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*Pediatrics* 2007;120;e553-e564; originally published online Aug 13, 2007; DOI: 10.1542/peds.2006-2836

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Trivalent Live Attenuated Intranasal Influenza Vaccine Administered During the 2003–2004 Influenza Type A (H3N2) Outbreak Provided Immediate, Direct, and Indirect Protection in Children

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Financial Disclosure: Dr Piedra has received grant support from MedImmune and Sanofi-Pasteur; served as a consultant to MedImmune, Novartis, and Roche; and has been a member of the speaker’s bureau for MedImmune. Dr Gaglani has received grant support from GlaxoSmithKline and MedImmune; served as a consultant to MedImmune; and has been a member of the speakers’ bureaus for Sanofi-Pasteur and MedImmune. Ms Herschler has been a member of the speaker’s bureau for MedImmune. Dr Glezen has served as a consultant to MedImmune, Roche, and Novartis and has been a member of the speaker’s bureau for MedImmune. All other authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

OBJECTIVE. Live attenuated influenza vaccine may protect against wild-type influenza illness shortly after vaccine administration by innate immunity. The 2003–2004 influenza A (H3N2) outbreak arrived early, and the circulating strain was antigenically distinct from the vaccine strain. The objective of this study was to determine the effectiveness of influenza vaccines for healthy school-aged children when administered during the influenza outbreak.

DESIGN/METHODS. An open-labeled, nonrandomized, community-based influenza vaccine trial was conducted in children 5 to 18 years old. Age-eligible healthy children received trivalent live attenuated influenza vaccine. Trivalent inactivated influenza vaccine was given to children with underlying health conditions. Influenza-positive illness was compared between vaccinated and nonvaccinated children. Medically attended acute respiratory illness and pneumonia and influenza rates for Scott and White Health Plan vaccinees were compared with age-eligible Scott and White Health Plan nonparticipants in the intervention communities. Herd protection was assessed by comparing age-specific medically attended acute respiratory illness rates in Scott and White Health Plan members in the intervention and comparison communities.

RESULTS. We administered 1 dose of trivalent live attenuated influenza vaccine or trivalent inactivated influenza vaccine to 6569 and 1040 children, respectively (31.5% vaccination coverage), from October 10 to December 30, 2003. The influenza outbreak occurred from October 12 to December 20, 2003. Significant protection against influenza-positive illness (37.3%) and pneumonia and influenza events (50%) was detected in children who received trivalent live attenuated influenza vaccine but not trivalent inactivated influenza vaccine. Trivalent live attenuated influenza vaccine recipients had similar protection against influenza-positive illness within 14 days compared with >14 days (10 of 25 vs 9 of 30) after vaccination. Indirect effectiveness against medically attended acute respiratory illness was detected in children 5 to 11 and adults 35 to 44 years of age.
CONCLUSION. One dose of trivalent live attenuated influenza vaccine was efficacious in children even when administered during an influenza outbreak and when the dominant circulating influenza virus was antigenically distinct from the vaccine strain. We hypothesize that trivalent live attenuated influenza vaccine provides protection against influenza by both innate and adaptive immune mechanisms.

THE CURRENT INFLUENZA vaccine recommendations (2006–2007) by the Advisory Committee on Immunization Prevention of the Centers for Disease Control and Prevention are prioritized on the basis of risk for serious influenza-associated complications.1 High-priority groups include individuals who are at risk for serious complications from influenza, health care workers with direct patient contact, and household contacts of infants who are younger than 6 months. This strategy has resulted in modest reduction in influenza-associated mortality and morbidity, but it has not controlled annual influenza epidemics. From 1979 to 2001, an annual average of 41 000 deaths were attributed to influenza.2 In the past 20 years (1976–1999), a significant increase has occurred in influenza-associated all-cause excess deaths.3 From 1990 to 1999, the annual number of influenza-associated all-cause deaths exceeded 50 000,3 and influenza-associated respiratory and circulation hospitalizations exceeded 380 000.4 Improved vaccination coverage for groups at risk for influenza complications has not resulted in a corresponding reduction in influenza-associated all-cause deaths and influenza-associated hospitalizations.1–4

Universal influenza vaccination of school-aged children is being considered as a complementary strategy to that currently advocated by the Advisory Committee on Immunization Prevention.5–7 Children have high rates of infection, medically attended illness, and hospitalization from influenza.8–16 Children play an important role in the transmission of influenza within families, schools, and communities.5,8,15 Intensity of respiratory illnesses in children early in the influenza season may be a harbinger of influenza-associated mortality in elderly adults.17 Vaccination with trivalent inactivated influenza vaccine (IIV-T) of ~80% of schoolchildren in a community has decreased respiratory illnesses in adults18 and excess deaths in the elderly.19 Vaccinating children in a child care facility reduced influenza-related morbidity among household members.20 In Russia, a mass vaccination campaign in children 3 to 17 years of age reduced significantly influenza-like illness in children and in unvaccinated elderly adults who lived in the home.21 In an ongoing study in central Texas, vaccination coverage of ~20% to 25% with trivalent live attenuated influenza vaccine (LAIV-T) in children 18 months to 18 years of age resulted in an 8% to 18% reduction against medi-
which is a major health care provider for those communities. A subset of SWC patients who were members of the Scott and White Health Plan (SWHP) provided defined populations for analysis. Age-specific rates for MAARI in the periods before, after, and during the influenza outbreak (2003–2004) were calculated for the intervention and comparison communities. The institutional review boards of Baylor College of Medicine and SWC approved this study. Informed consent was obtained from the legal guardians of enrolled participants.

**Participant Population**
Age-eligible healthy children received LAIV-T when they were 5 to 18 years of age, had residence in T-B, and had signed informed consent by the legal guardian or adult participant. Participants who were using nasal steroids were not excluded from receiving LAIV-T. Age-eligible children who had underlying risk conditions for influenza or who resided with immunocompromised household contact were offered IIV-T.

**Immunization**
At enrollment, all participants received a single dose of an FDA-approved influenza vaccine: 0.5 mL of LAIV-T by nasal spray or 0.5 mL of IIV-T by intramuscular injection. A second vaccine dose was offered 4 to 6 weeks after the first dose to children who were younger than 9 years and received the vaccine for the first time. The composition of both vaccines was A/New Caledonia/20/99 (H1N1)-like, A/Panama/2007/99 (H3N2)-like, and B/Hong Kong/330/2001-like.

**Community Demographics**
Demographic characteristics of the intervention and comparison communities have been previously described using US Census Bureau, Census 2000 data. The populations’ ethnic and racial distributions were comparable. Approximately 30% of the populations for the intervention and comparison communities were ≥19 years of age. The intervention communities had a higher proportion of individuals who were ≥65 years of age (14.7% vs 9.8%), and the comparison communities had a higher proportion of young adults who were 20 to 34 years of age (21.0% vs 32.4%). The average household size was larger in the comparison communities (2.63 vs 2.73). Population size using the US Census 2000 data were also determined using zip codes to define the intervention and comparison communities.

**Database**
Demographic information of LAIV-T and IIV-T recipients were entered and tracked in a computerized immunization registry as previously described. The SWC and SWHP clinical records were retrievable electronically for all of the SWCs of Central Texas. Demographic information and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for MAARI were extracted electronically from the SWHP administrative database.

**MAARI and Pneumonia and Influenza (P&I) Diagnosis Codes**
The ICD-9-CM codes for MAARI visits included those for otitis media and sinusitis (381–383, 461.x), upper respiratory tract illness (79.x, 460, 462–463, 465, 487.1), and lower respiratory tract illness (464.x, 466.x, 480.x–487.0, 490.x–496.x, 510.x–513.x, 515.x–516.x, 518.x, and 786.1). The ICD-9-CM codes for the Centers for Disease Control and Prevention defined P&I included those for lower respiratory tract illness and influenza (480.x–487.0). Each medical encounter had up to 6 ICD-9-CM codes. Medical encounters included those in clinics, emergency departments, and hospitals. Multiple entries on a single day were counted as 1 encounter. MAARI is a nonspecific case definition for influenza; P&I is a more specific clinical case definition for influenza.

**Influenza Surveillance**
Central Texas surveillance was performed as previously described. In brief, children and adults who presented to an SWC facility with a history of a febrile respiratory illness were candidates for a throat culture for virus isolation. Throat cultures that were obtained from the SWC surveillance sites were processed at the viral diagnostic laboratory of Scott and White Hospital in Temple, Texas. The outbreak or epidemic period was defined as the weeks with the most intense influenza activity accounting for 80% to 85% of all positive influenza cultures.

**Statistical Analysis**
SWHP membership status and census were determined from the SWHP database on December 31, 2003. Primary outcomes were direct and indirect effectiveness. Direct effectiveness of the influenza vaccines was evaluated in the intervention communities. It compared MAARI and P&I rates during the influenza epidemic outbreak in LAIV-T and IIV-T SWHP vaccinees compared with MAARI and P&I rates in age-eligible SWHP nonparticipants who had never received LAIV-T or had not received IIV-T in 2003. Indirect effectiveness compared age-specific MAARI rates during the influenza outbreak for SWHP members in the intervention and comparison communities. For assessment of effectiveness, point estimates and 95% confidence intervals (CIs) for the incidence rate ratios (RRs) were calculated. Effectiveness of the influenza vaccine was equal to (1 – RR) × 100%. Age-specific MAARI rates in the preepidemic and postepidemic periods were also co-
pared between SWHP members in the intervention and comparison communities to check for potential health care use bias.

RESULTS

LAIV-T and IIV-T Immunization of Children 5 to 18 Years of Age

The influenza immunization campaign started on October 10, 2003, and ended on December 30, 2003. We vaccinated 7609 children with an influenza vaccine; 6569 children received LAIV-T, and 1040 received IIV-T. Approximately 24% of the children whom we vaccinated (1608 LAIV-T and 193 IIV-T vaccinees) lived in areas outside the intervention communities. An additional 1097 children who were 5 to 18 years of age and living in the intervention communities received IIV-T from the SWC. Thus 4961 and 1944 children who were 5 to 18 years of age and resided within the zip code–defined intervention communities received LAIV-T and IIV-T vaccines, respectively.

A total of 897 (35%) of 2564 LAIV-T vaccinees who were 5 to <9 years of age were eligible for a second dose because of not having received a previous influenza vaccine. A total of 163 (18.2%) of the 897 LAIV-T vaccinees received a second vaccine dose. Seventy-five children received the second dose on December 20, 2003 (end of the influenza outbreak), or later. A total of 737 IIV-T vaccinees were 5 to <9 years of age. The number of IIV-T vaccinees who were eligible for a second dose was not known. Thirty-six IIV-T vaccinees received a second vaccine dose; 8 children received the second dose of IIV-T on December 20, 2003, or later.

A total of 52.4% of LAIV-T recipients were female, and 32.9% were of minority ethnicity or race (Hispanic: 20.1%; black: 6.9%; other: 5.9%). A total of 45.3% of IIV-T recipients were female, and 37.3% were of minority ethnicity or race (Hispanic: 20.4%; black: 11.5%; other: 5.4%). The racial/ethnic distribution in the intervention communities was 65.1% white, 18.8% Hispanic, 13.9% black, and 2.1% other. In the previous year, 2002–2003, LAIV-T was not available in the intervention or comparison communities; however, 3242 current LAIV-T vaccinees received LAIV-T as study participants 1 or more of the study years from 1998–1999 to 2001–2002.26

LAIV-T and IIV-T Coverage in Children 5 to 18 Years of Age in the Intervention Communities

In our previous report, we had estimated vaccination coverage on the basis of population data extracted from the US census 2000 for the T-B intervention communities.20 The true vaccination coverage may have been overestimated. We therefore estimated vaccination coverage for the 2003–2004 season on the basis of 3 methods: (1) population data from the US census 2000 for the T-B intervention communities, (2) population data from the US census 2000 using zip codes to define the T-B intervention communities, and (3) age-eligible children who attended public schools in the independent school districts of the T-B intervention communities (Table 1). Influenza vaccination coverage in school-age children using defined populations on the basis of either zip codes or school attendance in the independent school districts (public schools) gave comparable estimates (31.5% and 30.7%). In contrast, influenza vaccination coverage on the basis of the census of the cities in the intervention communities underestimated the population, thereby inflating the influenza vaccination coverage to 40.6%.

IIV-T Coverage in Individuals Who Attended SWCs in the Intervention and Comparison Communities

The SWC population was used as a surrogate to estimate the age-specific influenza vaccination coverage in the

![Table 1](image-url)
intervention and comparison communities. The current procedural terminology, which is a uniform language for medical services and procedures used for administrative management purposes such as processing claims, was used to identify influenza vaccine administration in the SWC population. The SWC administrative data files were used to determine age-specific denominators, which consisted of individuals who had received medical service in the SWC clinic, emergency department, or hospital during the study year (July 1, 2003, to June 30, 2004).

To determine the penetration of IIV-T use in the intervention and comparison communities, we used age-specific rates for IIV-T in the SWC population during the 2003 study year (Table 2). Overall rates for IIV-T use among the SWC population were similar in the intervention and comparison communities (18,263 [27.5%] of 66,509 vs 14,570 [28.8%] of 50,565). The rate of IIV-T vaccine use was significantly greater in children who were younger than 5 years (28.5% vs 23.6%; \( P < .01 \)) and adults who were \( \geq 65 \) years (61.4% vs 57.6%; \( P < .01 \)) and residing in the intervention communities. The IIV-T vaccination rates were significantly greater (\( P < .01 \)) among the other age-specific groups who were living in the comparison communities (5 to <10 years: 14.7% vs 18.1%; 10 to <19 years: 14.4% vs 17%; 19 to <35 years: 9.9% vs 15.8%; and 35 to <65 years: 27.1% vs 32.2%). It is important to note that at least 64.1% of the population in the intervention communities received medical care at the SWC in contrast to 16.2% of the population in the comparison communities (Table 2).

Few (\( n = 154 \)) age-eligible children in the comparison communities received LAIV-T through the SWC.

### Influenza Viral Surveillance

The 2003–2004 influenza epidemic occurred early throughout the United States. Influenza virus surveillance defined the influenza outbreak in Central Texas, from October 12, 2003 (week 42), to December 20, 2003 (week 51), with peak activity occurring in week 47, the week of Thanksgiving (Fig 1B). A total of 1077 (46.4%) of 2320 specimens that were obtained in our viral surveillance network were positive for influenza; 1076 were type A and 1 was type B. All influenza A isolates that were subtyped were H3N2. A total of 74.5% and 25.5% of our isolates that were characterized by the Centers for Disease Control and Prevention were A/Fujian/411/2002-like and A/Panama/2007/99-like, respectively. A/Fujian/411/2002 (H3N2)-like was also the predominant influenza virus in the United States. A/Fujian/411/2002 (H3N2) was a significant antigenic variant that was distinct from the vaccine virus A/Panama/2007/99 (H3N2). Vaccination of children in our study paralleled the influenza outbreak (Fig 1); this greatly limited the administration of the second dose of influenza vaccine to children who were younger than 9 years and received the vaccine for the first time. Approximately 58% of the first vaccine doses had been administered by the beginning of the peak week (November 16, 2003) for influenza activity.

### Protection Against Influenza-Positive, Medically Attended Acute Febrile Respiratory Illness

We established an influenza virus surveillance network in the intervention and comparison communities. People who sought medical care for an acute febrile respiratory illness were cultured for influenza. During the influenza outbreak, 450 (44.8%) of 1003 people in the intervention communities and 280 (51.2%) of 547 people in the comparison communities had an influenza culture–positive acute febrile respiratory illness.

The impact of influenza vaccination status on influenza-positive acute febrile illness was determined in children who were 5 to 19 years of age and resided in the intervention communities during the influenza outbreak (Table 3). All influenza-positive acute febrile respiratory illnesses after influenza vaccine administration were included in the analysis. Children who were vaccinated with LAIV-T in 2003 had significant protection against influenza-positive acute respiratory illness. Children

<table>
<thead>
<tr>
<th>Age, y</th>
<th>No. (%) in Intervention Communities</th>
<th>No. (%) in Comparison Communities</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Population( ^a ) SWC SWC-IIV-T</td>
<td>Population( ^b ) SWC SWC-IIV-T</td>
</tr>
<tr>
<td>&lt;5</td>
<td>7483 5523 1572 (28.5)</td>
<td>21 284 3329 785 (23.6) ( ^b )</td>
</tr>
<tr>
<td>5 to &lt;10</td>
<td>7635 5004 736 (14.7)</td>
<td>20 652 3264 590 (18.1) ( ^b )</td>
</tr>
<tr>
<td>10 to &lt;19</td>
<td>14 302 8388 1204 (14.4)</td>
<td>40 376 5706 968 (17%) ( ^b )</td>
</tr>
<tr>
<td>19 to &lt;35</td>
<td>22 052 12 428 1232 (9.9)</td>
<td>107 698 11 853 1873 (15.8) ( ^b )</td>
</tr>
<tr>
<td>35 to &lt;65</td>
<td>37 864 23 550 6387 (27.1)</td>
<td>90 689 19 112 6146 (32.2) ( ^b )</td>
</tr>
<tr>
<td>( \geq 65 )</td>
<td>14 383 11 616 7132 (61.4)</td>
<td>31 377 7301 4208 (57.6) ( ^b )</td>
</tr>
<tr>
<td>Total</td>
<td>103 719 66 509 18 263 (27.5)</td>
<td>312 076 50 565 14 570 (28.8)</td>
</tr>
</tbody>
</table>

\( ^a \) Population extracted from the US Census Bureau, Census 2000 defined by zip codes.

\( ^b \) Significant differences (\( z \) test for comparison of proportions; \( P < .001 \)) were observed in the use of IIV-T by age-specific SWC patients in the intervention communities compared with age-specific SWC patients in the comparison communities.
who received LAIV-T in \( \geq 1 \) year from 1998 to 2001 but not in 2003 approached protection against influenza-positive acute febrile respiratory illness. No reduction in influenza-positive acute febrile respiratory illness was among IIV-T recipients.

To determine the onset of protection that was provided by LAIV-T in children who were enrolled in this community trial, we evaluated the date when an influenza-positive acute febrile respiratory illness occurred in relation to influenza vaccine administration in the intervention communities (Table 4). Children who received LAIV-T in 2003 had similar frequencies of influenza-positive acute febrile respiratory illnesses (25%–45.5%) in weeks 1, 2, 3, 4, or \( >4 \) after vaccine administration. In contrast, the IIV-T recipients had 7 of 9 acute febrile respiratory illness episodes positive for influenza within the first 2 weeks of vaccine administration. No acute febrile respiratory illnesses were cultured in weeks 3 and 4 after IIV-T administration, and after week 4, influenza-positive acute respiratory illness was detected in 46.7% (7 of 15) of the cultured episodes.

**Direct Effectiveness Measures**

The influenza immunization campaign started on October 10, 2003, and ended on December 30, 2003, encompassing the influenza outbreak (October 12 to December 20). Direct effectiveness of the influenza vaccines was calculated from day 1 after vaccination to the end of the influenza outbreak (week 51). MAARI and P&I incidence rates during the influenza outbreak in LAIV-T and IIV-T SWHP vaccinees was compared with age-eligible SWHP nonparticipants who had never received an in-
fluence vaccine in the intervention communities. Also included were children who had previously received LAIV-T in ≥1 year from 1998 to 2001 but not in the study year (2003). Point estimates and 95% CIs for the incidence RRs were calculated. Children who were 5 to 9, 10 to 18, and 5 to 18 years and received LAIV-T or IIV-T did not have a significant reduction in MAARI during the influenza outbreak compared with age-eligible children who never received an influenza vaccine (Table 5). Using a more specific case definition for influenza disease (P6I), LAIV-T vaccinees who were 5 to 9 (RR: 0.2; 95% CI: 0.04–0.60) and 5 to 18 (RR: 0.5; 95% CI: 0.2–0.9) years of age experienced a significant reduction in P6I events compared with age-eligible participants who were never vaccinated. No significant reduction against P6I was observed in the IIV-T group.

Indirect Effectiveness Measure
Age-specific MAARI rates were compared between SWHP members who resided in the intervention and comparison communities during the 2003 influenza outbreak (October 12 to December 20, 2003; Table 6). Because of the potential for differences in the incidence rates between intervention and comparison communities, age-specific MAARI rates were also compared during the preepidemic period (June 29 to October 11, 2003) and postepidemic period (December 21, 2005, to July 3, 2004). Children who were 5 to 11 years of age in the intervention communities had significantly lower MAARI incidence rates during the influenza outbreak compared with those in the comparison communities (RR: 0.87; 95% CI: 0.80–0.95). The MAARI rates before and after the epidemic were comparable between children who were 5 to 11 years in the intervention and comparison communities, suggesting that the observed decrease in MAARI rate during the epidemic period in the intervention communities was attributed to protection that was provided by the influenza vaccines that were delivered during the community influenza immunization campaign. Adults who were 35 to 44 years of age in the intervention communities during the epidemic period also had lower MAARI rates (RR: 0.91; 95% CI: 0.83–1.00). The intervention communities generally had lower MAARI incidence rates in adults who were ≥45 of age during the preepidemic, epidemic, and postepidemic influenza periods (Table 6). Therefore, this decrease in MAARI rates during the influenza outbreak in adults who were ≥45 years of age could not be attributed to the community influenza immunization campaign in school-aged children.

Age-specific biweekly MAARI rates for the intervention and comparison communities are illustrated in Figs 1A and 2. The biweekly MAARI rates during the preepidemic and postepidemic periods in children who were 5 to 17 years of age were similar between the intervention and comparison communities. In this age group a substantial reduction in the biweekly MAARI rates occurred during the first half of the influenza outbreak in the intervention communities (Fig 1A). A similar pattern of lower biweekly MAARI rates during the first half of the influenza outbreak was observed in the other age groups in the intervention communities (Fig 2).

**DISCUSSION**

The 2003–2004 influenza epidemic was notable in that it arrived unusually early in the United States; it was considered a moderately severe epidemic with a large number of pediatric deaths; the epidemic influenza virus, A/Fujian/411/2002 (H3N2), was a drift variant from the vaccine virus A/Panama/2007/99 (H3N2)-like, and it was the first year that LAIV-T was licensed for use in healthy individuals 5 to 49 years of age. Our ongoing community-based influenza vaccination program in children to control epidemic influenza provided us the opportunity to assess the effectiveness of LAIV-T and IIV-T when they were administered during an influenza

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**TABLE 5**  
**Direct Effectiveness Against MAARI in Children Who Were 5 to 18 Years of Age, Were Members of SWHP, and Resided in the Intervention Communities During the 2003 Influenza Outbreak**

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Age, y</th>
<th>No. of Children</th>
<th>No. of MAARI Events</th>
<th>Child-Days Rate per 10,000</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Never vaccinated</td>
<td>S–9</td>
<td>645</td>
<td>140</td>
<td>45 150</td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>10–18</td>
<td>2208</td>
<td>362</td>
<td>154 560</td>
<td>23.4</td>
</tr>
<tr>
<td></td>
<td>S–18</td>
<td>2853</td>
<td>502</td>
<td>199 710</td>
<td>25.1</td>
</tr>
<tr>
<td>LAIV-T in 2003</td>
<td>S–9</td>
<td>667</td>
<td>81</td>
<td>29 731</td>
<td>27.2</td>
</tr>
<tr>
<td></td>
<td>10–18</td>
<td>877</td>
<td>90</td>
<td>37 079</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>S–18</td>
<td>1544</td>
<td>171</td>
<td>66 810</td>
<td>25.6</td>
</tr>
<tr>
<td>LAIV-T in 1998–2001*</td>
<td>S–9</td>
<td>194</td>
<td>49</td>
<td>13 580</td>
<td>36.1</td>
</tr>
<tr>
<td></td>
<td>10–18</td>
<td>709</td>
<td>148</td>
<td>49 630</td>
<td>29.8</td>
</tr>
<tr>
<td></td>
<td>S–18</td>
<td>903</td>
<td>197</td>
<td>63 210</td>
<td>31.2</td>
</tr>
<tr>
<td>IIV-T in 2003</td>
<td>S–9</td>
<td>195</td>
<td>41</td>
<td>86 766</td>
<td>47.3</td>
</tr>
<tr>
<td></td>
<td>10–18</td>
<td>295</td>
<td>36</td>
<td>12 331</td>
<td>29.2</td>
</tr>
<tr>
<td></td>
<td>S–18</td>
<td>490</td>
<td>77</td>
<td>21 007</td>
<td>36.7</td>
</tr>
</tbody>
</table>

*Influenza outbreak period was from October 12 to December 20, 2003. Point estimates and 95% CIs for the incidence RRs were calculated.
* Age-eligible children who had received LAIV-T in ≥1 year from 1998 to 2001 but not in 2003.
TABLE 6  Indirect Effectiveness: Age-Specific Incidence Rates of MAARI of SWHP Members in the Intervention and Comparison Communities Before, During, and After the 2003 Influenza Outbreak

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Intervention Communities</th>
<th>Comparison Communities</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>During</td>
<td>After</td>
</tr>
<tr>
<td>&lt;5</td>
<td>33.1</td>
<td>57.7</td>
<td>42.5</td>
</tr>
<tr>
<td>5–11</td>
<td>11.2</td>
<td>18.8</td>
<td>14.4</td>
</tr>
<tr>
<td>12–17</td>
<td>6.0</td>
<td>15.8</td>
<td>8.2</td>
</tr>
<tr>
<td>18–24</td>
<td>5.3</td>
<td>10.3</td>
<td>6.8</td>
</tr>
<tr>
<td>25–34</td>
<td>6.1</td>
<td>11.4</td>
<td>7.8</td>
</tr>
<tr>
<td>35–44</td>
<td>5.2</td>
<td>9.6</td>
<td>7.1</td>
</tr>
<tr>
<td>45–54</td>
<td>4.1</td>
<td>8.4</td>
<td>6.5</td>
</tr>
<tr>
<td>55–64</td>
<td>4.0</td>
<td>8.4</td>
<td>6.3</td>
</tr>
<tr>
<td>≥65</td>
<td>3.7</td>
<td>8.3</td>
<td>6.6</td>
</tr>
</tbody>
</table>

The preepidemic period was from June 29 to October 11, 2003; the epidemic period was from October 12 to December 20, 2003; the postepidemic period was from December 21, 2003, to July 3, 2004. Difference in incidence rates between intervention and comparison were calculated using Mantel-Haenszel estimates. The point estimates of incidence rates and their 95% CIs were used to determine statistical differences between populations.

* The 95% upper bound CI does not cross 1.

outbreak. Most children who were younger than 9 years and had never previously received an influenza vaccine were able to receive only 1 dose of an influenza vaccine because of the time constraint imposed by the influenza outbreak. Despite this limitation, children who were 5 to 18 years of age and received LAIV-T had a significant reduction in influenza-positive medically attended febrile respiratory illness (Table 3) and P&I medically attended illness during the influenza outbreak. The vaccine effectiveness [% = (1 – RR) × 100] was most apparent in children who were 5 to 9 years of age, with 80% effectiveness against P&I medically attended illness (95% CI: 40%–96%).

The 2003 Advisory Committee on Immunization Practices and the package inserts recommend that 2 doses of IIV-T (FluMist; MedImmune Inc, Gaithersburg, MD) be administered to children who are younger than 9 years if they have never received an influenza vaccine. There are ample data for the necessity of 2 doses 4 weeks apart for IIV-T and at least 6 weeks apart if LAIV-T (FluMist; MedImmune Inc, Gaithersburg, MD) be administered to children who are younger than 9 years because (1) most children who were younger than 9 years and had not previously received an influenza vaccine were able to receive only 1 dose of IIV-T during the outbreak, (2) IIV-T was associated with modest heterotypic protective antibody response to the variant A/Fujian/411/2002 (H3N2) epidemic virus, (3) MAARI and P&I during the outbreak were not sufficiently specific definitions for influenza, or (4) the reference group (children who never received an influenza vaccine) in the intervention communities was an inadequate comparison group for those who had received IIV-T. The reference group may not have been adequate for comparison with the IIV-T group because many of the IIV-T recipients had asthma or other chronic medical conditions compared with our reference group, who were mostly healthy children. Higher MAARI rates have been reported in IIV-T-vaccinated children with asthma compared with unvaccinated children with asthma, probably because of severity of underlying disease. In our study, LAIV-T in children 5 to 18 years of age and had received 2 doses of IIV-T (beginning 2 weeks after the second dose). No significant protection against P&I was observed in partially vaccinated children (children with only 1 dose and no previous influenza vaccination or children with 2 doses but sought medical attention <14 days after the second dose). In a study of health care workers, the 2003–2004 influenza vaccine was not effective against influenza-like illness, but when a more specific case definition was used (laboratory-confirmed influenza), vaccine effectiveness was estimated at 52% in healthy adults 50 to 64 years of age.

In our study, a single dose of IIV-T was not associated with a significant reduction in culture-positive medically attended influenza illness (Table 3) or P&I medically attended illness during the influenza outbreak. The lack of protection with IIV-T in our study may be because (1) most children who were younger than 9 years and had not previously received an influenza vaccine were able to receive only 1 dose of IIV-T during the outbreak, (2) IIV-T was associated with modest heterotypic protective antibody response to the variant A/Fujian/411/2002 (H3N2) epidemic virus, (3) MAARI and P&I during the outbreak were not sufficiently specific definitions for influenza, or (4) the reference group (children who never received an influenza vaccine) in the intervention communities was an inadequate comparison group for those who had received IIV-T. The reference group may not have been adequate for comparison with the IIV-T group because many of the IIV-T recipients had asthma or other chronic medical conditions compared with our reference group, who were mostly healthy children. Higher MAARI rates have been reported in IIV-T-vaccinated children with asthma compared with unvaccinated children with asthma, probably because of severity of underlying disease.
was associated with a vaccine effectiveness of 37.3% ($P < .05$) against influenza-positive medically attended febrile respiratory illness and of 50% (95% CI: 10%–80%) against P&I medically attended illness during the influenza outbreak. The LAIV-T effectiveness in children 5 to 9 years of age was 80% (95% CI: 40%–96%) against P&I medically attended illness despite that most of these children received only 1 dose of LAIV-T. In the initial phase III trial of LAIV-T in children who were 15 to 71 months of age and had never been vaccinated against
influenza, 1 dose of LAIV-T achieved an efficacy of 89% (95% CI: 65%–96%) for the prevention of culture-confirmed influenza compared with 94% (95% CI: 88%–97%) with 2 doses given ~60 days apart. Before licensure of LAIV-T in the United States, we implemented a 1-dose annual regimen of LAIV-T in children 18 months to 18 years of age and showed it to be safe and effective against influenza-associated medically attended illnesses. It is not surprising that 1 dose of LAIV-T protected children against influenza. Other attenuated live virus vaccines, such as measles-mumps-rubella and varicella zoster, are administered once at 12 to 15 months of age for protection against infection. A subsequent booster later in life is required for waning of immunity. Live virus vaccines in general require fewer doses compared with inactive virus vaccines in children and generate a protective immune response similar to that of natural infection.

LAIV-T vaccinees had significant protection against influenza-positive acute febrile respiratory illness (Table 3). The percentage of LAIV-T vaccinees who were protected against influenza-positive acute febrile respiratory illness was similar for those who were infected within 1, 2, 3, or ≥4 weeks after vaccine administration, although the findings are limited by small numbers (Table 4). We speculate that LAIV-T may provide protection against influenza infection by both innate and adaptive immunity. LAIV-T induces influenza-specific serum and respiratory mucosal antibodies that are good correlates of immune protection. LAIV-T may interfere with wild-type influenza infection shortly after vaccine administration by eliciting an innate antiviral state for 1 to 2 weeks after vaccination. Influenza virus replication in the nasal mucosa produces proinflammatory cytokines such as interferons and tumor necrosis factor-α, which may be the first line of defense against influenza infection. The innate antiviral state that is produced by replication of LAIV-T in the upper respiratory tract may protect children from illnesses that are associated with influenza and other circulating respiratory viruses within the first weeks of vaccination. Protection against disease with wild-type influenza has been observed in the ferret model with co-administration of LAIV and wild-type influenza virus. Results from an influenza challenge study performed in human volunteers suggested that LAIV induced an antiviral effect that protected against illness from an experimental challenge with wild-type influenza virus. In an earlier study, we reported on the significant reduction in MAARI, otitis media/sinusitis, upper respiratory tract illness, and lower respiratory tract illness that sometimes occurred within the first 2 weeks after LAIV-T administration in children and before the onset of the influenza season. Taken together, there is a growing body of evidence that supports that LAIV-T protects against influenza illness shortly after administration possibly through stimulation of the innate antiviral immune response.

Several studies have documented the direct and indirect (herd protection) benefit against influenza by implementing an influenza vaccination program in preschool and school-aged children. We recently reported that vaccination coverage of 20% to 25% of age-eligible children was associated with an 8% to 18% reduction in MAARI rates in adults who were ≥35 years of age during the influenza season. Our estimation of vaccination coverage was based on the US Census 2000 city population data. If we had used US Census data based on zip codes that defined the intervention communities, then the influenza vaccination coverage (LAIV-T and IIV-T) in the original report would have been reduced to 15.3% to 17.6%. In this report, we demonstrate that vaccination coverage of school-aged children based on US Census 2000 city population data overestimated the influenza vaccination coverage. A more accurate estimate was obtained using either US Census 2000 zip code data or 2003 Census data of school children who attended public schools in the intervention communities. Census defined by zip code increased the population by ~5000 children who were 5 to 18 years of age and reduced the influenza vaccination coverage from 40.6% to 31.5%. The influenza vaccination coverage of children who attended public schools in the intervention communities was 30.7% (vaccination coverage for children 5 to <9 years was 40.6% and for 10 to <19 years was 26.4%). Therefore, it seems that in this study, we achieved influenza vaccination coverage of ~31% in children 5 to 18 years of age. MAARI rates were available through administrative data sets for SWHP members who lived in the intervention and comparison communities. These data were used to estimate indirect effectiveness (herd protection) in the intervention communities attributed to our community-based influenza vaccination program in children 5 to 18 years of age. A 13% reduction in MAARI events during the influenza outbreak was detected in SWHP children who were 5 to 11 years of age and living in the intervention communities compared with SWHP children who were 5 to 11 years of age and residing in the comparison communities (Table 6). Herd protection was also observed in SWHP adults who were 35 to 44 years of age. LAIV-T was not provided by our program or through SWC in the comparison communities. Age-specific IIV-T coverage rates were comparable among individuals who used SWC in the intervention and comparison communities (Table 2), suggesting that IIV-T alone did not account for the herd protection that was observed in the intervention communities. Significantly lower MAARI rates were detected in adults who were ≥45 years of age before and after the influenza outbreak in the intervention communities. This may bias the significant reduction in MAARI that was experienced by adults who were
≥45 years of age during the 2003–2004 influenza outbreak in the intervention communities (Table 6). The reduction of MAARI risk noted before and after the 2003–2004 influenza outbreak may be consistent with a healthier SWHP adult population in the intervention communities. In future years, we will need to continue to evaluate for bias in estimates of indirect protection against influenza as it was recently demonstrated in observational studies conducted in elderly adults. However, it should be noted that herd protection was demonstrated for adults who were 35 to 44 years of age, who may have had most contact with children in the elementary schools who had the highest vaccine uptake.

CONCLUSIONS
Our community-based influenza vaccination program in children 5 to 18 years of age improved the influenza vaccination coverage in the intervention communities. One dose of LAIV-T administered to children 5 to 18 years of age during the influenza outbreak was well tolerated and associated with protection against influenza-positive febrile respiratory illness, direct effectiveness against P&I medically attended illness, and indirect effectiveness against MAARI. Protection provided by LAIV-T may have been attributed to a combination of both innate and adaptive immunity.

ACKNOWLEDGMENTS
This trial was supported by National Institutes of Health grant 2 R01 AI041050.

MedImmune Inc provided the live attenuated influenza vaccine free of charge.

We thank Ira M. Longini and M. Elizabeth Halloran for critical review of the manuscript. We appreciate the support provided by Linda Lambert, PhD, and Sonnie Kim (Influenza Program Officer, National Institute of Allergy and Infectious Diseases), and Jeff Stoddard, MD (MedImmune Inc). Hope Gonzales, Patricia Smith, and Dr Robert L. Fader supported viral surveillance. This study would not be possible without the staff and physician support from Baylor College of Medicine, Scott and White Hospital/Clinics, and Scott and White Health Plan. We are extremely grateful to the Temple and Belton communities and the independent school districts for support and participation.

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Trivalent Live Attenuated Intranasal Influenza Vaccine Administered During the 2003-2004 Influenza Type A (H3N2) Outbreak Provided Immediate, Direct, and Indirect Protection in Children

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*Pediatrics* 2007;120;e553-e564; originally published online Aug 13, 2007;
DOI: 10.1542/peds.2006-2836

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