs). Households were also reminded to report any acute URTIs to the study hotline as soon as possible after illness onset. Home visits were triggered by the presence of any of the following 2 symptoms or signs: fever ≥37.8°C, C, chills, headache, sore throat, cough, presence of phlegm, coryza, or myalgia in any household member; visits were repeated at 3-day intervals until acute URTIs resolved. During home visits, pooled nose and throat swab samples were collected from all household members regardless of illness. Households were compensated with supermarket vouchers (and book tokens for children) worth US$65 for participation in the study, US$13 for each serum specimen provided and US$6.5 for each home visit.

Ethics
Proxy written consent from parents or legal guardians was obtained for the subjects who were all aged 17 years and younger, with additional written assent from those aged 8 to 17 years. The study protocol was approved by the Institutional Review Board of Hong Kong University.

Outcome Measures
The primary outcome measures were influenza virus infection confirmed by reverse-transcription polymerase chain-reaction (RT-PCR), or indicated by a ≥4-fold increase in antibody titer from after vaccination to the end of the study. Secondary outcomes included (1) acute respiratory illness (ARI) defined as fever ≥37.8°C, headache, sore throat, cough, myalgia [18], and (2) febrile ARI (FARI) defined as fever ≥37.8°C plus cough or sore throat [18, 20, 21]. We defined episodes of ARI and FARI as periods of ≥1 day when participants met the criteria for ARI or FARI, respectively, and episodes occurring within 7 days were merged together. RT-PCR-confirmed infections and illness episodes were analyzed for each subject from 14 days after vaccination until collection of the final serum specimen. Acute reactions were recorded by parents as none, mild, moderate, or severe for 4 days after vaccination.

Sample Size Justification
Assuming conservatively that 10% of subjects in the control arm would be infected with a prevalent influenza strain [22], inclusion of 800 subjects would have 75% power to detect a vaccine efficacy of ≥50%, with a 5% type I error rate. An unbalanced randomization scheme was proposed, where more subjects were included in the intervention arm to enhance acceptability.

Randomization, Allocation Concealment and Blinding
Randomization lists were prepared by a biostatistician (V. J. F). Eligible study participants were randomly allocated to the TIV or placebo group at a ratio of 3:2 using a random number generator (R software). A block-randomization sequence was generated, with randomly permuted block sizes of 5, 10, and 15.

Blinding of households and study nurses was achieved by identical repackaging of TIV/placebo into numbered syringes by a trained nurse not involved in vaccine administration. A research assistant who had no access to the randomization list allocated unique numbers to participating households based
on their order of attendance and these were subsequently matched to vaccine packages. Allocation of TIV/placebo was concealed to participating households, study nurses, and laboratory staff, and was revealed to investigators only after completion of follow-up.

**Laboratory Methods**

All serum specimens were tested for antibody responses to the vaccine strains A/Brisbane/59/2007(H1N1) and B/Brisbane/60/2008-like (Victoria lineage), the prevalent seasonal strain A/Perth/16/2009-like(H3N2), and the pandemic strain A/California/7/2009(H1N1) by hemagglutination inhibition assays using standard methods, as described elsewhere [18, 21]. The serum specimens were tested in serial doubling dilutions from an initial dilution of 1:10. Pooled nose and throat swab samples were tested by RT-PCR for influenza A and B using standard methods, as described elsewhere [18, 21].

**Statistical Analysis**

Fisher’s exact tests were used to compare risks of adverse reactions between children who received TIV and those who received placebo. To assess vaccine immunogenicity, χ² tests were used to compare the proportions of subjects with antibody titers ≥1:40 before and after vaccination between children who received TIV and those who received placebo, and Wilcoxon signed rank tests were used to compare ratios of pre- to postvaccination titers.

Poststudy and postvaccination antibody titers were compared to determine serologic evidence of infection during the study period. For the subset of subjects with midstudy serum specimens available, overall estimates of cumulative incidence of infection were compared with estimates based on poststudy versus midstudy and midstudy versus postvaccination titers. We used Poisson regression offset by the duration of follow-up to estimate the incidence rate ratio of confirmed influenza, ARI, and FARI in TIV or placebo recipients. Vaccine efficacy was estimated as 1 minus the incidence rate ratio. All analyses of study outcomes were performed under the principle of intention to treat [23]. We used multiple imputation with 10 imputations to account for a small amount of missing data [24]. Statistical analyses were conducted using R software (version 2.11.0; R Development Core Team).

**RESULTS**

Figure 1 shows the flow of subjects throughout the study. Subjects in the TIV and placebo groups had similar characteristics (Table 1). One subject withdrew from the study after randomization but before the intervention was administered, and 13 of the 795 subjects who received the intervention did not complete the study. Following the principle of intention to treat, we included all 796 subjects in the primary analyses.
Immune Response to Vaccine
A single dose of TIV led to substantial and statistically significant increases in antibody titers to seasonal influenza strains among study subjects (Table 2). There was no statistically significant difference in geometric mean rises in antibody titers to pH1N1 after receipt of TIV or placebo, whereas about half of the subjects had postvaccination titers of ≥1:40 against pH1N1.

Reported Reactogenicity
Myalgia and local reactions, including swelling, redness, and pain or soreness at the injection site, were more frequently reported after receipt of TIV (Supplementary Table 1). Only a small number of participants reported severe systemic or local adverse reactions. No serious adverse events were reported after vaccination.

Incidence of Influenza
Vaccinations were administered toward the end of the first wave of pH1N1. During the winter-spring influenza season in early 2010 there was circulation of pH1N1 and seasonal influenza B, whereas the summer influenza season occurred slightly later than in previous years [18, 25, 26] and was dominated by seasonal influenza A(H3N2; Figure 2).

A total of 757 ARI episodes were reported by subjects during the follow-up period, and we were able to confirm 56 influenza A and B infections by RT-PCR on 477 swab samples collected during 229 episodes. We were also able to confirm 2 pH1N1 infections from 738 swab samples collected from subjects when a household contact reported illness but the subject was not ill. Among the 58 confirmed influenza A and B infections, the most common symptom was cough (81%), and 72% of the confirmed infections were associated with a febrile illness (Supplementary Table 2). Fever, ARI and FARI were reported more commonly by individuals with confirmed seasonal influenza A(H3N2) and B than pH1N1.

Vaccine Efficacy
Subjects who received TIV had significantly lower risk of seasonal B infection confirmed by RT-PCR or serology, with vaccine efficacy estimates of 66% (95% confidence interval [CI], 31%–83%) and 83% (95% CI, 46%–95%) respectively (Table 3). Subjects who received TIV also had significantly lower incidence rates of pH1N1 infection by serology, with vaccine efficacy of 47% (95% CI, 15%–67%). Stratifying subjects by month of entry to the study, we did not observe statistically significant differences in vaccine efficacy against pH1N1 (data not shown). There were no statistically significant differences in incidence rates of seasonal influenza A

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### Table 1. Baseline Characteristics of Children Who Received Trivalent Inactivated Influenza Vaccine or Placebo and Their Household Contacts

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Missing Data</th>
<th>TIV (n = 479)</th>
<th>Placebo (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study subjects, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0</td>
<td>231 (48)</td>
<td>141 (44)</td>
</tr>
<tr>
<td>Age group, years</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–8</td>
<td></td>
<td>170 (35)</td>
<td>104 (33)</td>
</tr>
<tr>
<td>9–11</td>
<td></td>
<td>152 (32)</td>
<td>107 (34)</td>
</tr>
<tr>
<td>12–17</td>
<td></td>
<td>157 (33)</td>
<td>106 (33)</td>
</tr>
<tr>
<td>Received influenza vaccination for 2008–2009 season</td>
<td>24</td>
<td>119 (26)</td>
<td>90 (29)</td>
</tr>
<tr>
<td>Households</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Household members, mean (SD), No.</td>
<td>0</td>
<td>3.8 (1.0)</td>
<td>3.8 (1.0)</td>
</tr>
<tr>
<td>Flat size, mean (SD), square feet</td>
<td>7</td>
<td>519 (229)</td>
<td>516 (263)</td>
</tr>
</tbody>
</table>

Abbreviations: SD, standard deviation; TIV, trivalent inactivated influenza vaccine.

* Including 1 child aged 5 years, 356 days.

### Table 2. Immunogenicity of 2009–2010 Seasonal Trivalent Inactivated Influenza Vaccine Against Seasonal and Pandemic Influenza Strains

<table>
<thead>
<tr>
<th>Virus</th>
<th>TIV (n = 479)</th>
<th>Placebo (n = 317)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seasonal influenza A(H1N1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody titer ≥1:40, %</td>
<td>Postvaccination 56</td>
<td>52</td>
<td>.34</td>
</tr>
<tr>
<td></td>
<td>Postvaccination 94</td>
<td>54</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>GMT increase after vaccination</td>
<td>Postvaccination 10.0</td>
<td>1.2</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Seasonal influenza A(H3N2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody titer ≥1:40, %</td>
<td>Postvaccination 58</td>
<td>64</td>
<td>.08</td>
</tr>
<tr>
<td></td>
<td>Postvaccination 96</td>
<td>64</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>GMT increase after vaccination</td>
<td>Postvaccination 13.2</td>
<td>1.1</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Seasonal influenza B/Brisbane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody titer ≥1:40, %</td>
<td>Postvaccination 15</td>
<td>13</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>Postvaccination 70</td>
<td>15</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>GMT increase after vaccination</td>
<td>Postvaccination 7.9</td>
<td>1.0</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Pandemic influenza A(H1N1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibody titer ≥1:40, %</td>
<td>Postvaccination 39</td>
<td>37</td>
<td>.59</td>
</tr>
<tr>
<td></td>
<td>Postvaccination 51</td>
<td>47</td>
<td>.38</td>
</tr>
<tr>
<td>GMT increase after vaccination</td>
<td>Postvaccination 1.5</td>
<td>1.3</td>
<td>.18</td>
</tr>
</tbody>
</table>

Abbreviations: GMT, geometric mean titer; TIV, trivalent inactivated influenza vaccine.

* P values were calculated with χ² and Wilcoxon signed rank tests. Antibody titers <1:10 were imputed as 1:5.
by RT-PCR or serology, or in incidence rates of ARI or FARI.

In the subset of subjects who provided midstudy serum specimens, estimation of cumulative incidence of infection in either winter or summer influenza seasons were 1.4 to 2 times higher than overall estimates based only on the baseline and poststudy serology (Supplementary Table 3). In this subset the estimate of vaccine efficacy against pH1N1 was 59% (95% CI, 20%–79%) over the winter 2009–2010 influenza season when pH1N1 circulated.

No substantial antibody cross-reactivity between seasonal and pandemic influenza was observed. None of 8 subjects

![Timeline of subject recruitment and follow-up in 2009–2010, compared with influenza virus detections in the reference laboratory for Hong Kong Island at Queen Mary Hospital. Seasonal influenza A(H1N1) viruses were not detected in Hong Kong after October 2009, apart from 1 detection in the public health reference laboratory (in 8802 specimens tested) in April 2010. Victoria-lineage strains predominated among the influenza B viruses detected, and Yamagata-lineage strains also circulated.](image)

**Table 3. Incidence Rates per Person-Year of Infection of Laboratory-Confirmed Influenza by Reverse-Transcription Polymerase Chain Reaction and Serology, Acute Respiratory Illness, and Febrile Acute Respiratory Illness Among Study Subjects Who Received Trivalent Inactivated Influenza Vaccine or Placebo**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Incidence Rates per Person-Year (95% CI)</th>
<th>TIV (n = 479)</th>
<th>Placebo (n = 317)</th>
<th>(P^a)</th>
<th>Vaccine Efficacy(^a) (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By RT-PCR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pandemic A(H1N1)</td>
<td>0.02 (.01–.04)</td>
<td>0.02 (.01–.04)</td>
<td>.61</td>
<td>−.32</td>
<td>(−2.86 to .55)</td>
</tr>
<tr>
<td>seasonal A(H3N2)</td>
<td>0.01 (.00–.03)</td>
<td>0.01 (.00–.03)</td>
<td>.90</td>
<td>−.10</td>
<td>(−3.60 to .74)</td>
</tr>
<tr>
<td>Seasonal B</td>
<td>0.03 (.02–.05)</td>
<td>0.08 (.05–.12)</td>
<td>&lt;.01</td>
<td>.66</td>
<td>(.31–.83)</td>
</tr>
<tr>
<td><strong>By serology</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pandemic A(H1N1)</td>
<td>0.09 (.06–.14)</td>
<td>0.17 (.12–.24)</td>
<td>.01</td>
<td>0.47</td>
<td>(.15–.67)</td>
</tr>
<tr>
<td>Seasonal A(H3N2)</td>
<td>0.05 (.02–.09)</td>
<td>0.07 (.04–.12)</td>
<td>.21</td>
<td>0.35</td>
<td>(.28–.67)</td>
</tr>
<tr>
<td>Seasonal B/Brisbane</td>
<td>0.02 (.01–.06)</td>
<td>0.11 (.08–.16)</td>
<td>&lt;.01</td>
<td>0.83</td>
<td>(.46–.95)</td>
</tr>
<tr>
<td>ARI(^b)</td>
<td>1.02 (.93–1.12)</td>
<td>1.02 (.91–1.14)</td>
<td>.96</td>
<td>0.00</td>
<td>(.16 to .13)</td>
</tr>
<tr>
<td>FARI(^b)</td>
<td>0.43 (.37–.49)</td>
<td>0.50 (.43–.59)</td>
<td>.15</td>
<td>0.15</td>
<td>(.06 to .31)</td>
</tr>
</tbody>
</table>

Abbreviations: ARI, acute respiratory illness; CI, confidence interval; FARI, febrile ARI; RT-PCR, reverse-transcription polymerase chain reaction; TIV, trivalent inactivated influenza vaccine.

\(^a\) \(P\) values are estimated from Poisson regression models, and vaccine efficacy is estimated as \(1 – \text{incidence rate ratio}\).

\(^b\) ARI is defined as \(\geq2\) of the following: body temperature \(\geq37.8°C\), cough, sore throat, headache, and myalgia; FARI, as body temperature \(\geq37.8°C\) plus cough or sore throat.
with seasonal A(H3N2) infections and only 2 of 35 subjects with seasonal B infections confirmed by RT-PCR were found to have a ≥4-fold rise in antibody titer against pH1N1. Only a small proportion of subjects with ≥4-fold in antibody titer against pH1N1 also had a ≥4-fold rise in antibody against influenza A(H3N2; 12%) and B (13%).

We investigated the correlation between postvaccination antibody titer against pH1N1 and subsequent serologic evidence of pH1N1 infection. Comparing TIV and placebo recipients with postvaccination antibody titer ≤1:20, the cumulative incidence of pH1N1 infection was significantly lower among the TIV recipients (Supplementary Table 4). Incidence of pH1N1 was low among TIV and placebo recipients with higher post-vaccination antibody titers against pH1N1.

**DISCUSSION**

We report the results of a large randomized controlled trial of seasonal TIV during a period when pH1N1 as well as seasonal influenza viruses circulated in the community. We observed statistically significant protection in TIV recipients against influenza B, but nonsignificant protection against influenza A (H3N2; Table 3), similar to findings in our pilot study [18]. Suboptimal vaccine efficacy against A(H3N2) could have been associated with an imperfect match between the vaccine component and the circulating A/Perth/16/2009-like strains [18, 21], as well as the longer interval between receipt of TIV and circulation of A(H3N2; Figure 2). Despite evidence of protection against confirmed influenza, there was no evidence that TIV protected children against ARI or FARI (Table 3). A similar observation was reported in our pilot study [27].

Because antibody titers tend to rise substantially shortly after vaccination and then decline, serology can underestimate the cumulative incidence of influenza infection in vaccinees and bias estimates of vaccine efficacy [2, 28]. However receipt of seasonal TIV did not raise antibody titers against pH1N1 substantially (Table 2) and therefore the estimates of cumulative incidence of pH1N1 infections based on serology may be more accurate than for seasonal influenza. According to the serologic data, children who received TIV seemed to have greater protection against pH1N1 with vaccine efficacy 47% (95% CI, 15%–67%; Table 3). Protection occurred despite poor serologic response induced by TIV against pH1N1 (Table 2) [3, 29, 30], and was conferred even to TIV recipients who did not achieve postvaccination antibody titers of ≥1:40 (Supplementary Table 4).

There is ongoing controversy over the change in risk of pH1N1 associated with receipt of seasonal TIV. Some observational studies of seasonal TIV have reported evidence of protection against illness associated with pH1N1 [4–6], whereas other studies have found no change in risk of illness associated with pH1N1 [7–14]. However, observational studies in Canada and Japan reported that receipt of seasonal TIV was associated with an increased risk of illness associated with pH1N1 infection [15, 16]. In our own pilot study in Hong Kong in 2008–2009, TIV in winter 2008–2009 was associated with reduced seasonal influenza infections in spring 2009 but increased pH1N1 infection in autumn 2009 [18], and we hypothesized that the effect was due to immunity against pH1N1 conferred by seasonal influenza infections [31–37]. In the present study pH1N1 circulated during and immediately after the vaccination period (Figure 2) and therefore we would not expect immunity associated with seasonal influenza infections to play any role in changing the risk of pH1N1.

We can speculate on 2 possible explanations for our findings, both of which deserve further investigation. First, the lack of apparent cross-reactive serologic responses against the novel pH1N1 virus [3, 29, 30] may underestimate a true protective effect of TIV. The criterion used for seasonal vaccine immunogenicity—that is, the assumption that a titer of ≥1:40 by hemagglutination inhibition is associated with 50% protection against seasonal influenza infection—is based on limited evidence, primarily from challenge studies in young adults [38], and may not apply to a novel virus. Moreover, it seemed during the pandemic that adults had some degree of protection against pH1N1 as indicated by low secondary infection risks in households of index cases with confirmed infection [21, 39], and low cumulative incidence of infection at a population level in those aged 30–50 years [40] despite very low seroprevalence of pH1N1 antibody against pH1N1 before the pandemic [18, 21, 40]. Second, TIV could have conferred temporary nonspecific protection against influenza, which waned over a shorter time frame than the protection against strains included in the vaccine, and protected TIV recipients against pH1N1 which circulated at the beginning of our study period (Figure 2). This would mirror the hypothesis of temporary immunity after infection [18, 41], and potential mechanisms worthy of further exploration would include cell-mediated or innate immune responses to TIV [42]. Recent studies have demonstrated antibodies binding to the stalk of the hemagglutinin that confer broad heterosubtypic immunity [43, 44]. If such antibodies are elicited after vaccination but are short lived, this may also explain the observations from our study.

Because vaccination was carried out in the period after the peak of the first wave of pH1N1 in Hong Kong during which approximately 45% of school-age children were infected [40], it may be argued that the protective effect of TIV on pandemic infection was mediated by boosting low or waning levels of immunity in those already infected by the pandemic H1N1 virus. The observation of protection even in those who had no detectable antibody 1 month after vaccination makes this explanation less plausible (Supplementary Table 4).
There are some limitations to our study. First, given the circulation of pH1N1 and seasonal A(H3N2) viruses that were not included or antigenically well matched in the seasonal TIV that we used, our study had reduced power to confirm lower vaccine efficacy against these strains. Second, although 18% of participants had evidence of influenza infection indicated by serology during the study, we were able to confirm only 17% of those infections by RT-PCR (Table 3), which is similar to the proportion of influenza infections that could be confirmed by virologic testing in our pilot study and other community-based cohort studies [11, 18, 45]. Identification of acute URTIs and timely collection of respiratory specimens is difficult even with the intense follow-up in our cohort study, and confirming a greater proportion of infections remains an important consideration when designing community-based studies of influenza infection and transmission. A rise in antibody may be detectable even in those in whom the vaccine protects from disease though failing to protect from infection. On the other hand, serologic indication of infection via a 4-fold rise in antibody titer across a period of influenza activity may not have ideal sensitivity and specificity to identify influenza infections owing to variability in antibody titers over time for other reasons unrelated to influenza infection status, changes in cross-reactive antibody associated with other infections, and imperfect reliability or repeatability of serologic tests. Third, as discussed above, we may have failed to detect some seasonal influenza infections in children who received TIV [28].

In conclusion, receipt of seasonal TIV prevented seasonal influenza B and pH1N1 infections in school-age children. Apparent protection against pH1N1 was detected only by serology but not by RT-PCR (Table 3), and occurred despite the poor cross-reactive serologic responses induced by the seasonal TIV against pH1N1 (Table 2). These results may have implications for the use of seasonal influenza vaccines in future pandemics even if initial studies were to suggest that seasonal vaccine was not immunogenic against the novel virus. The importance of the timing of the seasonal vaccination in relation to pandemic activity was also highlighted in this study. However, the mechanism for protection remains unclear, and seasonal TIV might be less effective against influenza A subtypes that human populations have not previously been exposed to, such as H5N1 and H9N2.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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