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ARTICLE

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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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 adults[18] 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-

cally attended acute respiratory illness (MAARI) in adults ≥35 years of age.[22] These observations are consistent with mathematical models for the control of influenza epidemics, which have illustrated that the greatest reduction in morbidity and mortality occurs through vaccination of school-aged children.[23]

Since 1998, we have been conducting an open-label, nonrandomized, community-based trial with the goal of controlling epidemic influenza through active immunization of school-aged children.[22,24–26] LAIV-T and IIV-T are safe and efficacious in children.[26–31] LAIV-T was approved by the Food and Drug Administration (FDA) in the summer of 2003 for use in healthy individuals 5 to 49 years of age. Our study reports on the efficacy of LAIV-T in its first year of licensure in the United States, which coincided with the unusually early arrival of the 2003–2004 influenza outbreak with a drifted variant, A/Fujian/411/2002 (H3N2). The early arrival of influenza coincided with our community vaccination campaign and provided the opportunity to determine the direct and indirect effectiveness (herd protection) of influenza vaccination of school-aged children through the influenza outbreak.

METHODS

Study Design

An open-label, nonrandomized, community-based trial with FDA-approved influenza vaccines was conducted in children 5 to 18 years of age. Age-eligible children who resided in the intervention communities were offered influenza vaccines. LAIV-T was offered to age-eligible, healthy children, and IIV-T was offered to age-eligible children with high risk conditions for influenza. During the enrollment period, age-eligible children in the intervention communities were vaccinated 7 days a week in the Scott and White Clinic (SWC), the mall, churches, and public and private schools. The intervention communities (T-B) comprise the adjacent cities of Temple and Belton in central Texas and their surrounding towns. Age-eligible children in the comparison communities, Waco, Bryan, and College Station, were not offered an influenza vaccine through our community-based study. Waco is ~40 miles north of Temple; Bryan and College Station, adjacent cities, are ~90 miles southeast of Temple. Community physicians in both the intervention and comparison communities were able to provide LAIV-T and IIV-T to children who were not enrolled in our community-based trial.

The intervention and comparison communities in central Texas were chosen because of the similarities between their demographics, the relative proximity between the communities that helps to ensure similar influenza outbreak periods and circulating influenza strains, and all of the communities are served by large multispecialty clinics of Scott and White Clinic (SWC),

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.[22] 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 (76501, 76502, 76504, 76513, 76554, 76534, 76569, 76571, and 76579) and comparison (77801, 77802, 77803, 77840, 77845, 76701, 76704, 76705, 76706, 76707, 76708, 76710, 76711, 76712, 76633, 76643, and 76557) communities.

Database

Demographic information of LAIV-T and IIV-T recipients were entered and tracked in a computerized immuniza-tion registry as previously described.[32] 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.[22,24–26] 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.[22,24–26]

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 $(1 - RR) \times 100\%$.[22,24] Age-specific MAARI rates in the preepidemic and postepidemic periods were also com-

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   Influenza Vaccination Coverage of Children Who Were 5 to 18 Years of Age and Living in the T-B Intervention Communities

Parameter	T-B Intervention Communities		
	Census Defined by City Population[a]	Census Defined by Zip Code[a]	Independent School Districts Census
Population	80 843	103 719	NA
No. of children	16 975[b]	21 937[b]	19 807[b]
LAIV-T vaccinees[c]	4956	4961	4362
IIV-T vaccines[c]	1930	1944	1717
Total vaccinees	6886 (40.6%)	6905 (31.5%)	6079 (30.7%)

NA indicates not applicable.

[a] US Census 2000 data define by city (Temple, Belton, Holland, Academy, Rogers, Salado, and Troy are the T-B intervention communities) or zip code (76501, 76502, 76503, 76504, 76505, 76508, 76513, 76534, 76554, 76569, 76571, and 76579) for the T-B intervention communities.

[b] Number of children in city and zip code is for children aged 5 to <19 years. Number of children who attended schools in the independent school districts is based on the census in the first 6 weeks for elementary, middle, and high school students in the T-B intervention communities.

[c] We vaccinated 7609 children 5 to 18 years of age with an influenza vaccine; 6569 children received LAIV-T, and 1040 received IIV-T. Approximately 24% of these children (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.

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 ≥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 dominant 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 18 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 2	IIV-T Coverage in SWC Population in the Intervention and Comparison Communities					
Age, y	No. (%) in Intervention Communities			No. (%) in Comparison Communities		
	Population[a]	SWC	SWC-IIV-T	Population[a]	SWC	SWC-IIV-T
<5	7483	5523	1572 (28.5)	21 284	3329	785 (23.6)[b]
5 to <10	7635	5004	736 (14.7)	20 652	3264	590 (18.1)[b]
10 to <19	14 302	8388	1204 (14.4)	40 376	5706	968 (17)[b]
19 to <35	22 052	12 428	1232 (9.9)	107 698	11 853	1873 (15.8)[b]
35 to <65	37 864	23 550	6387 (27.1)	90 689	19 112	6146 (32.2)[b]
≥65	14 383	11 616	7132 (61.4)	31 377	7301	4208 (57.6)[b]
Total	103 719	66 509	18 263 (27.5)	312 076	50 565	14 570 (28.8)

The SWC administrative data files were used to determine age-specific denominators, which consisted of individuals who had receive medical service in the SWC, emergency department, or hospital during the study year (July 1, 2003, to June 30, 2004). Current procedural terminology data were used to estimate the usage of IIV-T in the SWC population in the intervention and comparison communities.

[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.
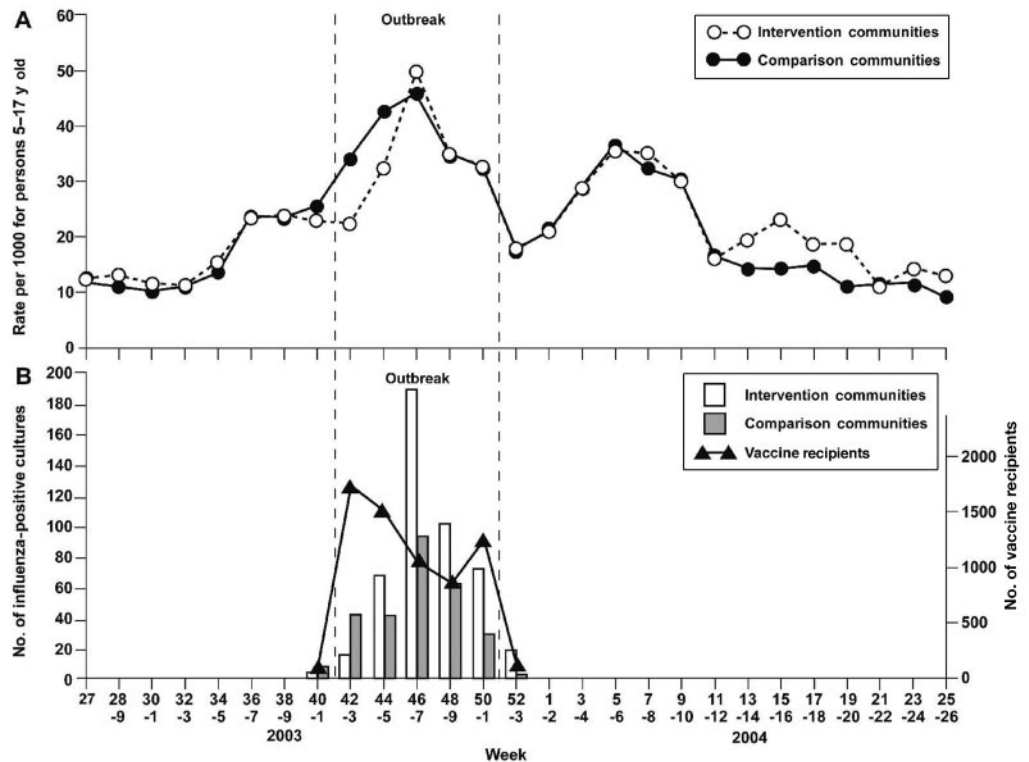
TABLE 3 Influenza-Positive Acute Febrile Respiratory Illness in Children Who Were 5 to 18 Years of Age and Resided in the Intervention Communities During the 2003 Influenza Outbreak

Influenza Vaccination Status	Influenza Positive, n/N (%)	P[a]	Efficacy, %[b]
Never vaccinated	127/231 (55)	Reference	Reference
LAIV-T in 2003	19/55 (34.5)	.006	37.3
LAIV-T in 1998–2001[c]	34/79 (43)	.07	21.8
IIV-T in 2003	14/24 (58.3)	NS	0

Influenza outbreak period was from October 12 to December 20, 2003.

[a] χ² test was used to determine for differences between the group that was never vaccinated and the group that was vaccinated. P ≤ .05 was considered significant.

[b] Efficacy = (1 − vaccine group/never vaccinated) × 100.

[c] Age-eligible children who had received LAIV-T in ≥1 year from 1998 to 2001 but not in 2003.

who received LAIV-T in ≥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

TABLE 4 Influenza-Positive Acute Febrile Respiratory Illness After Influenza Vaccine Administration in Children Who Were 5 to 18 Years of Age and Resided in the Intervention Communities During the 2003 Influenza Outbreak

Vaccine	Influenza-Positive Acute Respiratory Illness, n/N (%)				
	Week 1 (0–6 d)	Week 2 (7–13 d)	Week 3 (14–20 d)	Week 4 (21–27 d)	>Week 4 (≥28 d)
LAIV-T	5/14 (35.7)	5/11 (45.5)	2/6 (33.3)	2/8 (25)	5/16 (31.3)
IIV-T	6/8 (75)	1/1 (100)	0/0 (0)	0/0 (0)	7/15 (46.7)

Influenza outbreak period was from October 12 to December 20, 2003.

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-

fluenza 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 (P&I), 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 P&I events compared with age-eligible participants who were never vaccinated. No significant reduction against P&I 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.[33,34] 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

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					
Vaccine	Age, y	No. of Children	No. of MAARI Events	Child-Days	Rate per 10 000	RR (95% CI)
Never vaccinated	5–9	645	140	45 150	31.0	Reference
	10–18	2208	362	154 560	23.4	Reference
	5–18	2853	502	199 710	25.1	Reference
LAIV-T in 2003	5–9	667	81	29 731	27.2	0.9 (0.7–1.2)
	10–18	877	90	37 079	24.3	1.0 (0.8–1.3)
	5–18	1544	171	66 810	25.6	1.0 (0.9–1.2)
LAIV-T in 1998–2001[a]	5–9	194	49	13 580	36.1	1.2 (0.8–1.6)
	10–18	709	148	49 630	29.8	1.3 (1.0–1.5)
	5–18	903	197	63 210	31.2	1.2 (1.0–1.5)
IIV-T in 2003	5–9	195	41	8676	47.3	1.5 (1.0–2.2)
	10–18	295	36	12 331	29.2	1.2 (0.9–1.8)
	5–18	490	77	21 007	36.7	1.5 (1.1–1.9)

Influenza outbreak period was from October 12 to December 20, 2003. Point estimates and 95% CIs for the incidence RRs were calculated.
[a] 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

Age, y	MAARI Rates per 1000 Person-Weeks								
	Intervention Communities			Comparison Communities			RR		
	Before	During	After	Before	During	After	Before	During	After
<5	33.1	57.7	42.5	33.2	60.6	42.9	1	0.95	0.99
5–11	11.2	18.8	14.4	10.1	21.6	13.6	1.12	0.87[a]	1.06
12–17	6.0	15.8	8.2	6.3	16.0	7.7	0.96	0.99	1.06
18–24	5.3	10.3	6.8	5.6	10.1	6.7	0.94	1.02	1.02
25–34	6.1	11.4	7.8	6.3	10.6	7.2	0.96	1.08	1.08
35–44	5.2	9.6	7.1	5.5	10.6	7.4	0.94	0.91[a]	0.96
45–54	4.1	8.4	6.5	5.0	9.9	7.8	0.81[a]	0.85[a]	0.84[a]
55–64	4.0	8.4	6.3	4.6	9.3	7.9	0.87[a]	0.90	0.79[a]
≥65	3.7	8.3	6.6	4.5	9.8	7.9	0.83[a]	0.85[a]	0.84[a]

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.

[a] 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 4 weeks apart for IIV-T and at least 6 weeks apart for LAIV-T (FluMist; MedImmune Inc, Gaithersburg, MD) be administered to children who are younger than 9 years if they have never received an influenza vaccine.[34,35] There are ample data for the necessity of 2 doses of IIV-T given at least 4 weeks apart in previously unvaccinated young children for induction of protective levels of serum antibodies and protection against influenza-associated morbidity.[35–44] This is because priming (first challenge) with either natural infection or IIV is required for induction of a protective immune response when a booster dose (second dose) with the inactivated influenza vaccine is administered.[36–38] The 2003 IIV-T immunogenicity in young children who were administered 2 doses at least 4 weeks apart were comparable to that observed in other studies except that the response to the influenza B component was low.[44] The antibody response to the epidemic influenza virus A/Fujian/411/2002 (H3N2) was not reported.[44] Vaccine effectiveness of 49% against P&I was observed in a retrospective cohort study among children who were 6 to 23 months of age

and had received 2 doses of IIV-T (beginning 2 weeks after the second dose).[45–47] 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).[45–47] In a study of health care workers, the 2003–2004 influenza vaccine was not effective against influenza-like illness,[46] 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.[45,46] 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.[32]

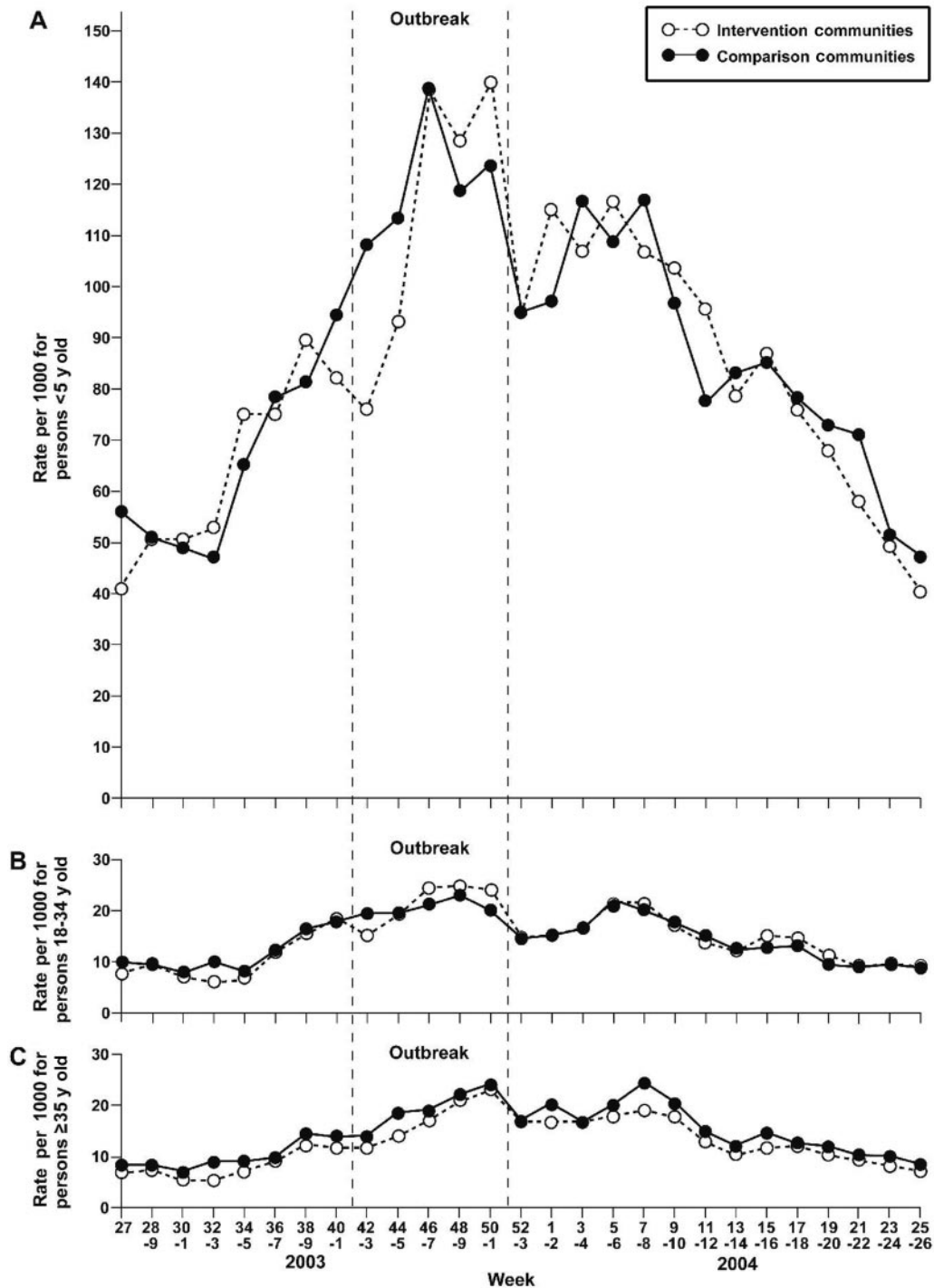In our study, LAIV-T in children 5 to 18 years of age

FIGURE 2

Biweekly MAARI rates in the intervention and comparison communities. Biweekly MAARI rates were determined for adults who were ≥35 years of age (A), adults who were 18 to 34 years of age (B), and children who were younger than 5 years of age (C) among SWHP members who resided in the intervention (O) and comparison communities (●) during the 2003–2004 study year. The preepidemic period was defined from June 29 to October 11, 2003; the influenza outbreak occurred from October 12 to December 20, 2003; and the postepidemic period was from December 21, 2003, to July 3, 2004.

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.[27] 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.[24–26] 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.[48]

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.[49,50] 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.[51,52] 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.[53] 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.[54] 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.[26] 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.[18–22] 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.[20] 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.[55,56] 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.

REFERENCES

1. Advisory Committee on Immunization Practices, Smith NM, Bresee JS, et al. Prevention and control of influenza. Recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep.* 2006;55:1–42
2. Dushoff J, Plotkin JB, Viboud C, Earn DJD, Simonsen L. Mortality due to influenza in the United states: an annualized regression approach using multiple-cause mortality data. *Am J Epidemiol.* 2006;163:181–187
3. Thompson WW, Shay DK, Weintraub E, Brammer L, Cox N, Anderson LJ, Fukuda K. Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA.* 2003;289:179–186
4. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalization in the United States. *JAMA.* 2004; 292:1333–1340
5. Glezen WP. Emerging infections: pandemic influenza. *Epidemiol Rev.* 1996;18:64–76
6. Wheeler JG. New Modalities for preventing and treating influenza. *Semin Pediatr Infect Dis.* 2002;12:235–245
7. Yogev R. Influenza vaccine confusion: a call for an alternative evidence-based approach. *Pediatrics.* 2005;116:1214–1215
8. Couch RB, Kasel JA, Glezen WP, et al. Influenza: its control in persons and populations. *J Infect Dis.* 1986;153:431–440
9. Perrotta DM, Decker M, Glezen WP. Acute respiratory disease hospitalizations as a measure of impact of epidemic influenza. *Am J Epidemiol.* 1985;122:468–476
10. Neuzil KM, Mellen BG, Wright PF, Mitchel EF Jr, Griffin MR. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. *N Engl J Med.* 2000;342: 225–231
11. Izurieta HS, Thompson WW, Kramarz P, et al. Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med.* 2000;342:232–239
12. Munoz FM. The impact of influenza in children. *Semin Pediatr Infect Dis.* 2002;13:72–78
13. Chiu SS, Lau YL, Chan KH, Wong WHS, Peiris JSM. Influenza-related hospitalization among children in Hong Kong. *N Engl J Med.* 2002;347:2097–2103
14. Weigl JAI, Puppe W, Schmitt HJ. The incidence of influenza-associated hospitalizations in children in Germany. *Epidemiol Infect.* 2002;129:525–533
15. Badger GF, Dingle JH, Feller AE, Hodges RG, Jordan WS Jr, Rammelkamp CH Jr. A study of illness in a group of Cleveland families. V. Introduction and secondary attack rates as indices of exposure to common respiratory diseases in the community. *J Hyg.* 1953;58:179–182
16. Poehling KA, Edwards KM, Weinberg GA, et al. The underrecognized burden of influenza in young children. *N Engl J Med.* 2006;355:31–40
17. Brownstein JS, Kleinman KP, Mandl KD. Identifying pediatric age groups for influenza vaccination using a real-time regional surveillance system. *Am J Epidemiol.* 2005;162:686–693
18. Monto AS, Davenport FM, Napier JA, Francis T Jr. Modification of an outbreak of influenza in Tecumseh, Michigan by vaccination of schoolchildren. *J Infect Dis.* 1970;122:16–25
19. Reichert TA, Sugaya N, Fedson DS, Glezen WP, Simonsen L, Tashiro M. The Japanese experience with vaccinating schoolchildren against influenza. *N Engl J Med.* 2001;433:889–896
20. Hurwitz ES, Haber M, Chang A, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. *JAMA.* 2000;284: 1677–1682
21. Ghendon YZ, Kaira AN, Elshina GA. The effect of mass influenza immunization in children on the morbidity of the unvaccinated elderly. *Epidemiol Infect.* 2006;134:71–78
22. Piedra PA, Gaglani MJ, Kozinetz CA, et al. Herd immunity in adults against influenza-related illnesses with use of the trivalent-live attenuated influenza vaccine (CAIV-T) in children. *Vaccine.* 2005;23:1540–1548
23. Weycker D, Edelsberg J, Halloran ME, et al. Population-wide benefits of routine vaccination of children against influenza. *Vaccine.* 2005;26:1284–1293
24. Gaglani MJ, Piedra PA, Herschler GB, et al. Direct and total effectiveness of the intranasal, live-attenuated, trivalent cold-adapted influenza virus vaccine against the 2000–2001 influenza A(H1N1) and B epidemic in healthy children. *Arch Pediatr Adolesc Med.* 2004;158:65–73

25. Halloran ME, Longini IM, Gaglani MJ, et al. Estimating efficacy of trivalent, cold-adapted influenza virus vaccine (CAIV-T) against influenza A(H1N1) and B using surveillance cultures. *Am J Epidemiol.* 2003;158:305–311

26. Piedra PA, Gaglani MJ, Riggs M, et al. Live attenuated influenza vaccine, trivalent, is safe in healthy children 18 months to 4 years, 5 to 9 years, and 10 to 18 years of age in a community-based, nonrandomized, open-label trial. *Pediatrics.* 2005; 116(3). Available at: www.pediatrics.org/cgi/content/full/116/ 3/e397

27. Belshe RB, Mendelman P, Treanor J, et al. Efficacy of trivalent live attenuated intranasal influenza vaccine in children. *N Engl J Med.* 1998;338:1405–1412

28. Piedra PA, Yan L, Kotloff K, et al. Safety of the trivalent, cold-adapted influenza vaccine in preschool-aged children. *Pediatrics.* 2002;110:662–672

29. Izurieta HS, Haber P, Wise RP, et al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. *JAMA.* 2005;294:2720–2725

30. Zangwell KM, Belshe RB. Safety and efficacy of trivalent inactivated influenza vaccine in young children: a summary for the new era of routine vaccination. *Pediatr Infect Dis J.* 2004;23: 189–197

31. Beyer WE, Palache AM, de Jong JC, Osterhaus AD. Cold-adapted live influenza vaccine versus inactivated vaccine: systemic vaccine reactions, local and systemic antibody response, and vaccine efficacy. A meta-analysis. *Vaccine.* 2002;20: 1340–1353

32. Gaglani M, Riggs M, Kamenicky C, Glezen WP. A computerized reminder strategy is effective for annual influenza immunization of children with asthma or reactive airway disease. *Pediatr Infect Dis J.* 2001;20:1155–1160

33. Centers for Disease Control and Prevention. 2003–04 U.S. influenza season summary. Available at: www.cdc.gov/flu/ weekly/weeklyarchives2003-2004/03-04summary.htm. Accessed April 19, 2005

34. Harper SA, Fukuda K, Cox NJ, Bridges CB; Advisory Committee on Immunization Practices. Using live, attenuated influenza vaccine for prevention and control of influenza: supplemental recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2003;52 (RR-13):1–8

35. Bridges CB, Harper SA, Fukuda K, et al. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep.* 2003;52 (RR-8):1–36

36. Bernstein DI, Cherry JD. Clinical reactions and antibody responses to influenza vaccines. *Am J Dis Child.* 1983;137: 622–626

37. Wright PF, Cherry JD, Foy HM, et al. Antigenicity and reactogenicity of influenza A/USSR/77 virus vaccine in children: a multicentered evaluation of dosage and safety. *Rev Infect Dis.* 1983;5:758–764

38. Levandowski RA, Regnery HL, Staton E, Burgess BG, Williams MS, Groothuis JR. Antibody responses to influenza B viruses in immunologically unprimed children. *Pediatrics.* 1991;88: 1031–1036

39. El-Madhun AS, Cox RJ, Soreide A, Olofsson J, Haaheim LR. Systemic and mucosal responses in young children and adults after parenteral influenza vaccination. *J Infect Dis.* 1998;178: 933–939

40. Hurwitz ES, Haber M, Chang A, et al., Studies of the 1996–1997 inactivated influenza vaccine among children attending day care: immunologic response, protection against infection, and clinical effectiveness. *J Infect Dis.* 2000;182: 1218–1221

41. Englund JA, Walter EB, Fairchok MP, Monto AS, Neuzil KM. A comparison of 2 influenza vaccine schedules in 6- to 23-month-old children. *Pediatrics.* 2005;115:1039–1047

42. Kumagai T, Nagai K, Okui T, et al. Poor immune responses to influenza vaccination in infants. *Vaccine.* 2004;22:3404–3410

43. Fujieda M, Maeda A, Kondo K, Kaji M, Hirota Y. Inactivated influenza vaccine effectiveness in children under 6 years of age during the 2002–2003 season. *Vaccine.* 2006;24:957–963

44. Mitchell DK, Ruben FL, Gravenstein S. Immunogenicity and safety of inactivated influenza virus vaccine in young children in 2003–2004. *Pediatr Infect Dis J.* 2005;24:925–926

45. Centers for Disease Control and Prevention. Assessment of the effectiveness of the 2003–04 influenza vaccine among children and adults: Colorado, 2003. *MMWR Morb Mortal Wkly Rep.* 2004;53:707–710

46. Centers for Disease Control and Prevention. Assessment of the effectiveness of the 2003–04 influenza vaccine among children and adults: Colorado, 2003. *JAMA.* 2004;292:1674–1675

47. Centers for Disease Control and Prevention. Preliminary assessment of the effectiveness of the 2003–04 influenza vaccine: Colorado, December 2003. *MMWR Morb Mortal Wkly Rep.* 2004; 53:8–11

48. Mims CA, Nash A, Stephens J, eds. *Vaccines and How they Work: Mim's Pathogenesis of Infectious Disease.* 5th ed. New York, NY: Academic Press; 2001:392–415

49. Belshe RB, Gruber WC, Mendelman PM, et al. Correlates of immune protection induced by live, attenuated, cold-adapted, trivalent, intranasal influenza virus vaccine. *J Infect Dis.* 2000; 181:1133–1137

50. Belshe R, Lee M-S, Walker RE, Stoddard J, Mendelman PM. Safety, immunogenicity and efficacy of intranasal, live attenuated influenza vaccine. *Expert Rev Vaccines.* 2004;3:643–654

51. Hayden FG, Fritz RS, Lobo MC, Alvord WG, Stober W, Strauss SE. Local and systemic cytokine responses during experimental human influenza A virus infection. *J Clin Invest.* 1998;101: 643–649

52. Seo SH, Webster RG. Tumor necrosis factor alpha exerts powerful anti-influenza virus effects in lung epithelial cells. *J Virol.* 2002;76:1071–1076

53. Whitaker-Dowling P, Maassab HF, Younger JS. Dominant-negative mutants as antiviral agents: simultaneous infection with the cold-adapted live-attenuated vaccine for influenza A protects ferrets from disease produced by wild-type influenza A. *J Infect Dis.* 1991;164:1200–1202

54. Younger JS, Treanor JJ, Betts RF, Whitaker-Dowling P. Effect of simultaneous administration of cold-adapted and wild-type influenza A viruses on experimental wild-type influenza infection in humans. *J Clin Microbiol.* 1994;32:750–754

55. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in senior. *Int J Epidemiol.* 2006;35:337–344

56. Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol.* 2006;35:345–352

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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