ORIGINAL ARTICLE

Live Attenuated versus Inactivated Influenza Vaccine in Infants and Young Children

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ABSTRACT

BACKGROUND

Universal vaccination of children 6 to 59 months of age with trivalent inactivated influenza vaccine has recently been recommended by U.S. advisory bodies. To evaluate alternative vaccine approaches, we compared the safety and efficacy of intranasally administered live attenuated influenza vaccine with those of inactivated vaccine in infants and young children.

METHODS

Children 6 to 59 months of age, without a recent episode of wheezing illness or severe asthma, were randomly assigned in a 1:1 ratio to receive either cold-adapted trivalent live attenuated influenza vaccine (a refrigeration-stable formulation of live attenuated intranasally administered influenza vaccine) or trivalent inactivated vaccine in a double-blind manner. Influenza-like illness was monitored with cultures throughout the 2004–2005 influenza season.

RESULTS

Safety data were available for 8352 children, and 7852 children completed the study according to the protocol. There were 54.9% fewer cases of cultured-confirmed influenza in the group that received live attenuated vaccine than in the group that received inactivated vaccine (153 vs. 338 cases, P<0.001). The superior efficacy of live attenuated vaccine, as compared with inactivated vaccine, was observed for both antigenically well-matched and drifted viruses. Among previously unvaccinated children, wheezing within 42 days after the administration of dose 1 was more common with live attenuated vaccine than with inactivated vaccine, primarily among children 6 to 11 months of age; in this age group, 12 more episodes of wheezing were noted within 42 days after receipt of dose 1 among recipients of live attenuated vaccine (3.8%) than among recipients of inactivated vaccine (2.1%, P=0.076). Rates of hospitalization for any cause during the 180 days after vaccination were higher among the recipients of live attenuated vaccine who were 6 to 11 months of age (6.1%) than among the recipients of inactivated vaccine in this age group (2.6%, P=0.002).

CONCLUSIONS

Among young children, live attenuated vaccine had significantly better efficacy than inactivated vaccine. An evaluation of the risks and benefits indicates that live attenuated vaccine should be a highly effective, safe vaccine for children 12 to 59 months of age who do not have a history of asthma or wheezing. (ClinicalTrials.gov number, NCT00128167.)

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Hospitalization rates for culture-confirmed influenza among young children are similar to those among the elderly, and outpatient visits for confirmed influenza are more frequent among infants and young children than in any other age group.[1] For these reasons, U.S. advisory bodies have recently recommended the routine vaccination of all children 6 to 59 months of age with the licensed trivalent inactivated influenza vaccine.[2] The implementation of this recommendation will be challenging because of the limited supplies of inactivated vaccine during many influenza seasons,[3-5] the modest efficacy of inactivated vaccine in young children,[6] and the frequent need to administer the inactivated vaccine by injection concurrent with multiple other parenteral vaccines.

Previous clinical trials of live attenuated trivalent influenza vaccine in young children have shown it to be highly effective.[7-9] Live attenuated influenza vaccine showed high efficacy when epidemic influenza viruses were not well matched to the recommended vaccine antigens.[7] Initial studies comparing the efficacy of cold-adapted trivalent live attenuated influenza vaccine with trivalent inactivated vaccine have shown the former to be more effective (35 to 53% reduction in the influenza attack rate with live attenuated vaccine, as compared with inactivated vaccine).[10,11] Although the safety of live attenuated influenza vaccine was assessed in children in both prospective and database studies,[12-15] additional prospective studies of both inactivated vaccine and live attenuated vaccine were needed. In one study,[15] but not in others,[10,11,16] wheezing events were more frequent among young children given formulations of live attenuated vaccine. The present trial was designed to assess the safety and relative efficacy of live attenuated intranasal influenza vaccine and inactivated vaccine in children 6 to 59 months of age.

METHODS

STUDY DESIGN

The study was proposed by a subgroup of the authors, and the protocol was developed by all the authors in collaboration with an advisory committee. Data were gathered at each study site by the local principal investigator and the local staff. The data were monitored by PPD in the United States and Europe and by Quintiles at the Asian sites. A data and safety monitoring board oversaw the study. The analysis was performed by biostatisticians employed by the sponsor. All authors had complete access to all data and all individual case-report forms, including data on all serious adverse events. All the authors vouch for the accuracy and completeness of the reported data.

The study was conducted at 249 sites (physicians' offices and primary care clinics) in 16 countries: the United States (49% of subjects), 12 countries in Europe and the Middle East (45% of subjects), and 3 countries in Asia (6% of subjects). The protocol and the informed consent forms were approved by the institutional review board at each participating center, and the study was conducted in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice.

After written informed consent had been obtained from a parent or guardian, children 6 to 59 months of age were randomly assigned on a 1:1 basis to receive either live attenuated vaccine or inactivated vaccine with the use of a centrally managed computer-generated randomization schedule. Subjects were stratified according to age on receipt of the first dose, the presence or absence of previous influenza vaccination, the presence or absence of a history of recurrent wheezing (defined as three or more wheezing episodes, each requiring medical follow-up or hospitalization, according to the parent's report or chart review), and country of residence. Children with a history of hypersensitivity to any component of the live attenuated vaccine or the inactivated vaccine were excluded; other exclusion criteria were a known immunosuppressive condition, medically diagnosed or treated wheezing within 42 days before enrollment, a history of severe asthma (as judged by the investigator), body temperature higher than 37.8°C (100°F) measured orally or the equivalent within 3 days before enrollment, and the use of aspirin or salicylate-containing products within 30 days before enrollment. Children with mild or moderate asthma or a history of wheezing (i.e., more than 42 days before enrollment) were included in the trial.

Children who had not previously been vaccinated against influenza were given two doses of

the assigned study vaccine; the first dose (dose 1) was administered on day 0 of the trial, and the second dose was administered 28 to 42 days later. Those who had previously been vaccinated against influenza were given only one dose. Subjects who were assigned to receive live attenuated vaccine, which was administered intranasally, also received a concurrent injection of intramuscular saline, and those assigned to receive inactivated vaccine, which was administered intramuscularly, also received a concurrent intranasal mist of saline.

VACCINES AND PLACEBO

The live attenuated intranasal vaccine was a refrigeration-stable (2 to 8°C) formulation of the currently licensed frozen FluMist (LAIV, MedImmune). This vaccine consisted of three cold-adapted reassortant influenza viruses grown in specific pathogen-free chicken eggs. Each dose of vaccine contained approximately 10^7 fluorescence focus assay units of each of the three strains of the 2004–2005 influenza season, as recommended by the Food and Drug Administration (A/New Caledonia/20/99 [H1N1], A/Wyoming/3/2003 [an A/Fujian/411/2002 (H3N2)–like virus], and B/Jilin/20/2003 [a B/Shanghai/361/2002-like virus]). A total of 0.2 ml of vaccine was administered (0.1 ml into each nostril with the use of an intranasal-spray device).

The licensed inactivated vaccine consisted of the recommended 2004–2005 influenza strains (A/New Caledonia/20/99 [H1N1], A/Wyoming/3/2003 [an A/Fujian/411/2002 (H3N2)–like virus], and B/Jiangsu/10/2003 [a B/Shanghai/361/2002-like virus]), and the vaccine was administered by intramuscular injection, according to the manufacturer's dosing instructions. In the United States and Asia, Fluzone (Aventis Pasteur) was used, and in Europe and the Middle East, Vaxigrip (Aventis Pasteur) was used. Children 6 to 35 months of age received 0.25 ml of intramuscular inactivated vaccine, and those 36 to 59 months of age received 0.5 ml of intramuscular inactivated vaccine.

Intranasal and intramuscular placebos were composed of physiologic saline and were given in a manner identical to the administration of the corresponding study vaccine. The subject, the subject's parent or guardian, the staff at the clinical site who were evaluating the subjects (including the investigators, study nurses, and coordinators), and the clinical, biostatistical, and data-management staff employed by the sponsor were unaware of the treatment assignments. The vaccines and placebos were maintained at 2 to 8°C and were shipped by express courier to the study sites.

SURVEILLANCE FOR OUTCOMES AND SYMPTOMS OF INFLUENZA

Parents or guardians recorded local reactions, daily temperatures (oral, axillary, or rectal), systemic adverse events, and concomitant medications on worksheets from the time that dose 1 was administered until 42 days after the administration of the second dose, or until 42 days after dose 1 among subjects who received only one dose. Data on medically significant wheezing and serious adverse events (defined as events that were life-threatening or that resulted in death, hospitalization or prolonged hospitalization, significant disability or incapacity, or another important medical event requiring intervention to prevent one of these outcomes) were collected from the day of dose 1 until the end of the influenza surveillance period, extending through May 31, 2005. Medically significant wheezing was prospectively defined as the presence of wheezing on a physical examination conducted by a health care provider, with a prescription for a daily bronchodilator; respiratory distress; or hypoxemia. Study staff contacted the children's parents or guardians every 7 to 10 days throughout the influenza surveillance period, and if symptoms defined in the study protocol as suggestive of influenza were reported, nasal swabs for viral cultures were obtained either at the study site or at the child's home. Virologic methods are summarized in the Supplementary Appendix (available with the full text of this article at www.nejm.org).

STATISTICAL ANALYSIS

Assuming a 3.0% attack rate in the group that received inactivated vaccine and a 1.8% attack rate in the group that received live attenuated vaccine (relative efficacy rate, 40%) and assuming that sufficient data would be collected for 90% of the children to be included in the according-to-protocol population, we calculated that a sample of 8500 children would provide more than 90% power to demonstrate the superiority of live attenuated vaccine to inactivated vaccine (see the Statistics

section in the Supplementary Appendix). The primary end point was the efficacy of live attenuated vaccine, as compared with that of inactivated vaccine, in preventing culture-confirmed influenza-like illness as defined by the Centers for Disease Control and Prevention (CDC), modified to account for the subject's age, caused by well-matched influenza strains. The modified CDC definition of influenza-like illness was an oral temperature of 37.8°C or higher or the equivalent in the presence of cough, sore throat, or runny nose or nasal congestion occurring on the same or consecutive days; the addition of runny nose or nasal congestion to the case definition accounts for the age modification. Culture-positive influenza strains were assessed according to whether the isolated virus was well matched or significantly drifted to the vaccine strains. For detailed information on the statistical methods, see the Supplementary Appendix.

Secondary efficacy end points included the efficacy of live attenuated vaccine, as compared with that of inactivated vaccine, in preventing culture-confirmed influenza-like illness (according to the modified CDC definition) caused by antigenically mismatched influenza viruses and by all influenza viruses. Other efficacy end points included any culture-confirmed symptomatic influenza infection (as distinguished from influenza-like illness that met the modified CDC definition), medically diagnosed acute otitis media with fever and antibiotic use, and medically diagnosed lower respiratory illness, all associated with a positive nasal-swab culture for influenza virus at any time during the interval between the seventh day before the onset of the illness and the seventh day after the end of the illness.

RESULTS

STUDY POPULATION AND FOLLOW-UP

From October 20 to October 29, 2004, a total of 8475 children were enrolled (for details on the study populations, see Fig. 1 in the Supplementary Appendix). On average, 34 children (range, 1 to 270; median, 26) underwent randomization at each study site. Safety data were available for 8352 children, 7852 of whom were included in the analysis of the according-to-protocol population. Demographic and other characteristics, including number of days of follow-up, were well balanced between the group that received live attenuated vaccine and the group that received inactivated vaccine (Table 1). A total of 1880 of the children had previously received an influenza vaccine, and 6472 had not previously been vaccinated. Of those who received dose 1 of the vaccine and were assigned to receive a second dose, 3002 (92.4%) in the live-attenuated-vaccine group and 3034 (94.0%) in the inactivated-vaccine group received both doses. Overall on entry into the trial, 5.7% of the children in each group had underlying medical conditions, 21% had a history of any wheezing (as reported by a parent, guardian, or health care provider), and 6% had recurrent wheezing. More than 20,000 nasal specimens were cultured during the surveillance period (2.4 cultures per child).

EFFICACY

Kaplan–Meier curves for the time of the acquisition of a culture-confirmed influenza-like illness (according to the modified CDC definition) in the two groups are shown in Figure 1, and the attack rates are summarized in Table 2. There were 185 (54.9%) fewer cases of influenza in the live-attenuated-vaccine group (153 cases; attack rate, 3.9%) than in the inactivated-vaccine group (338 cases; attack rate, 8.6%) ($P<0.001$). According to the virus subtype, vaccination with live attenuated vaccine resulted in 89.2% fewer cases of influenza A/H1N1 ($P<0.001$), 79.2% fewer cases of influenza A/H3N2 ($P<0.001$), and 16.1% fewer cases of influenza B ($P=0.19$). The live attenuated vaccine was significantly more protective against both well-matched and mismatched influenza A viruses (Table 2). All isolates of H1N1 virus were regarded as antigenically matched. All isolates of H3N2 virus were antigenically mismatched. In contrast, the circulating B strains were divided into two lineages, Yamagata-like (strains that were antigenically matched and mismatched to vaccine) and Victoria-like (antigenically mismatched to vaccine). Although the difference was not significant, live attenuated vaccine showed a relative efficacy of 27%, as compared with inactivated vaccine, against the matched B strains, but there was no significant difference in efficacy against mismatched B strains.

For all culture-confirmed symptomatic influenza, the overall attack rates were 5.0% in the group

that received live attenuated vaccine and 10.0% in the group that received inactivated vaccine, with a 50.6% reduction in the live-attenuated-vaccine group, as compared with the inactivated-vaccine group (P<0.001). Significant reductions were also seen in the overall attack rates of acute otitis media and lower respiratory illness associated with positive influenza cultures, as diagnosed by a health care provider, with a relative efficacy in the live-attenuated-vaccine group of 50.6% (P=0.004) and 45.9% (P=0.046), respectively (see Table 1 in the Supplementary Appendix).

ADVERSE EVENTS

The incidence of pain, redness, and swelling at the injection site, with most instances reported as mild to moderate in severity, was higher in the group that received inactivated vaccine than in the group that received intramuscular placebo. Among subjects being vaccinated for the first time, 57.0% of those receiving intramuscular placebo and 46.3% of those receiving intranasal placebo had a runny or stuffy nose within 10 days after vaccination. With fever defined as a temperature of more than 37.8°C, fever occurred in 5.4%

Table 1. Characteristics and Follow-up of Subjects Included in the Safety Population.*

Variable	Live Attenuated Vaccine	Inactivated Vaccine	Total
No. of subjects	4179	4173	8352
History of influenza vaccination — no. (%)	933 (22.3)	947 (22.7)	1880 (22.6)
Mean age at first vaccination — mo	25.7	25.6	25.6
Age distribution — no. (%)			
6–23 mo	1992 (47.7)	1975 (47.3)	3967 (47.5)
6–11 mo	684 (16.4)	683 (16.4)	1367 (16.4)
12–23 mo	1308 (31.3)	1292 (31.0)	2600 (31.1)
24–35 mo	1372 (32.8)	1379 (33.0)	2751 (32.9)
36–59 mo	815 (19.5)	818 (19.6)	1633 (19.6)
60 mo	0	1 (<0.1)	1 (<0.1)
Sex — no. (%)			
Male	2142 (51.3)	2147 (51.4)	4289 (51.4)
Female	2037 (48.7)	2026 (48.6)	4063 (48.6)
Race or ethnic group — no. (%)†			
White and non-Hispanic	3351 (80.2)	3356 (80.4)	6707 (80.3)
Black	171 (4.1)	156 (3.7)	327 (3.9)
Hispanic	267 (6.4)	272 (6.5)	539 (6.5)
Asian	309 (7.4)	307 (7.4)	616 (7.4)
Other	81 (1.9)	82 (2.0)	163 (2.0)
History of any wheezing — no. (%)	899 (21.5)	863 (20.7)	1762 (21.1)
History of recurrent wheezing — no. (%)	271 (6.5)	239 (5.7)	510 (6.1)
History of asthma — no. (%)	164 (3.9)	169 (4.0)	333 (4.0)
Duration of follow-up — days			
Median	219	219	219
Range	0–224	0–224	0–224

* The categories of any wheezing, recurrent wheezing, and asthma were not mutually exclusive.
† Race or ethnic group was reported by the child's parent or guardian.

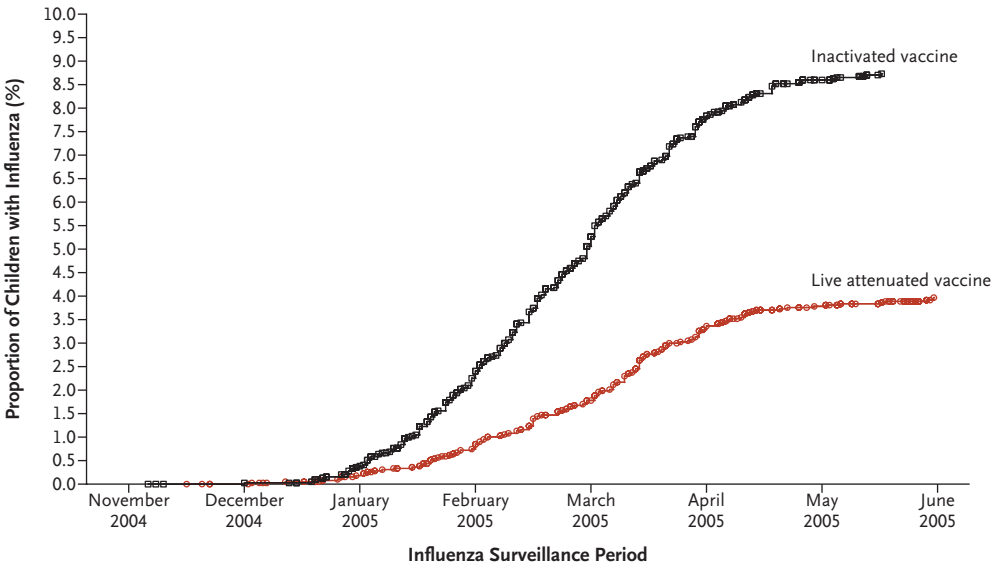

Figure 1. Kaplan–Meier Curves for the Time to the First Culture-Confirmed Report of Influenza in the Two Vaccine Groups.

Culture-confirmed influenza was caused by any wild-type influenza strain (regardless of antigenic match or mismatch to vaccine) in children who received a study vaccine according to the study protocol (P<0.001 by the log-rank test). Of 3936 children given inactivated vaccine, 338 had influenza, and of 3916 children given live attenuated vaccine, 153 had influenza. Each square denotes one infected child in the inactivated-vaccine group, and each circle one infected child in the live-attenuated-vaccine group.

of the live-attenuated-vaccine group and 2.0% of the inactivated-vaccine group on day 2 after receipt of dose 1 of vaccine (P<0.001). With the use of a higher temperature cutoff (fever defined as 38.9°C [>102°F]), the incidence of fever was low (<1% on day 2, after receipt of dose 1) in both vaccine groups. No significant differences in fever were found between the two groups after the second dose (see Fig. 2 in the Supplementary Appendix).

The rates of medically significant wheezing during the 42-day period after each dose of vaccine are shown in Table 3. Overall, there was no significant difference in medically significant wheezing between the two groups. In previously unvaccinated children, after dose 1, there were 74 cases of medically significant wheezing (2.3%) among children given live attenuated vaccine, as compared with 48 cases (1.5%) among those given inactivated vaccine, with a significant adjusted rate difference of 0.77% (95% confidence interval [CI], 0.12 to 1.46). The increase in medically significant wheezing was seen primarily during the second, third, and fourth weeks after vaccination (Fig. 3 in the Supplementary Appendix). Among previously unvaccinated children 24 months of age or older, there was no significant difference in the rates of medically significant wheezing between the two groups. Among those younger than 24 months of age, 55 children (3.2%) in the live-attenuated-vaccine group and 34 children (2.0%) in the inactivated-vaccine group had medically significant wheezing after receipt of dose 1, with an adjusted difference of 1.18 (95% CI, 0.13 to 2.29). The difference in the incidence of medically significant wheezing was seen primarily in children less than 12 months of age (see Fig. 4 in the Supplementary Appendix), with 12 more episodes of wheezing after dose 1 in children in this age group who received live attenuated vaccine than in those who received inactivated vaccine (3.8% vs. 2.1%, P=0.08).

A review of hospital records for children less than 24 months of age who were hospitalized with medically significant wheezing indicated a

Table 2. Influenza Attack Rates in the According-to-Protocol Population.*

Variable	Similarity to Vaccine†	Live Attenuated Vaccine (N=3916)‡		Inactivated Vaccine (N=3936)§		Reduction in Attack Rate with Live Vaccine¶
		Cases	Attack Rate	Cases	Attack Rate	
		no.	%	*no.*	%	% *(95% CI)*
Virus	Well matched	53	1.4	93	2.4	44.5 (22.4 to 60.6)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		0	0	0	0	—
B		50	1.3	67	1.7	27.3 (–4.8 to 49.9)
Age at first vaccination (any influenza virus)	Well matched					
6–23 mo		23	1.3	32	1.7	29.1 (–21.2 to 59.1)
24–35 mo		17	1.3	24	1.8	32.6 (–25.8 to 64.5)
36–59 mo		13	1.7	37	4.7	65.6 (36.3 to 82.4)
Previous vaccination (any influenza virus)	Well matched					
Yes		18	1.9	29	3.1	39.3 (–9.2 to 66.9)
No		35	1.2	64	2.1	46.9 (20.0 to 65.2)
Virus	Not well matched	102	2.6	245	6.2	58.2 (47.4 to 67.0)
A/H1N1		0	0	0	0	—
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		66	1.7	71	1.8	6.3 (–31.6 to 33.3)
Virus	Regardless of match	153	3.9	338	8.6	54.9 (45.4 to 62.9)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		115	2.9	136	3.5	16.1 (–7.7 to 34.7)

* Children had influenza-like illness and culture-positive infection. Modified CDC influenza-like illness was defined as the presence of an increased oral temperature (>100°F [37.8°C] or the equivalent) in the presence of cough, sore throat, runny nose, or nasal congestion occurring on the same or consecutive days. The analysis of the primary end point in subgroups (stratified according to age, vaccination status, and presence or absence of a history of recurrent wheezing) provided estimates of the relative efficacy of live attenuated vaccine of 24.0 to 65.6%, a finding consistent with the relative efficacy of 44.5% observed in the overall according-to-protocol population. Higher estimates of the relative efficacy of live attenuated vaccine, as compared with inactivated vaccine, against matched influenza strains were seen in 13 of the 15 countries in which matched strains were isolated.

† Viruses were characterized as antigenically similar to vaccine or not well matched to vaccine. Reference antiserum provided by the CDC was used to characterize isolates antigenically and a difference by a factor of 4 or more in the hemagglutination-inhibition titers was considered indicative of antigenic variation between two viruses.

‡ Four subjects had both influenza A/H3N2 and influenza B virus infections; two isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

§ Two subjects had both influenza A/H1N1 and influenza B virus infections; six subjects had both influenza A/H3N2 and influenza B virus infections; five isolates could not be characterized as antigenically well matched or not well matched to vaccine virus antigen.

¶ The analysis of subjects in the intention-to-treat population confirmed the results in the according-to-protocol population. The observations were robust in all subgroups (stratified according to age, vaccination status, presence or absence of a history of recurrent wheezing, and country of residence). Among children 6 to 23 months of age, in whom the overall attack rates of influenza were 3.2% in the live-attenuated-vaccine group and 7.2% in the inactivated-vaccine group, the relative efficacy of live attenuated vaccine of 55.7% was significant.

Table 3. Incidence in the Safety Population of Medically Significant Wheezing within 42 Days after Receiving Vaccine.*

Variable	Live Attenuated Vaccine	Inactivated Vaccine	Adjusted Rate Difference (95% CI)†
	no./total no. of cases (%)		
All children (6–59 mo of age)			
Previously vaccinated			
After dose 1	19/933 (2.0)	17/947 (1.8)	0.03 (–1.24 to 1.38)
Not previously vaccinated			
After dose 1	74/3246 (2.3)	48/3226 (1.5)	0.77 (0.12 to 1.46)
After dose 2	73/3002 (2.4)	67/3034 (2.2)	0.20 (–0.56 to 0.97)
Children <24 mo‡			
Previously vaccinated			
After dose 1	7/267 (2.6)	3/269 (1.1)	1.34 (–1.11 to 4.30)
Not previously vaccinated			
After dose 1	55/1725 (3.2)	34/1706 (2.0)	1.18 (0.13 to 2.29)
After dose 2	57/1578 (3.6)	39/1595 (2.4)	1.15 (–0.04 to 2.38)
Children ≥24 mo‡			
Previously vaccinated			
After dose 1	12/666 (1.8)	14/678 (2.1)	–0.49 (–2.07 to 1.10)
Not previously vaccinated			
After dose 1	19/1521 (1.2)	14/1520 (0.9)	0.30 (–0.46 to 1.09)
After dose 2	16/1424 (1.1)	28/1439 (1.9)	–0.85 (–1.83 to 0.05)
Children with a history of recurrent wheezing (6–59 mo of age)			
Previously vaccinated			
After dose 1	10/98 (10.2)	7/78 (9.0)	1.08 (–8.52 to 10.26)
Not previously vaccinated			
After dose 1	12/173 (6.9)	12/161 (7.5)	–0.43 (–6.31 to 5.38)
After dose 2	10/148 (6.8)	14/140 (10.0)	–3.26 (–10.10 to 3.33)
Children without a history of recurrent wheezing (6–59 mo of age)			
Previously vaccinated			
After dose 1	9/835 (1.1)	10/869 (1.2)	–0.07 (–1.14 to 1.02)
Not previously vaccinated			
After dose 1	62/3073 (2.0)	36/3065 (1.2)	0.84 (0.21 to 1.50)
After dose 2	63/2854 (2.2)	53/2894 (1.8)	0.37 (–0.35 to 1.13)

* The health care provider documented the wheezing as accompanied by tachypnea, retractions, or dyspnea, an oxygen saturation of less than 95%, while breathing ambient air, or receipt of a new prescription for daily bronchodilators.

† Differences in rates were adjusted for the subject's age and the presence or absence of a history of recurrent wheezing.

‡ The proportion of subjects with medically significant wheezing who were younger than 24 months of age in the two study groups who had tachypnea, dyspnea, retractions, or hypoxemia after dose 1 was similar (27% in the live-attenuated-vaccine group and 26% in the inactivated-vaccine group). A total of 12 subjects younger than 24 months of age (9 [0.5%] and 3 [0.2%], respectively) were hospitalized in association with medically significant wheezing within 42 days after receiving a dose of vaccine. No child was treated in an intensive care unit, received mechanical ventilation, or died because of medically significant wheezing. The difference in the rate of medically significant wheezing after dose 1 among previously unvaccinated children 6 to 23 months of age occurred primarily among those who were 6 to 11 months of age (3.8% in the live-attenuated-vaccine group vs. 2.1% in the inactivated-vaccine group; adjusted rate difference, 1.61% [95% CI, –0.18 to 3.53]); among children 12 to 23 months of age who had medically significant wheezing (2.8% in the live-attenuated-vaccine group vs. 2.0% in the inactivated-vaccine group), the adjusted rate difference (0.9% [95% CI, –0.42 to 2.27]) was not significant.

Table 4. Medically Significant Wheezing, Serious Adverse Events, and Rates of Hospitalization According to Age Group, through 180 Days after the Last Dose of Vaccine.*

Age	Event	Live Attenuated Vaccine	Inactivated Vaccine
		no./total no. (%)	
6–11 mo	Medically significant wheezing	93/684 (13.6)	71/683 (10.4)
	Any serious adverse event	44/684 (6.4)	23/683 (3.4)
	Hospitalization for any cause	42/684 (6.1)	18/683 (2.6)
12–59 mo	Medically significant wheezing	272/3495 (7.8)	255/3490 (7.3)
	Any serious adverse event	92/3495 (2.6)	105/3490 (3.0)
	Hospitalization for any cause	88/3495 (2.5)	101/3490 (2.9)
6–59 mo	Medically significant wheezing	365/4179 (8.7)	326/4173 (7.8)
	Any serious adverse event	136/4179 (3.3)	128/4173 (3.1)
	Hospitalization for any cause	130/4179 (3.1)	119/4173 (2.9)

* Medically significant wheezing, serious adverse events, and hospitalizations were analyzed from the day of the first dose through 180 days after the last dose of vaccine (for a breakdown according to causes of hospitalization and diagnostic category, see Table 4 in the Supplementary Appendix).

similar severity of illness among those receiving live attenuated vaccine and those receiving inactivated vaccine and in the duration of stay in the hospital, associated diagnoses, and treatment (Table 2 and Table 3 in the Supplementary Appendix). Beyond 42 days after vaccination, the rates of medically significant wheezing did not differ significantly between the two groups among children less than 24 months of age (7.6% in the live-attenuated-vaccine group and 7.1% in the inactivated-vaccine group). The proportion of those less than 24 months of age who had medically significant wheezing within 42 days after vaccination and who had at least one additional medically significant wheezing episode during the study period was similar in the two groups (32% in the live-attenuated-vaccine group and 28% in the inactivated-vaccine group); the proportion of these children who had two or more additional medically significant wheezing episodes was 4.3% and 5.3%, respectively.

The incidence of serious adverse events in the two groups was similar (136 in the live-attenuated-vaccine group and 128 in the inactivated-vaccine group) (Table 4). Six serious adverse events in the live-attenuated-vaccine group (bronchiolitis in two children, and asthma exacerbation, wheezing, acute gastroenteritis, and reactive airway disease in one child each) and five in the inactivated-vaccine group (pneumonia, wheezing, febrile convulsion, febrile convulsion and pneumonia, and viral gastroenteritis in one child each) were considered by the investigator, who was unaware of the treatment assignments, to be potentially related to the study vaccine. One death occurred in each vaccine group — one because of aspiration of a foreign body and one because of a house fire. New diagnoses of chronic diseases assessed within 180 days after the last dose of vaccine were infrequent in the two groups, with overall incidence rates of 1.7% in the live-attenuated-vaccine group and 1.3% in the inactivated-vaccine group.

A post hoc analysis for the study period through 180 days after the last dose of vaccine showed that children 6 to 11 months of age were hospitalized for any cause at a higher rate in the live-attenuated-vaccine group than in the inactivated-vaccine group (6.1% vs. 2.6%; difference in rate, 3.5% [95% CI, 1.4 to 5.8]) (Fig. 2 and Table 4, and Table 4 in the Supplementary Appendix). The rate of hospitalization for respiratory diagnoses in this age group was 3.2%, as compared with 1.2% in the two groups, respectively (absolute difference, 2.0% [95% CI, 0.5 to 3.8]). The differences in hospitalization rates among children 12 to 23 months of age (3.2% in the live-attenuated-vaccine group and 3.5% in the inactivated-vaccine group) and among children 24 to 59 months of age were not significant. Although not statistically significant, there was a trend toward a higher rate of hospitalization for any cause among children receiving live attenuated vaccine who were 6 to 47 months of age and had a history

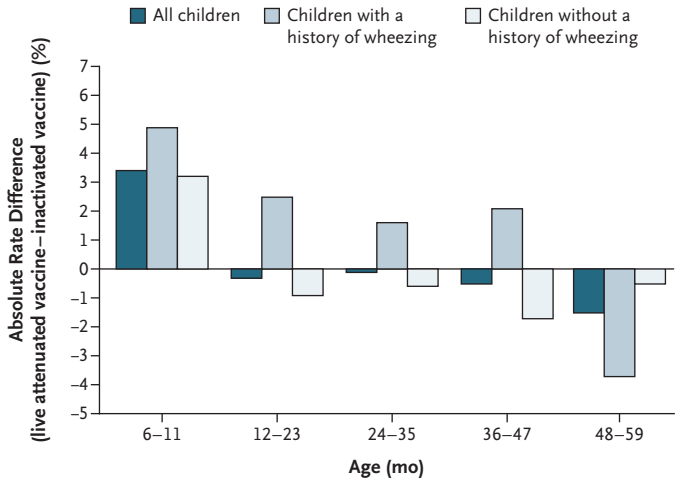

Figure 2. Difference in Rates of Hospitalization between the Two Vaccine Groups, According to Age and the Presence or Absence of a History of Wheezing Illness before Vaccination.

Among children 6 to 11 months of age, for the comparison between live attenuated vaccine and inactivated vaccine among all children regardless of whether there was a history of wheezing illness, P=0.002, and for the comparison between live attenuated vaccine and inactivated vaccine among children with a history of wheezing illness, P=0.004. Among children 48 to 59 months of age, for the comparison between live attenuated vaccine and inactivated vaccine among children without a history of wheezing, P=0.039. For all other comparisons, P>0.05. P values were calculated by inverting two one-sided tests on the basis of asymptotic methods and with the use of StatXact software, version 6.2 (Statistical Solutions).

of wheezing than among those receiving inactivated vaccine who were in the same age group and had a history of wheezing. Among children 12 to 59 months of age who did not have a history of wheezing, the rates of hospitalization for any cause were lower in the live-attenuated-vaccine group than in the inactivated-vaccine group (P=0.07).

DISCUSSION

Many believe that the successful control of annual influenza epidemics depends on vaccinating a high proportion of children.[16-18] As U.S. public health authorities move toward this goal, highly effective vaccines are needed, including vaccines with efficacy against antigenically drifted influenza strains. The live attenuated influenza vaccine we used has many of the characteristics that are desirable for the control of epidemic influenza. In addition to its high acceptability because of the mode of administration, the significantly higher efficacy of this live attenuated vaccine than of the licensed inactivated vaccine suggests that it can play an important role in the control of influenza. This higher efficacy was seen not only for well-matched strains but also for viruses that were antigenically drifted from the antigen in the vaccine.

Some earlier studies have suggested the potential for wheezing in young children after receipt of live attenuated influenza vaccine,[15] whereas others have not.[10,16] Our comprehensive, prospective safety study showed an increased risk of medically significant wheezing (within 42 days after vaccination) among recipients of live attenuated vaccine who were younger than 12 months of age. The pathogenesis of wheezing in some children given live attenuated vaccine remains unknown, although in our study, the wheezing developed after the peak of viral replication and at the time when immune responses to the viruses are expected — that is, during weeks 2, 3, and 4 after vaccination.

The incidence of serious adverse events did not differ significantly between the two groups. However, in post hoc analyses, rates of hospitalization for any cause among infants 6 to 11 months of age were significantly higher in the live-attenuated-vaccine group than in the inactivated-vaccine group. In addition, higher, but not significantly higher, rates of hospitalization were observed among children in the age groups of 12 to 23 months, 24 to 35 months, and 36 to 47 months who had a history of wheezing illness before entering the study. These observations require further study. Children 12 months of age or older who had no history of wheezing illness before vaccination and who received live attenuated vaccine had lower rates of hospitalization for any cause during the study than those who received inactivated vaccine. On the basis of our results, the risk–benefit ratio for live attenuated vaccine appears favorable among children 12 to 47 months of age who have no history of wheezing.

Until additional data are available, the observations related to medically significant wheezing and rates of hospitalization will restrict the use of live attenuated vaccine in children younger than 1 year and in children 12 to 47 months of age who have a history of asthma or wheezing. Additional studies to determine the optimal use of both vaccines in infants and young children are warranted.

The high influenza attack rate among children in the inactivated-vaccine group who were less than 12 months of age and had a history of wheezing (14%) suggests that inactivated vaccine has low efficacy in this group. Further studies might show whether an initial dose of inactivated vaccine followed by live attenuated vaccine would provide optimal protection for children younger than 1 year of age while also ensuring maximum vaccine safety.

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APPENDIX

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