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Prevention of Symptomatic Seasonal Influenza in 2005–2006 by Inactivated and Live Attenuated Vaccines

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Abstract

Background—The efficacy of influenza vaccines may vary annually. In 2004–2005, when antigenically drifted viruses were circulating, a randomized, placebo-controlled trial involving healthy adults showed that inactivated vaccine appeared to be efficacious, whereas live attenuated vaccine appeared to be less so.

Methods—In 2005–2006, we continued our trial, examining the absolute and relative efficacies of the live attenuated and inactivated vaccines in preventing laboratory-confirmed symptomatic influenza.

Results—A total of 2058 persons were vaccinated in October and November 2005. Studywide influenza activity was prolonged but of low intensity; type A (H3N2) virus was circulating, which was antigenically similar to the vaccine strain. The absolute efficacy of the inactivated vaccine was 16% (95% confidence interval [CI], −171% to 70%) for the virus identification end point (virus isolation in cell culture or identification through polymerase chain reaction) and 54% (95% CI, 4%–77%) for the primary end point (virus isolation or increase in serum antibody titer). The absolute efficacies of the live attenuated vaccine for these end points were 8% (95% CI, −194% to 67%) and 43% (95% CI, −15% to 71%), respectively.

Conclusions—With serologic end points included, efficacy was demonstrated for the inactivated vaccine in a year with low influenza attack rates. The efficacy of the live attenuated vaccine was slightly less than that of the inactivated vaccine, but not statistically greater than that of the placebo.

Trial registration—ClinicalTrials.gov identifier: NCT00133523.

Influenza vaccines for seasonal protection need to be updated annually because of the mutability of influenza viruses [1]. The efficacy of the vaccines may vary in different years, depending on how closely the circulating strains resemble those in the vaccines [2]. There may also be differences in efficacy in a given year between the 2 kinds of currently licensed influenza vaccine—the replicating live attenuated vaccine and the inactivated vaccine.

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In 2004–2005, a drifted influenza A (H3N2) virus, A/California/07/2004, circulated [3]. In addition, 2 lineages of type B were prevalent, only one of which was included among the recommended vaccine strains [4]. In that year, 3 studies of vaccine efficacy were conducted [5–7]. One compared the efficacy of live attenuated vaccine with that of inactivated vaccine in young children and indicated that overall, the live attenuated vaccine offered more protection [5]. A small study of healthy adults that involved a new formulation of recombinant vaccine containing only viral hemagglutinin suggested that it had high protective efficacy against the drifted type A (H3N2) virus [6]. We also conducted the first year of a continuing study in healthy adults [7]. We demonstrated significant protective efficacy for the inactivated vaccine, compared with placebo, for the primary outcome, which was isolation in cell culture or increase in serum antibody titer, and for virus identification end points; the efficacy of the live attenuated vaccine was less, in part because of lower efficacy against influenza type B.Wereport here the results from the second year of the study (2005–2006), in which a type A (H3N2) virus, antigenically similar to the strain included in the vaccine, circulated [8].

METHODS

Study design and objectives

The study was a multiyear, randomized, double-blind, placebo-controlled, community-based trial [7]. Our primary objective each year was to evaluate the absolute efficacies of the inactivated and live attenuated influenza vaccines (vs. placebo) in preventing laboratory-confirmed symptomatic influenza caused by circulating strains. Secondary objectives included estimating the relative efficacy of one vaccine, compared with that of the other, and examining the humoral immune response to vaccination.

Participant enrollment and follow-up

Participants were healthy men and women, aged 18 to 48 years, recruited at 6 study sites (4 University sites and 2 community sites) in Michigan. Persons with any health condition for which the inactivated vaccine was recommended or for whom either vaccine was contra-indicated were excluded [9]. The study was approved by the institutional review board at the University of Michigan Medical School.

At enrollment, written informed consent was obtained and participants were randomly assigned to receive a single intervention: the inactivated influenza vaccine or matching placebo (i.e., physiologic saline) by intramuscular injection or the live attenuated influenza vaccine or matching placebo (i.e., normal allantoic fluid) by intranasal spray, in ratios of 5:1 and 5:1, respectively. Participants and nurses administering study interventions were unaware of whether vaccine or placebo was administered, but they were aware of the route of administration. Persons initially enrolled in year 1 of the study (2004 –2005) who reenrolled in year 2 received the same intervention that they had been randomly assigned in year 1. Additional subjects were enrolled for the first time in year 2 of the study to supplement the sample size so that it reached planned levels. Blood specimens were collected immediately prior to vaccination, one month after vaccination, and at the end of the influenza season for evaluation of immune response to vaccination and serologic determination of influenza infection. Participants recorded data on solicited local and systemic reactions to vaccination on diary cards each day for 7 days after vaccination. From November 2005 through April 2006, participants reported the occurrence of illnesses with 2 or more respiratory or systemic signs or symptoms, and throat swab specimens were collected for influenza isolation and identification.

Vaccines and placebos

Both the inactivated vaccine (Fluzone; Sanofi Pasteur) and the live attenuated vaccine (FluMist; MedImmune) were licensed for use during the 2005–2006 influenza season. Each 0.5-mL dose of Fluzone for intramuscular administration was formulated to contain 15 μg hemagglutinin from each of the following strains: A/New Caledonia/20/99 (H1N1), A/New York/55/2004 (H3N2) [A/California/7/2004 like], and B/Jiangsu/10/2003 [B/Shanghai/361/2002 like]. Each 0.5-mL dose of FluMist for intranasal administration was formulated to contain a median tissue-culture infective dose of $10^{6.5}$–$10^{7.5}$ live attenuated influenza virus reassortants of the same strains.

Efficacy measurements

Symptomatic influenza-like illness was characterized by at least 1 respiratory symptom (cough or nasal congestion) plus at least 1 systemic symptom (fever or feverishness, chills, or body aches). Eligible illnesses also had to have occurred during the period of surveillance-defined influenza activity. The predetermined primary outcome was development of symptomatic influenza A or B illness that was laboratory-confirmed, either by isolation of influenza virus in cell culture or by comparison of paired post-vaccination (preseason) and postseason serum samples that showed a ≥4-fold increase in hemagglutination-inhibition antibody titer to a circulating influenza strain. Secondary end points included illnesses confirmed by identification of virus in real-time polymerase chain reaction (PCR) assays.

Laboratory assays

Laboratory tests were performed in the influenza laboratory at the University of Michigan, School of Public Health [7]. All throat swab samples collected during surveillance were tested in cell culture to identify participants with culture-positive influenza and to define the period of local influenza activity. Throat swab samples obtained from participants with symptomatic influenza-like illness were tested in real-time PCR assays (Applied Biosystems) with primers and probes designed by the Influenza Division of the Centers for Disease Control and Prevention (CDC) for universal detection of influenza A and B viruses. All isolates were strain typed and evaluated for antigenic relatedness to vaccine strains by the CDC Influenza Division. Serum samples collected from all participants with symptomatic influenza-like illnesses and serum samples from a subset of randomly identified participants without similar illnesses were tested with the hemagglutination-inhibition assay to measure the immune response to vaccination and for serologic determination of influenza infection. The viral antigens used in the assay represented the virus strains present in the vaccines plus the circulating A (H3N2) variant, A/Wisconsin/67/2005 [8].

Statistical analysis

Absolute and relative efficacy were estimated by calculation of the relative risk of laboratory-confirmed symptomatic influenza in each vaccine group, compared with the placebo group, and in one vaccine group compared to the other, respectively, with calculation of exact confidence intervals [7]. For the purpose of efficacy analyses, the group who received injected placebo and the group who received nasal spray placebo were considered equivalent and combined. Point estimates of vaccine efficacy were calculated as follows: (1 − the relative risk) × 100. Estimates were adjusted for participation in year 1 of the study (2004 – 2005). Differences in the proportions of reactions reported after vaccination between each vaccine group and the matching placebo group were examined using Fisher's Exact test. $P < .05$ or a positive lower bound of the confidence interval for vaccine efficacy was considered to indicate statistical significance. Statistical analyses were generated using the SAS (version 8.2; SAS Institute) and StatXact (version 7; Cytel) statistical packages.

Assuming absolute vaccine efficacies of 80%, the study was planned to have statistical power sufficient to estimate efficacy with a 2-sided 95% confidence interval (CI) with a positive lower bound. Given a conservative attack rate of 5% for community influenza, we estimated that we would need to enroll 1800 subjects.

RESULTS

Participants

A total of 2058 participants received study interventions during October and November 2005. Of 1247 participants initially enrolled in year 1 of the study (2004–2005), 972 (77.9%) continued to participate in year 2; the proportion of prior-year study participants did not significantly vary by intervention group ($P = .76$). In addition, 1086 new subjects were enrolled in year 2 of the study and randomly assigned to a study intervention. Participant characteristics were similar across intervention groups; the mean age of participants was 24.9 years, 1440 (70.0%) of the participants were <25 years old, and 1246 (60.5%) were women. There were 73 participants (3.5%) who failed to complete all scheduled visits; loss to follow-up did not significantly vary by intervention group ($P = .76$).

Reported reactogenicity

Table 1 compares the frequencies of reported reactions for each vaccine group and the group that received the matching placebo, similarly administered. Arm soreness, arm redness, and muscle aches were all significantly associated with receipt of the inactivated vaccine; trouble breathing and red eyes, reported in other studies as ocular respiratory syndrome [10], were also associated with receipt of the inactivated vaccine, but smaller risk differences were measured. Sore throat and runny nose or congestion were the only reactions significantly associated with receipt of the live attenuated vaccine.

Serious Adverse Events

A total of 3 serious adverse events occurred among participants within 30 days after receipt of study interventions, and 18 additional events occurred during the next 6 months that participants were followed up. Only 1 adverse event—hospitalization for viral meningitis after receipt of the live attenuated vaccine—was considered to be possibly related to the study intervention.

Immune response to vaccine

Serum samples collected from all 526 participants who developed symptomatic influenza-like illness and serum samples from a subset of 480 participants who did not develop similar illnesses (1006 [49%] of 2058 participants) were tested with the hemagglutination-inhibition assay. Comparison of paired serum samples collected before vaccination and 30 days after vaccination showed a ≥4-fold increase in hemagglutination-inhibition antibody titer to an influenza strain in the following groups: 341 participants (76.5%) who received inactivated vaccine and 88 participants (20.4%) who received live attenuated vaccine, to the A/H3 vaccine strain ($P < .001$); 333 participants (74.7%) who received inactivated vaccine and 118 participants (27.4%) who received live attenuated vaccine, to the A/H3 variant that circulated in 2005–2006 ($P < .001$); 230 participants (51.6%) who received inactivated vaccine and 42 participants (9.7%) who received live attenuated vaccine, to the A/H1 vaccine strain ($P < .001$); and 255 participants (57.2%) who received inactivated vaccine and 86 participants (20.0%) who received live attenuated vaccine, to the type B vaccine strain.

Studywide influenza activity

Among the reported illnesses, 621 illness episodes that occurred in 526 participants (25.6%) met the criteria and qualified as symptomatic influenza-like illness cases. Influenza A (H3N2) circulated in the study area from early January through mid-April; influenza type B also circulated, but at very low levels. This situation was similar to that observed nationally and in the state as a whole [8,11].

Laboratory-confirmed symptomatic influenza

Of 526 participants with symptomatic influenza-like illness, 24 (4.6%) had culture-confirmed influenza. All 23 isolates recovered from participants with culture-confirmed influenza A were strain-typed as theA(H3N2) circulating variant, A/Wisconsin/67/2005 [8]. The single influenza B isolate recovered was strain-typed as B/Ohio/01/2005 like, part of the Victoria lineage not included in the vaccine. Thirty-two participants (6.1%) with symptomatic influenza-like illness had PCR-confirmed influenza; 31 of the confirmed illnesses were type A (H3N2) and 1 was type B. Forty-seven participants (8.9%) with symptomatic influenza-like illness had serologic evidence of influenza infection; 46 were serologically confirmed as type A (H3N2) and 1 was type B.

Vaccine efficacies

Influenza virus was identified by culture or PCR in only 6 participants (1.8%) in the placebo group (table 2). Given the lower than expected attack rate, for these end points the study was underpowered to measure statistically significant vaccine efficacy. The absolute efficacy of the inactivated vaccine was 23% (95% CI, − 153% to 73%) for both the “virus isolation in culture” end point and the “real-time PCR identification” end point; absolute efficacy was 16% (95% CI, − 171% to 70%) for the combined “virus isolation and/or real-time PCR identification” end point. The absolute efficacy of the live attenuated vaccine was 8% (95% CI, −194% to 67%) for end points that considered PCR results, but it was 61% (95% CI, −48% to 89%) for the virus isolation end point.

The attack rate in the placebo group increased to 4.7% when we added cases in which infection was identified by serologic testing, resulting in increased statistical power. The absolute efficacy of the inactivated vaccine was 54% (95% CI, 4%–77%) for the primary study end point—virus isolation in culture and/or increase in antibody titer. The absolute efficacy of the live attenuated vaccine for the primary end point was slightly less, at 43% (95% CI, −15% to 71%), but not statistically greater than that of the placebo.

DISCUSSION

In 2004–2005, the first year of our ongoing study, subject enrollment fell short of projected targets; however, the influenza season was a typical one, with various indicators above epidemic threshold levels [3]. A drifted type A (H3N2) virus, A/California/07/2004, and type B viruses of both lineages circulated. In our study in that year, the attack rate in the placebo group as measured by virus isolation and/or real-time PCR identification was 7.8%, and thus we had sufficient statistical power to assess the significant efficacy of either vaccine against placebo. The vaccine efficacy for this combined end point was 75% (95% CI, 42%–90%) for the inactivated vaccine and 48% (95% CI, −7% to 74%) for the live attenuated vaccine [7].

In 2005–2006, more participants than projected were enrolled; however, the influenza season was protracted and of low intensity. Attack rates in the placebo group, as determined by virus isolation and/or real-time PCR identification, were only 1.8%—far lower than expected in most years [8]. With such low attack rates, statistically significant reductions produced by vaccine were difficult to demonstrate, and in fact, neither vaccine showed significant benefit over

placebo for the “virus isolation and/or real-time PCR identification” end points. The primary end point (which was determined when the Investigational New Drug agreement under which the study was carried out was approved) —virus isolation combined with serologic identification of infection—produced an attack rate in the placebo group of 4.7%, and higher efficacy of the vaccines was demonstrated. The absolute efficacy of the inactivated vaccine was 54% and significantly greater than that of the placebo, whereas the absolute efficacy of the live attenuated vaccine was modestly less. Interpretation of efficacy estimates using serologic end points must be approached with caution; it is known that, for several reasons, they will favor the inactivated vaccine over the live attenuated vaccine [12,13].

In 2004–2005, the live attenuated vaccine performed less well than the inactivated vaccine when each was compared with the placebo group, but in the second year of the study there was little evidence of a difference. How can this be explained? First, in contrast to the first year, the low attack rates in 2005–2006 made statistically significant reductions produced by either vaccine difficult to demonstrate. Second, in the first year, the differences between the 2 vaccines appeared to be related, in part, to differences in efficacy against type B influenza, with the live attenuated vaccine performing less well; the 2005–2006 season did not offer an opportunity to test efficacy against type B influenza. Likewise, the type A/H3 virus circulating in the first year of the study was drifted from the vaccine strain, whereas in the second year of the study, the circulating virus was similar to the vaccine strain. Finally, it is possible that there was variable susceptibility to the live attenuated vaccine virus at the time of vaccination in year 1 of the study, compared with year 2; for example, the A/H3 vaccine virus in 2004–2005 was similar to the Fujian strain, a virus that had caused major outbreaks during the previous year [14].

With the low attack rate in 2005–2006, the efficacy estimates were unstable and varied with the particular laboratory criteria that were used. Still, we did demonstrate continuing efficacy at least for the inactivated vaccine. Because vaccine efficacy can change from year to year and because, given the experience in the previous year, efficacy may not be consistently related to drift, further evaluation of vaccines in different situations is warranted. In particular, it is important to determine additional correlates of protection, of which serologic antibody titer is only one. All of this will help to develop improved and perhaps more predictably efficacious vaccines.

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Table 1

Local and systemic reactions reported by 1917 participants in the 2005–2006 study within 7 days after receipt of study interventions.

Reported reaction	Intervention administered by intramuscular injection				Intervention administered by intransal spray			
	Inactivated vaccine (*n* = 818)	Placebo (*n* = 155)	Difference in risk, %	*P*	Live attenuated vaccine (*n* = 787)	Placebo (*n* = 157)	Difference in risk, %	*P*
Fever	62 (7.6)	11 (7.1)	0.5	.83	62 (7.9)	10 (6.4)	1.5	.52
Chills	55 (6.7)	8 (5.2)	1.5	.47	45 (5.7)	7 (4.5)	1.2	.53
Runny nose or congestion	201 (24.6)	29 (18.7)	5.9	.12	336 (42.7)	49 (31.2)	11.5	**.008**
Cough	119 (14.6)	15 (9.7)	4.9	.11	127 (16.1)	17 (10.8)	5.3	.09
Sore throat	133 (16.3)	24 (15.5)	0.8	.81	212 (26.9)	26 (16.6)	10.3	**.006**
Headache	225 (27.5)	34 (21.9)	5.6	.15	261 (33.2)	52 (33.1)	0.1	.99
Muscle aches	110 (13.5)	9 (5.8)	7.7	**.008**	112 (14.2)	15 (9.6)	4.6	.12
Weakness	180 (22.0)	27 (17.4)	4.6	.20	181 (23.0)	27 (17.2)	5.8	.11
Abdominal pain	40 (4.9)	4 (2.6)	2.3	.20	28 (3.6)	5 (3.2)	0.4	.82
Trouble breathing	23 (2.8)	0 (0.0)	2.8	**.018**	20 (2.5)	3 (1.9)	0.6	.22
Red eyes	20 (2.4)	0 (0.0)	2.4	**.030**	15 (1.9)	3 (1.9)	0.0	1.00
Arm soreness	412 (50.4)	22 (14.2)	36.2	**<.001**	33 (4.2)	8 (5.1)	−0.9	.61
Arm redness	58 (7.1)	1 (0.7)	6.4	**.002**	5 (0.6)	2 (1.3)	−0.7	.23
Other[a]	48 (5.9)	8 (5.2)	0.7	.73	62 (7.9)	11 (7.0)	0.9	.71

NOTE. Data are no. (%) of participants, unless otherwise indicated. Data on reactions was obtained from 93.1% of 2058 participants; reported reactions were selected from a list of solicited reactions. The trivalent inactivated influenza vaccine used was Fluzone (Sanofi Pasteur), and the trivalent live attenuated influenza vaccine used was FluMist (MedImmune). The placebo used was physiologic saline administered as an intramuscular injection or normal allantoic fluid administered as an intranasal spray. Bold type indicates significant *P* values.

[a] Other reported reactions reported by at least 5 participants included nausea (*n* = 34), diarrhea (*n* = 12), sneezing (*n* = 10), rash (*n* = 8), dizziness (*n* = 7), itchiness (*n* = 6), ear ache (*n* = 5). None of these reactions were significantly more likely to be reported by participants who received a vaccine, compared with those who received the matching placebo.

Table 2

Estimated absolute and relative efficacies of the trivalent inactivated influenza vaccine (TIV) and the live attenuated influenza vaccine (LAIV) during the 2005–2006 influenza season in Michigan.

End point	Cumulative incidence, no. (%) of participants			RR (95% CI)			Relative reduction[a] (95% CI)		
							Absolute efficacy		
	TIV (*n* = 867)	LAIV (*n* = 853)	Placebo (*n* = 338)	TIV vs. placebo	LAIV vs. placebo	TIV vs. LAIV	TIV vs. placebo	LAIV vs. placebo	Relative efficacy, TIV vs. LAIV
Virus isolation[b]	12 (1.4)	6 (0.7)	6 (1.8)	0.77 (0.27 to 2.53)	0.39 (0.11 to 1.48)	1.95 (0.68 to 6.39)	23 (−153 to 73)	61 (−48 to 89)	−95 (−539 to 32)
Real-time PCR identification[c]	12 (1.4)	14 (1.6)	6 (1.8)	0.77 (0.27 to 2.53)	0.92 (0.33 to 2.94)	0.84 (0.36 to 1.96)	23 (−153 to 73)	8 (−194 to 67)	16 (−96 to 64)
Virus isolation and/or real-time PCR identification[d]	13 (1.5)	14 (1.6)	6 (1.8)	0.84 (0.30 to 2.71)	0.92 (0.33 to 2.94)	0.91 (0.40 to 2.10)	16 (−171 to 70)	8 (−194 to 67)	9 (−110 to 60)
Seropositivity[e]	10 (1.2)	23 (2.7)	14 (4.1)	0.28 (0.11 to 0.67)	0.65 (0.32 to 1.37)	0.43 (0.18 to 0.93)	72 (33 to 89)	35 (−37 to 68)	57 (7 to 82)
Virus isolation and/or seropositivity[f]	19 (2.2)	23 (2.7)	16 (4.7)	0.46 (0.23 to 0.96)	0.57 (0.29 to 1.15)	0.81 (0.42 to 1.56)	54 (4 to 77)	43 (−15 to 71)	19 (−56 to 58)
Virus isolation and/or real-time PCR identification and/or seropositivity[g]	19 (2.2)	24 (2.8)	16 (4.7)	0.46 (0.23 to 0.96)	0.60 (0.30 to 1.20)	0.78 (0.40 to 1.48)	54 (4 to 77)	40 (−20 to 70)	22 (−48 to 60)

NOTE. The population was all 2058 enrolled participants who were randomly assigned to a vaccine or placebo group and who received vaccine or placebo. The TIV used was Fluzone (Sanofi Pasteur), and the LAIV used was FluMist (MedImmune). The placebo was physiologic saline administered as an intramuscular injection or normal allantoic fluid administered as an intranasal spray. Efficacy estimates were adjusted for participation in year 1 (2004–2005); exact 95% confidence intervals (CIs) were calculated. RR, relative risk; PCR, polymerase chain reaction.

[a] Point estimates of vaccine efficacy were calculated as follows: (1−RR) × 100.

[b] Defined as a symptomatic influenza illness episode that was laboratory-confirmed as influenza by isolation of virus in cell culture and identification by fluorescent antibody assay.

[c] Defined as a symptomatic influenza illness episode that was laboratory-confirmed as influenza by means of real-time PCR assay.

[d] A combined end point, defined as a symptomatic influenza illness episode that was laboratory-confirmed as influenza by virus isolation in cell culture and/or by means of real-time PCR assay.

[e] Defined as a symptomatic influenza illness episode in which a ≥4-fold increase in antibody titer was observed (when preseason [obtained 30 days after vaccination] and postseason blood samples were compared) to vaccine or circulating influenza A or B strain, as determined by hemagglutination-inhibition assay.

[f] A combined end point and the primary study end point, defined as a symptomatic influenza episode that was laboratory-confirmed as influenza by virus isolation in culture or by serologic analysis, as defined above.

[g] A combined end point, defined as a symptomatic influenza episode that was laboratory-confirmed as influenza by isolation in culture, identification by real-time PCR, and/or serologic analysis, as defined above.