Comparative Efficacy of Inactivated and Live Attenuated Influenza Vaccines

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ABSTRACT

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BACKGROUND

The efficacy of influenza vaccines may vary from year to year, depending on a variety of factors, and may differ for inactivated and live attenuated vaccines.

METHODS

We carried out a randomized, double-blind, placebo-controlled trial of licensed inactivated and live attenuated influenza vaccines in healthy adults during the 2007–2008 influenza season and estimated the absolute and relative efficacies of the two vaccines.

RESULTS

A total of 1952 subjects were enrolled and received study vaccines in the fall of 2007. Influenza activity occurred from January through April 2008, with the circulation of influenza types A (H3N2) (about 90%) and B (about 9%). Absolute efficacy against both types of influenza, as measured by isolating the virus in culture, identifying it on real-time polymerase-chain-reaction assay, or both, was 68% (95% confidence interval [CI], 46 to 81) for the inactivated vaccine and 36% (95% CI, 0 to 59) for the live attenuated vaccine. In terms of relative efficacy, there was a 50% (95% CI, 20 to 69) reduction in laboratory-confirmed influenza among subjects who received inactivated vaccine as compared with those given live attenuated vaccine. The absolute efficacy against the influenza A virus was 72% (95% CI, 49 to 84) for the inactivated vaccine and 29% (95% CI, −14 to 55) for the live attenuated vaccine, with a relative efficacy of 60% (95% CI, 33 to 77) for the inactivated vaccine.

CONCLUSIONS

In the 2007–2008 season, the inactivated vaccine was efficacious in preventing laboratory-confirmed symptomatic influenza A (predominately H3N2) in healthy adults. The live attenuated vaccine also prevented influenza illnesses but was less efficacious. (ClinicalTrials.gov number, NCT00538512.)

TWO DIFFERENT TYPES OF VACCINE FOR the prevention of seasonal influenza are currently licensed, one containing inactivated viruses and the other containing live attenuated viruses. Both vaccines are trivalent, with the three components updated annually as needed on the basis of national and international recommendations.[1] The efficacy of both vaccines can be affected by a number of factors, including the age and health of the vaccine recipients, and by the extent of antigenic similarity between the strains included in the vaccines and those that actually circulate months later.[2-6] Thus, there can be differences in efficacy from year to year. There are also issues related to the fact that although two distinct type B lineages have recently been in circulation each year, only one can be included in the licensed vaccines.[7] Similar issues may be encountered if the novel influenza A (H1N1) virus of swine origin continues to circulate along with viruses of human origin.[8]

Beginning in the 2004–2005 influenza season, we conducted a series of annual studies to estimate the absolute and relative efficacies of licensed inactivated and live attenuated vaccines in healthy adults younger than 50 years of age.[9,10] We report here estimates of the efficacies of the two vaccines in the 2007–2008 season, using end points determined by viral culture and polymerase-chain-reaction (PCR) assay. Influenza-related morbidity was high in 2007–2008, a year in which type A (H3N2) viruses predominated; these viruses were characterized by a slight antigenic drift from the type A (H3N2) viral strain included in the vaccine.[11,12]

METHODS

STUDY DESIGN AND OBJECTIVES

This randomized, double-blind, placebo-controlled, community-based trial was conducted over a 4-year period, beginning in 2004. As previously described, our primary objective each year was to evaluate the absolute efficacies of the inactivated and live attenuated influenza vaccines (i.e., the efficacy of each compared with placebo) in preventing laboratory-confirmed, symptomatic influenza caused by circulating strains (whether or not they were antigenically similar to the strains included in the vaccines).[9,10] A secondary objective was to estimate the relative efficacy (i.e., the efficacy of one vaccine as compared with the other) for each year of the study.

For the first 3 years, the study was supported by a grant from the National Institute of Allergy and Infectious Diseases and in year 4 (2007–2008) by an unrestricted grant from Sanofi Pasteur. MedImmune provided the live attenuated vaccine, and Sanofi Pasteur the inactivated vaccine. These companies had no role in the design, analysis, interpretation, or reporting of the study. The study was designed by the authors, who also carried it out and analyzed the data; the authors take full responsibility for the data, the analysis, and the completeness and accuracy of this article.

ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

Eligible subjects were healthy men and women 18 to 49 years of age. Persons with any health condition for which the inactivated vaccine was specifically recommended and persons for whom either vaccine was contraindicated were excluded.[1] Subjects were recruited from the community at study sites located on four university campuses in Michigan. Subjects who participated in previous study years were eligible, but they had to respond to open enrollment. The study was approved by the institutional review board at the University of Michigan Medical School. Written informed consent was obtained from all the participants before enrollment.

All eligible subjects were randomly assigned to receive one of the interventions: the inactivated influenza vaccine or matching placebo (physiologic saline) administered by intramuscular injection or the live attenuated influenza vaccine or matching placebo (physiologic saline) administered by intranasal spray, in ratios of 5:1:5:1, respectively. Participants and nurses administering study interventions were not aware of whether vaccine or placebo was administered, but they were aware of the route of administration. After they had received the study vaccine or placebo, the participants were given diary cards listing possible reactions to vaccination and were asked to fill out a card each day for 7 days, recording any reactions that they had. From November 2007 through April 2008, participants who had two or more respiratory or systemic symptoms were asked to report them, and specimens were collected by means of throat swabs from those with evidence of illness for influenza virus isolation and identification.

VACCINES AND PLACEBOS

Both the inactivated trivalent vaccine (Fluzone, Sanofi Pasteur) and the live attenuated trivalent vaccine (FluMist, MedImmune) were licensed and approved for the 2007–2008 influenza season. Each 0.5-ml dose of the inactivated vaccine was formulated to contain 15 μg of hemagglutinin from each of the following strains: A/Solomon Islands/3/2006 (H1N1), A/Wisconsin/67/2005 (H3N2), and B/Malaysia/2506/2004 (B/Victoria lineage). Each 0.2-ml dose of the live attenuated vaccine was formulated to contain $10^{6.5-7.5}$ fluorescent focus units of live attenuated influenza virus reassortants of the same strains. Vaccines and placebos were handled and administered as previously described.[9,10]

EFFICACY MEASUREMENTS

Symptomatic influenza was defined as illness characterized by at least one respiratory symptom (cough or nasal congestion) plus at least one constitutional symptom (fever or feverishness, chills, or body aches). The primary end point was a case of symptomatic illness that was confirmed as influenza A or B by either isolation of the virus in cell culture or its identification by means of a real-time PCR assay.

LABORATORY ASSAYS

Assays to isolate and identify influenza viruses A and B were performed as described previously.[9,10] All influenza A viral isolates were submitted to the Influenza Division of the Centers for Disease Control and Prevention (CDC) for further antigenic characterization by means of hemagglutination-inhibition assays with the use of postinfection ferret antiserum raised against various viral strains. In addition, the HA1 genes of type A (H3N2) viruses, chosen to represent those viruses from persons given each vaccine and placebo, were sequenced to determine their lineage.

STATISTICAL ANALYSIS

For the purpose of efficacy analyses, the injection and nasal-spray placebo groups were determined to be equivalent and were combined. Absolute and relative efficacies were estimated by calculating the relative risk of laboratory-confirmed symptomatic influenza in each vaccine group as compared with the combined placebo group and in one vaccine group as compared with the other vaccine group, respectively, with calculation of exact confidence intervals. Point estimates of vaccine efficacy were calculated as (1−the relative risk) × 100. Differences in cumulative incidence proportions and confidence intervals for risk differences were calculated for the groups that were compared (see the Results section in the Supplementary Appendix, available with the full text of this article at NEJM.org). Differences in the proportions of reactions reported after vaccination between each vaccine group and the matching placebo group were examined with the use of Fisher's exact test.

Statistical analyses were conducted with the use of SAS (release 9.1, SAS Institute) and StatXact (version 7, Cytel) software. A P value of less than 0.05 or a positive lower limit of the confidence interval for vaccine efficacy or difference in risk was considered to indicate statistical significance. Assuming an absolute vaccine efficacy of 80% and an attack rate of 5% for influenza in the community, enrollment of 1800 subjects would provide approximately 87% power to estimate an efficacy statistically greater than zero, at an alpha level of 0.05.

RESULTS

PARTICIPANTS

Enrollment began in early October and continued through early November 2007. A total of 1963 subjects were eligible; 1952 became participants and provided a preintervention blood specimen, were randomly assigned to an intervention, and received that intervention (see Fig. 1 in the Supplementary Appendix). The mean age of the participants was 23.3 years; 1214 (62.2%) were women, and 731 (37.5%) reported having received an influenza vaccine at some time in the past (Table 1). Seventy participants (3.6%) did not complete all scheduled visits; the number of participants lost to follow-up did not vary significantly according to the study group (P=0.73).

REPORTED REACTIONS

The only local and systemic reactions that were reported by significantly more vaccine recipients than placebo recipients were arm soreness (reported by 52.6% of recipients of inactivated vaccine vs. 21.3% of recipients of corresponding placebo, P<0.001) and runny nose or congestion (52.3% of recipients of live attenuated vaccine vs. 37.7% of recipients of corresponding placebo, P=0.001).

Table 1. Baseline Characteristics of the 1952 Subjects, According to Study Group, during the 2007–2008 Influenza Season in Michigan.*

Characteristic	TIV Group (N=814)	LAIV Group (N=813)	Placebo Group (N=325)†	Total (N=1952)
Total participants — %	41.7	41.6	16.7	100.0
Age — yr	23.2±7.4	23.5±7.7	22.9±6.7	23.3±7.4
Age category — no. (%)				
18–19 yr	289 (35.5)	283 (34.8)	114 (35.1)	686 (35.1)
20–24 yr	355 (43.6)	340 (41.8)	140 (43.1)	835 (42.8)
25–34 yr	90 (11.1)	99 (12.2)	44 (13.5)	233 (11.9)
35–49 yr	80 (9.8)	91 (11.2)	27 (8.3)	198 (10.1)
Sex — no. (%)				
Female	494 (60.7)	519 (63.8)	201 (61.8)	1214 (62.2)
Male	320 (39.3)	294 (36.2)	124 (38.2)	738 (37.8)
Race or ethnic group — no. (%)‡				
White	697 (85.6)	682 (83.9)	264 (81.2)	1643 (84.2)
Nonwhite	117 (14.4)	131 (16.1)	61 (18.8)	309 (15.8)
Previous receipt of influenza vaccine — no. (%)	307 (37.7)	288 (35.4)	136 (41.8)	731 (37.4)

* Plus–minus values are means ±SD. LAIV denotes trivalent live attenuated influenza vaccine, and TIV trivalent inactivated influenza vaccine.
† Placebo was physiologic saline administered as an intramuscular injection (in 163 participants) or as an intranasal spray (in 162 participants). For the purposes of efficacy analyses, the two placebo groups were considered equivalent and were combined.
‡ Race or ethnic group was self-reported. "Nonwhite" included black, Asian, Hispanic, and other or mixed.

SERIOUS ADVERSE EVENTS

Only one serious adverse event occurred within the first 30 days: hospitalization for depression and anxiety in a recipient of intranasal placebo. This event was considered to be unrelated to the intervention. Fourteen additional serious adverse events occurred within approximately 6 months after receipt of either vaccine or placebo: eight in recipients of inactivated vaccine, four in recipients of live attenuated vaccine, and two in recipients of intranasal placebo. None of these events were considered to be related to the intervention.

CIRCULATING VIRUSES

Influenza A virus circulated in the study area from early January through late March 2008, with influenza A (H3N2) virus predominating; influenza B virus circulated from early January through mid-April 2008 (see Fig. 2 in the Supplementary Appendix). Hemagglutination-inhibition assays with the use of postinfection ferret antiserum showed that 52% of type A (H3N2) viral isolates were classified as high reactors to the A/Wisconsin/67/2005

vaccine strain, whereas the remainder were classified as low reactors. This result was interpreted as indicating variation not in antigenic identity but rather in specificity for the erythrocytes used in the assay.[13] When the HA1 genes of the viruses were sequenced, all were found to genetically resemble the A/Brisbane/10/2007 variant; this strain predominated in the United States during the winter months of 2007–2008.[11] The single influenza A (H1N1) viral isolate was characterized as A/Brisbane/59/2007-like, a recent antigenic variant of the 2007–2008 vaccine strain. All influenza B viral isolates were characterized as belonging to the B/Yamagata lineage; this lineage predominated nationally and was not represented among the 2007–2008 vaccine components.

LABORATORY-CONFIRMED INFLUENZA

A total of 119 participants (6.1%) had laboratory-confirmed symptomatic influenza (Table 2): 108 (90.8%) had influenza A (107 with the A/H3N2 viral strain and 1 with the A/H1N1 strain) and 11 (9.2%) had influenza B. In 90 participants (75.6%),

Table 2. Estimated Absolute and Relative Efficacies of the Trivalent Inactivated and Live Attenuated Influenza Vaccines.*

Confirmation of Symptomatic Influenza†	Cumulative Incidence of Influenza			Relative Risk (95% CI)			Percent Relative Reduction (95% CI)‡		
	TIV (N=813)	LAIV (N=814)	Placebo (N=325)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV	Absolute Efficacy, TIV vs. Placebo	Absolute Efficacy, LAIV vs. Placebo	Relative Efficacy, TIV vs. LAIV
	no. of participants (%)								
Positive culture	21 (2.6)	38 (4.7)	31 (9.5)	0.27 (0.15–0.49)	0.49 (0.30–0.81)	0.55 (0.31–0.97)	73 (51–85)	51 (19–70)	45 (3–69)
Positive PCR	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)
Positive culture, positive PCR, or both	28 (3.4)	56 (6.9)	35 (10.8)	0.32 (0.19–0.54)	0.64 (0.41–1.00)	0.50 (0.31–0.80)	68 (46–81)	36 (0–59)	50 (20–69)

* The study population included all 1952 enrolled participants who were randomly assigned to a vaccine or a placebo group and who actually received vaccine or placebo. The trivalent inactivated influenza vaccine (TIV) used was Fluzone (Sanofi Pasteur), and the trivalent live attenuated influenza vaccine (LAIV) used was FluMist (MedImmune). The placebo was physiologic saline administered as an intramuscular injection or as an intranasal spray. Exact 95% confidence intervals (CI) were calculated.
† Case-eligible episodes of symptomatic influenza-like illness were confirmed by culture, real-time polymerase-chain-reaction (PCR) assay, or both. Confirmation by culture was defined as isolation of virus by cell culture and subsequent identification by fluorescence antibody assay.
‡ The percent relative reduction in vaccine efficacy was defined as (1−relative risk)×100.

including all 11 with influenza B, the virus was identified by isolation in cell culture, and all 90 isolates were verified by real-time PCR assays; in 29 cases the virus was identified by real-time PCR assay only.

ESTIMATES OF ABSOLUTE AND RELATIVE VACCINE EFFICACY

With the use of culture alone to confirm cases of influenza, the absolute efficacy (the efficacy of vaccine vs. placebo) was 73% (95% confidence interval [CI], 51 to 85) for the inactivated vaccine and 51% (95% CI, 19 to 70) for the live attenuated vaccine. In terms of relative efficacy, there was a 45% (95% CI, 3 to 69) reduction in culture-confirmed cases of influenza among recipients of the inactivated vaccine as compared with recipients of the live attenuated vaccine (Table 2).

With the use of culture, real-time PCR, or both to confirm influenza cases, the absolute efficacy was 68% (95% CI, 46 to 81) for the inactivated vaccine and 36% (95% CI, 0 to 59) for the live attenuated vaccine (Table 2). In terms of relative efficacy, there was a 50% reduction (95% CI, 20 to 69) in culture-confirmed or PCR-identified influenza among recipients of the inactivated vaccine as compared with those given the live attenuated vaccine.

Vaccine efficacy, with the use of the primary end point, was also calculated separately for cases of influenza A and influenza B (Table 3). Absolute vaccine efficacy in preventing laboratory-confirmed influenza A was 72% (95% CI, 49 to 84) for the inactivated vaccine but only 29% (95% CI, −14 to 55) for the live attenuated vaccine. Relative efficacy estimates indicated that the inactivated vaccine had outperformed the live attenuated vaccine by 60% (95% CI, 33 to 77) for protection against influenza A. Too few cases of influenza B were identified to allow a reasonable analysis; however, our results suggested that neither of the vaccines was significantly better than placebo in providing protection against type B.

DISCUSSION

For many years, the serious consequences of influenza were generally thought to be limited to older persons and those with underlying chronic conditions. Use of vaccine was directed to these groups. Gradually, however, the recommendations for influenza vaccination were expanded to include, first, young children and, subsequently, all those 18 years of age or younger.[1,14-16] Persons who are in close contact with those at increased risk, whatever their age, are also included in the current recommendations for vaccination, which thus apply to a major portion of the population.

Since the only group that is not currently included in the recommendations for vaccination is healthy younger adults, this is the one population, at least in the United States, in which randomized, placebo-controlled trials can be ethically conducted.

With the availability of two types of vaccines, decisions about which one to use will be based on a variety of factors, including cost, route of administration, and side effects.[9,10,17] Differential vaccine efficacy will also be a major consideration in the choice of vaccine. Unlike the situation in children — particularly, but not limited to, those younger than 6 years of age, for whom the live attenuated vaccine appears to be superior to the inactivated vaccine[18] — the relative and even absolute efficacies of the live attenuated vaccine in adults have not previously been well established.[3,5]

Our multiyear study of comparative vaccine efficacy was initiated in 2004–2005 to resolve some of these questions. In the first year of our trial, in which an influenza A virus with moderate antigenic drift and two lineages of influenza B virus circulated, we found that the absolute efficacy of the inactivated vaccine in preventing symptomatic influenza was 67 to 78%, on the basis of several laboratory-confirmed end points.[9] In that same year, we did not find a significant absolute efficacy of the live attenuated vaccine with use of the same end points. Laboratory-confirmed outcomes were too few in number to determine whether the inactivated vaccine significantly outperformed the live attenuated vaccine. Influenza activity was relatively low in the subsequent influenza season (2005–2006). In that year, despite an enrollment that exceeded the target number, absolute efficacy was shown for only the inactivated vaccine and only when serologic end points were included.[10]

The results reported here for 2007–2008, with increased numbers of outcomes, have settled some of the issues concerning differences in vaccine efficacy suggested by the results from study year 1 (2004–2005). Whereas the earlier data were only suggestive of the superior performance of the inactivated vaccine, the current data provide clear evidence of significant differences between the two vaccines in providing protection against influenza A (H3N2) virus. These differences, indicating the superior performance of the inactivated vaccine, were apparent with the use of viral

Table 3. Absolute and Relative Efficacies of the Trivalent Inactivated and Live Attenuated Influenza Vaccines According to Influenza Type.*

Confirmation of Influenza by Culture, PCR, or Both†	Cumulative Incidence of Influenza			Relative Risk (95% CI)			Percent Relative Reduction (95% CI)‡		
	TIV (N=813)	LAIV (N=814)	Placebo (N=325)	TIV vs. Placebo	LAIV vs. Placebo	TIV vs. LAIV	Absolute Efficacy, TIV vs. Placebo	Absolute Efficacy, LAIV vs. Placebo	Relative Efficacy, TIV vs. LAIV
	no. of participants (%)								
Influenza A	22 (2.7)	55 (6.8)	31 (9.5)	0.28 (0.16 to 0.51)	0.71 (0.45 to 1.14)	0.40 (0.23 to 0.67)	72 (49 to 84)	29 (−14 to 55)	60 (33 to 77)
Influenza B	6 (0.7)	1 (0.1)	4 (1.2)	0.60 (0.14 to 2.89)	0.10 (0.00 to 1.01)	6.01 (0.73 to 276.3)	40 (−189 to 86)	90 (−1 to 100)	−501 (−27,530 to 27)

* The population included all 1952 enrolled participants who were randomly assigned to a vaccine or a placebo group and who actually received vaccine or placebo. The TIV (trivalent inactivated influenza vaccine) used was Fluzone (Sanofi Pasteur), and the LAIV (trivalent live attenuated influenza vaccine) used was FluMist (MedImmune). The placebo was physiologic saline administered as an intramuscular injection or as an intranasal spray. Exact 95% confidence intervals (CI) were calculated.

† Case-eligible episodes of symptomatic influenza-like illness were confirmed by culture, real-time polymerase-chain-reaction (PCR) assay, or both. Confirmation by culture was defined as isolation of virus by cell culture and subsequent identification by fluorescence antibody assay.

‡ The percent relative reduction in vaccine efficacy was defined as (1 − relative risk) ×100.

identification by culture, real-time PCR, or both as end points.

The circulating type A (H3N2) viruses in the first year of the study (2004–2005) were considered to show moderate antigenic drift from the vaccine strain (differences in dilutions by a factor of eight in cross hemagglutination-inhibition assays with the use of ferret antiserum).[9,19] In 2007–2008, the antigenic differences between the A/Wisconsin vaccine strain and the A/Brisbane circulating strain were found to be twofold with the use of the same assays, indicating a low level of drift.[12] Despite these differences in the degree of drift between vaccine and circulating type A (H3N2) strains during the study years 2004–2005 and 2007–2008, estimates of efficacy for the inactivated vaccine were similar.

Conclusive evidence regarding the efficacy of the two vaccines for the influenza B viruses is not yet available. In the first year, type B viruses from both lineages circulated, and in 2007–2008, the circulating type B viruses were all of the lineage not included in the vaccine. Thus, it is difficult to draw conclusions other than to speculate that not having the correct type B lineage represented in the vaccine might be a problem for adults as well as for children.[20]

Overall, in 2007–2008, the inactivated vaccine was 50% more efficacious than the live attenuated vaccine in the only adult population in which both vaccines are approved for use. As before, the exact explanation for age-specific differences in efficacy is a matter of speculation, but these differences could be related to the inability of the live attenuated viruses to infect some adults because of their past exposure to similar strains. This would be consistent with the known prob-lem in using the live attenuated vaccine in older persons.[21] This situation might be different in years in which there is major antigenic drift, which was not the case for type A viruses during the 4 years of our study.

We are entering a new era of influenza control, one in which different types of vaccines may be appropriate for different age groups. The developments in this area, based in part on the work on pandemic vaccines, could result in improved vaccines for older persons.[22,23] The emergence of the novel influenza A (H1N1) virus will also need to be considered. In preliminary testing of pre-vaccination and postvaccination serum samples collected as part of the current study, a small proportion of the participants who received the inactivated vaccine in the fall of 2007 had antibody responses to the novel virus, but none of the recipients of the live attenuated vaccine had a similar response.[24] Ideally, data from direct comparison of the vaccines will be made available to inform the choices that will be required as we go forward into relatively uncharted territory.

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