

CORRESPONDENCE



Influenza Vaccines

TO THE EDITOR: In their report on the use of inactivated and live attenuated influenza vaccines to prevent antigenically drifted influenza, Ohmit et al. (Dec. 14 issue)¹ conclude that the live attenuated vaccine was less efficacious than the inactivated vaccine in their study population of healthy adults. This conclusion is not warranted, for three reasons. First, the study was not a head-to-head comparison of the two vaccines. The design was actually that of two separate studies: a comparison of inactivated vaccine with injectable placebo and a comparison of live attenuated vaccine with intranasal placebo. Second, 1800 participants were estimated to be needed to achieve the planned statistical power of the study, but only 876 participants were included in the per-protocol analyses. Consequently, none of the analyses involving the live attenuated vaccine had significant results. Third, the only apparent superiority in efficacy of the inactivated vaccine over the live attenuated vaccine was for type B influenza. Despite the random assignment of participants to study interventions, these results could easily have

been affected by the chance occurrence of more infections with viruses of the Victoria lineage (not included in the vaccine) in the group receiving live attenuated vaccine than in the group receiving inactivated vaccine.

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Dr. Boyce reports receiving speaking fees from Sanofi Pasteur and MedImmune.

1. Ohmit SE, Victor JC, Rotthoff JR, et al. Prevention of antigenically drifted influenza by inactivated and live attenuated vaccines. *N Engl J Med* 2006;355:2513-22.

TO THE EDITOR: King et al. (Dec. 14 issue)¹ report the beneficial effects of school-based influenza vaccination. The study was well designed, but we wonder why the serious adverse event of asthmatic exacerbation 36 days after vaccination was judged to be unrelated to the vaccine by investigators who were aware of study-group assignments. Asthmatic exacerbations in persons with a history of asthma have been considered one type of adverse event that can occur after the administration of live attenuated intranasal influenza vaccine.² The interval from vaccination to the onset of symptoms may range from a few hours to more than a month. Children 18 months to 4 years of age are also reported to have a higher relative risk of asthmatic events 15 to 42 days after vaccination than earlier.³ We are concerned that the lack of blinding may have affected the assessment of causality for adverse events.

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1. King JC Jr, Stoddard JJ, Gaglani MJ, et al. Effectiveness of school-based influenza vaccination. *N Engl J Med* 2006;355:2523-32.
2. Izurieta HS, Haber P, Wise RP, et al. Adverse events reported following live, cold-adapted, intranasal influenza vaccine. *JAMA* 2005;294:2720-5. [Erratum, *JAMA* 2005;294:3092.]
3. 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):e397-e407.

DRS. OHMIT AND MONTO REPLY: Although we do not use the term “head to head” in describing our study, we disagree with Dr. Boyce’s statement that it was actually two studies. Participants were randomly assigned to one of the study groups as they were enrolled, and since the trial was double-blind, all observers were unaware of whether the participant was receiving vaccine or placebo. The percentage of persons in each group who reported influenza-like illnesses did not differ among groups, indicating that the route of vaccine administration did not bias the reporting of illness. Although the planned number of participants in the study was not achieved, insufficient power cannot be used to explain our results, since the community attack rate was higher than that assumed in the sample-size calculations and since the required number of end points occurred. The only difference between the per-protocol population (876 participants) mentioned by Dr. Boyce and the intention-to-treat population (1247 participants) was the timing of collection of the post-intervention blood specimens, which made the increase in antibody titer (the serologic end point) not useful in the larger group. We did not stress the serologic end point in our analyses, mainly because it put the live attenuated influenza vaccine at a disadvantage¹; instead, we focused on the end points related to virus identification: isolation of the virus in cell culture and through real-time polymerase chain reaction (PCR).

To say that the differences in efficacy were related to type B only is incorrect, and to explain the differences as being related to B-lineage differences is only speculation. In the analyses that considered outcomes associated with type A influenza only, the efficacies of the live attenuated influenza vaccine and the inactivated vaccine, calculated with the use of culture-only end points, were identical; however, when the combined cul-

ture and PCR results were examined, the efficacy of the live attenuated influenza vaccine was reduced. In contrast, in a single year in which drifted viruses circulated, analyses using multiple end points showed that the inactivated vaccine was consistently efficacious.

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1. Treanor JJ, Kotloff K, Betts RF, et al. Evaluation of trivalent, live, cold-adapted (CAIV-T) and inactivated (TIV) influenza vaccines in prevention of virus infection and illness following challenge of adults with wild-type influenza A (H1N1), A (H3N2), and B viruses. *Vaccine* 1999;18:899-906.

DR. KING REPLIES: As noted by Takahashi et al., the unblinded nature of our study could have biased the investigators. However, the study design was not intended to definitively assess vaccine safety. Site investigators, all of whom had extensive experience in conducting clinical trials, made assessments of the possible relationship of adverse events to immunization. It is difficult to assign causation of wheezing to a vaccine in patients with asthma, who naturally have occasional exacerbations. This vaccine has been administered safely to over 2000 school-age children with asthma, who have had no increase in asthmatic exacerbations as compared with recipients of parenteral influenza vaccine.¹ Also, despite clear recommendations that children with asthma should receive a yearly influenza vaccine, the proportion who are immunized is low² in a population of children in whom wild-type influenza is likely to be a greater risk than vaccine-induced asthmatic exacerbation.

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Dr. King reports receiving, since the publication of his article, consulting fees from MedImmune.

1. Fleming DM, Crovari P, Wahn U, et al. Comparison of the efficacy and safety of live attenuated cold-adapted influenza vaccine, trivalent, with trivalent inactivated influenza virus vaccine in children and adolescents with asthma. *Pediatr Infect Dis J* 2006;25:860-9.
2. Gnanasekaran SK, Finkelstein JA, Lozano P, Farber HJ, Chi FW, Lieu TA. Influenza vaccination among children with asthma in Medicaid managed care. *Ambul Pediatr* 2006;6:1-7.