Half- vs Full-Dose Trivalent Inactivated Influenza Vaccine (2004-2005)

Age, Dose, and Sex Effects on Immune Responses

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Background: Optimal public health strategies for managing influenza vaccine shortages are not yet defined. Our objective was to determine the effects of age, sex, and dose on the immunogenicity of intramuscular trivalent inactivated vaccine (TIV).

Methods: Healthy adults aged 18 to 64 years, stratified by age (18-49 and 50-64 years) and sex, were randomized to receive full- or half-dose TIV. Hemagglutination inhibition titers against vaccine antigens were measured before and 21 days after immunization. A primary outcome of noninferiority was defined as a difference of less than 20% in the upper 95% confidence interval (CI) of the proportion of subjects with strain-specific hemagglutination inhibition antibody titers of 1:40 or higher after vaccination. Secondary outcomes included geometric mean titers, after vaccination side effects, and occurrences of influenza-like illnesses.

Results: Among previously immunized subjects (N=1114) receiving half- vs full-dose TIV (age, 18-49 years, n=284 [half] and n=274 [full]; and age 50-64 years, n=276 [half] and n=280 [full]), CIs for proportions of subjects with hemagglutination inhibition antibody titers of 1:40 or higher excluded substantial reduction for all antigens in the 18- to 49-year age group and for B/Shanghai/361/2002 (B) and A/Fujian/411/2002 (A/H3N2) in the 50- to 64-year age group. Geometric mean titer in the female 18- to 49-year age group exceeded male responses for all strains: responses to half-dose TIV that were comparable with male full-dose responses for A/New Caledonia/20/99 (A/H1N1) antigen, 25.4 (95% CI, 20.9-30.9) vs 25.6 (95% CI, 21.3-30.9); A/H3N2 antigen, 60.8 (95% CI, 50.8-72.7) vs 44.1 (95% CI, 37.6-51.8); and B antigen, 64.4 (95% CI, 53.9-76.9) vs 60.7 (95% CI, 51.4-71.7) (findings were similar for the 50- to 64-year age group). Some injection site and systemic reactions (myalgias and/or arthralgias [P<.05], headache [P<.001], and impact of fatigue [P<.05]) were significantly lower in men. The relative risk of medical visits and hospitalizations for influenza-like illnesses were similar in the half- and full-dose groups regardless of age.

Conclusions: Antibody responses to intramuscular half-dose TIV in healthy, previously immunized adults were not substantially inferior to the full-dose vaccine, particularly for ages 18 to 49 years. Significantly higher geometric mean titer responses in women were identified for all ages, regardless of dose or influenza strain. Half-dose vaccination may be an effective strategy for healthy adults younger than 50 years in the setting of an influenza vaccine shortage.

Trial Registration: clinicaltrials.gov Identifier: NCT00283283

Arch Intern Med. 2008;168(22):2405-2414

The efficacy and cost-effectiveness of trivalent inactivated vaccine (TIV) has resulted in expanded recommendations for immunization, particularly for healthy populations involved in caregiving and first responder missions. Since 2002, optimum influenza vaccine delivery has been impaired as a result of supply shortages. With the abrupt loss of half the anticipated national influenza vaccine supply in October 2004, the option of using a reduced dose for immunization of healthy, high-priority groups became a critical consideration. A prior study by Treanor et al (2001-2002 season) suggested that immune response differences among subjects given a half dose of TIV were not substantially inferior in healthy subjects aged 18 to 49 years.

For editorial comment see page 2402

The need to extend the evaluation of reduced TIV doses to a different formulation resulted in the development of a rapid-response, interagency collaborative protocol implemented in November
2004 by the Walter Reed Health Care System (WRHCs) Allergy-Immunology Department and Vaccine Healthcare Center (VHC) on behalf of the Office of the Army Surgeon General. The trial was designed to replicate the noninferiority study and include healthy subjects aged 50 to 64 years. The primary outcome measure was the development of serum hemagglutination inhibition (HAI) antibody titers of 1:40 or higher to the A/Fujian/411/2002 (A/H3N2)-like, A/New Caledonia/20/99 (A/H1N1)-like, and B/Shanghai/361/2002 (B)-like antigens used in the 2004-2005 TIV. Antibody responses correlate with protection and are used as measures of immunologic comparability.10

Although not designed to be an efficacy study, the project included secondary end points of inpatient and outpatient health care encounters during the 2004-2005 influenza season using an existing medical encounter database for Military Health System (MHS) medical services both within and outside military medical facilities.

STUDY DESIGN

This prospective, single-blind, randomized clinical trial was approved by the Walter Reed Army Medical Center (WRAMC) Department of Clinical Investigation. Study implementation included compliance with good clinical practices as defined by published guidelines for studies involving an investigational new drug (IND #12019 held by the Office of the Army Surgeon General). The US Army Medical Materiel Development Activity served as the sponsor’s representative. All subjects provided written informed consent.

The goal of the study was to provide additional information for future public health decisions concerning the best use of limited influenza vaccine supply. In that situation, moderately diminished responses shared by a large segment of the population would be preferred to maximum responses in a more restricted group, particularly since lower responses are still correlated with clinical benefit, particularly in populations receiving repeated doses.10,11 The study was not intended to demonstrate equivalence of antibody responses using half-dose vaccine, since diminished antibody responses have previously been described.

Healthy MHS beneficiaries in the National Capital Region of Washington, DC, were enrolled from 2 sites: Allergy-Immunology-Immunization Clinic, WRAMC, and Pentagon/DiLorenzo Health Clinic, Arlington, Virginia. There were 8 randomization strata based on sex, age group (18-49 years vs 50-64 years), and/or DoD priority prior to the shortage announcement.13 Additional exclusion criteria were based on the Centers for Disease Control and Prevention (CDC) and/or Department of Defense (DoD) criteria for priority immunization (eg, deployment to the Middle East) were excluded from participation and were referred to the standard influenza vaccination program. Additional inclusion criteria were based on the remaining CDC and/or DoD priority prior to the shortage announcement.15

According to the emergency vaccine supply shortage and public health guidelines in effect after October 5, 2004, enrolled subjects would not have been eligible for immunization; this fact was considered ethical justification for blinding subjects. Vaccination of nonpriority individuals in the study was considered ethical because the study used less than 0.01% of the DoD supply and had a potential for obtaining information that could benefit large populations in future influenza seasons.

ANTIBODY ASSAYS

Serum samples were coded to ensure laboratory blinding related to subjects’ identities and study groups. Hemagglutination inhibition was conducted in a single laboratory using standardized methods (N.J.C., Influenza Branch, CDC).9,10,11 Paired serum samples from each subject were tested simultaneously.

STATISTICAL ANALYSIS

With 640 subjects within each age stratum (18-49 or 50-64 years), the noninferiority study design provided 89% power to show that the half-dose vaccine does not cause a 20% or greater loss in the proportion of subjects with postimmunization HAI
were analyzed. These margin assumptions assuming the true loss is 10% (ie, proportions of 85% vs 75% for antibody titers of 1:40 or higher for each vaccine antigen, as-
in proportions were calculated assuming asymptotic normal-
be no more than moderately diminished if the 95% confidence
in GMTs or greater increase reduced by more than 20%; and ratio of GMTs
for full vs half dose of 1:5 or higher
titer of 1:40 or higher after immunization; sec-
body responses. The primary end point was the frequency of
immunization with half-dose vaccine include the following: pro-
be no more than moderately diminished if the 95% confidence
in GMTs or greater increase reduced by more than 20%; and ratio of GMTs
for full vs half dose of 1:5 or higher
In each analysis, the half-dose response was concluded to be no more than moderately diminished if the 95% confidence intervals (CIs) of the dose-related differences were within the established limit of acceptability. The 95% CI for differences in proportions were calculated assuming asymptotic normality for sample proportions; CIs for ratios of GMTs were calcu-
alated by first deriving CIs for the log titers using a t distribution and then back-transforming to the original scale.
Unadjusted χ² tests were used to compare proportions; the Fisher exact test was used when expected counts were below 5. Continuous variables and titer measurements were compared using unpaired t tests adjusted for unequal variances when the F test for equality of variances had a P value lower than .05. The possibility that halving the vaccine dose affected responses differently in different groups (eg, by age or sex) was examined by assessing the interaction in analysis of variance or linear regression (for log₂ titers) and in logistic regression (for dichotomous responses). Side effects data were collapsed into 2 catego-
Abbreviations: A/H1N1, A/New Caledonia/20/99; A/H3N2,
A/Fujian/411/2002; B, B/Shanghai/361/2002; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CI, confidence interval; GMT, geometric mean titer; NA, not applicable; NS, non-significant (P > .05).

Table 1. Baseline Characteristics by Age Group in 1114 Previously Vaccinated Subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aged 18-49 y (n=558)</th>
<th>Aged 50-64 y (n=556)</th>
<th>P Value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (95% CI), y</td>
<td>42.3 (41.8-42.7)</td>
<td>55.6 (55.3-55.9)</td>
<td>NA</td>
</tr>
<tr>
<td>Female sex, No. (%)</td>
<td>247 (44.3)</td>
<td>237 (42.6)</td>
<td>NS</td>
</tr>
<tr>
<td>Ethnicity, No. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>454 (81.4)</td>
<td>491 (88.3)</td>
<td>.02</td>
</tr>
<tr>
<td>African American</td>
<td>54 (11.5)</td>
<td>46 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>16 (2.9)</td>
<td>6 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>14 (2.5)</td>
<td>7 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>10 (1.8)</td>
<td>6 (1.1)</td>
<td></td>
</tr>
<tr>
<td>BMI, mean (95% CI)</td>
<td>26.0 (25.6-26.3)</td>
<td>26.7 (26.3-27.1)</td>
<td>.02</td>
</tr>
<tr>
<td>A/H1N1 antibody Titer ≥ 1:40, No. (%)</td>
<td>175 (31.4)</td>
<td>108 (19.4)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>GMT, mean (95% CI)</td>
<td>16.2 (14.9-17.7)</td>
<td>11.4 (10.5-12.4)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>A/H3N2 antibody Titer ≥ 1:40, No. (%)</td>
<td>211 (37.8)</td>
<td>235 (42.3)</td>
<td>NS</td>
</tr>
<tr>
<td>GMT, mean (95% CI)</td>
<td>20.7 (19.0-22.6)</td>
<td>22.0 (19.9-24.3)</td>
<td>NS</td>
</tr>
<tr>
<td>B antibody Titer ≥ 1:40, No. (%)</td>
<td>264 (47.3)</td>
<td>192 (34.5)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>GMT, mean (95% CI)</td>
<td>26.2 (24.0-28.6)</td>
<td>18.6 (17.2-20.6)</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

A total of 1316 eligible subjects were enrolled in November 2004. Serologic analyses are reported for 1114 (92.6%) previously vaccinated subjects. As illustrated in Figure 1,
serologic data analyses excluded subjects not previously vaccinated (n=56 [too small for analysis]), those satisfying exclusion criteria identified after enrollment (n=15), and/or those without evaluable paired specimens (n=137). Of the 1316 subjects, 1259 (95.7%) completed the 3-day diary, including 1203 subjects who were previously vaccinated in the past 3 years.

Table 1 summarizes the baseline characteristics of previously vaccinated subjects. Significant differences were noted between age groups in ethnicity and body mass index (P=.02 for both). The younger group had significantly higher baseline antibody levels (proportion with titers ≥1:40 GMTs) than the older group for the influenza A/H1N1 and B antigens (P<.001 for both) but not for A/H3N2. Overall, randomization yielded relative balance on baseline characteristics between the full- and half-dose groups; only GMT for A/H1N1 and ethnicity showed modest differences within the older age group (data not shown). Previously vaccinated subjects without serologic data showed no differences in baseline characteristics from the 1114 subjects with serologic data. Previously vaccinated subjects had significantly higher (P<.001 for all, data not shown) baseline HAI antibody titers for all 3 antigens (data not shown).

Figure 2 illustrates the reverse cumulative distribution graphs for antibody titers within each age group, by viral strain and vaccine dose.

Table 2 summarizes the differences in antibody responses according to vaccine dose and age group.
proportions of subjects aged 18 to 49 years with titers of 1:40 or higher against influenza A/H1N1, A/H3N2, and B antigens after immunization were 11.8%, 8.3%, and 5.0% higher, respectively, among subjects given a full dose compared with those given a half dose and 15.7%, 9.5%, and 8.8% higher, respectively, among subjects aged 50 to 64 years. In both age groups, GMTs and proportion with 4-fold or higher increases in antibody titer were significantly higher (P < .05 to P < .001, see detailed P values in Table 2) in the group given a full dose, with the exception of the proportion with an HAI antibody titer of 1:40 or higher against influenza B (P = .19 in the younger age group and P = .09 for A/H1N1, a 4-fold rise in the older age group). However, when analyzing serologic end points for “substantially diminished response,” there was no evidence of substantial inferiority of half dose in subjects aged 18 to 49 years (Figure 3A), which is similar to results of Treanor et al7 (Figure 3B). Figure 3C illustrates the corresponding result for subjects aged 50 to 64 years. Differences due to dose appeared greater in subjects aged 50 to 64 years, but they were not significantly greater (logistic regression and analysis of variance for interaction). It is noteworthy that 90% of the 18- to 49-year age group were 35 years or older; in the 50- to 64-year age group, 81% were between the ages of 50 and 59 years, limiting the relevance of the analyses for those 60 years or older.

Table 3 provides a further breakdown of GMTs by sex. For all 3 antigens, women tended to have higher GMTs than men in the same age and dose group. The GMTs for women given a half dose were similar to the GMTs for men given a full dose. We also performed regression analyses of log postimmunization titers that adjusted for age group, dose level, sex, and preimmunization antibody titers. These analyses showed that the difference attributable to female sex equaled or exceeded that between the full- and half-dose vaccine. Similar patterns were observed when analyzing the effects of the same factors on postimmunization titer of 1:40 or higher and 4-fold or greater rise in titer (data not shown). When not adjusting for preexisting antibody, the sex effect was again at least similar to the dosage effect (data not shown).

Table 2. Serum Hemagglutination-Inhibition (HAI) Antibody Responses After Immunization With 2004-2005 TIV by Vaccine Strain, Dose, and Age Groups

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Vaccine Dose</th>
<th>Differences With 95% CI (Absolute Titer or Titer-Fold Increase) and Ratio of GMTs With 95% CI</th>
<th>P Value</th>
<th>Ratio of GMTs With 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A/H1N1</td>
<td>Full Dose</td>
<td>118 (3.5 to 20.0)</td>
<td>.005</td>
<td>2</td>
</tr>
<tr>
<td>Titer ≥ 1:40, No. (%)</td>
<td>148 (54.0)</td>
<td>120 (42.3)</td>
<td>1.35 (1.13 to 1.61) &lt;.001</td>
<td></td>
</tr>
<tr>
<td>≥ 4 fold, No. (%)</td>
<td>45 (16.4)</td>
<td>28 (9.9)</td>
<td>6.6 (1.0 to 12.2) .02</td>
<td></td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>28.8 (25.2 to 32.8)</td>
<td>21.3 (18.9 to 24.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A/H3N2</td>
<td>Full Dose</td>
<td>207 (75.5)</td>
<td>.03</td>
<td>2</td>
</tr>
<tr>
<td>Titer ≥ 1:40, No. (%)</td>
<td>104 (38.0)</td>
<td>84 (29.6)</td>
<td>8.4 (0.5 to 16.2) .04</td>
<td></td>
</tr>
<tr>
<td>≥ 4 fold, No. (%)</td>
<td>55.2 (48.7 to 62.5)</td>
<td>45.0 (39.7 to 50.9)</td>
<td>1.23 (1.03 to 1.46) .02</td>
<td></td>
</tr>
<tr>
<td>GMT (95% CI)</td>
<td>69.6 (61.4 to 78.9)</td>
<td>54.8 (49.1 to 61.2)</td>
<td>1.27 (1.08 to 1.50) .005</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: A/H1N1, A/New Caledonia/20/99; A/H3N2, A/Fujian/411/2002; B, B/Shanghai/361/2002; CI, confidence interval; GMT, geometric mean titer; NS, nonsignificant (P > .05).

*Antibodies were measured by serum hemagglutination inhibition; the “titer ≥ 1:40” is the number (percentage) of subjects achieving a postvaccination serum hemagglutination inhibition antibody titer of 1:40 or higher; the “≥ 4-fold” is the number (percentage) of subjects with a 4-fold or greater increase in titer comparing postvaccination with prevaccination values.

*For “titer ≥ 1:40” and “≥ 4-fold,” the differences represent the arithmetic difference (full dose−half dose [percentage]) and 95% CI. No more than a 20% difference (full- vs half-dose groups) in the percentage of subjects who achieve a titer of 40 or higher or have a 4-fold titer increase represents a noninferior response. Zero (0) equals equivalence between full- and half-dose groups. For the GMT, the difference represents the ratio (full-dose GMT/half-dose GMT) with corresponding 95%.

*Comparisons of full- vs half-dose antibody levels after immunization do not reflect the “substantial differences” analysis detailed in Figure 3.

*Age group: 50 to 64 years (n=559), with 280 full-dose and 276 half-dose revaccination subjects only.

*Age group: 18 to 49 years (n=558), with 274 full-dose and 284 half-dose revaccination subjects only.

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A total of 1,259 subjects completed the day 0 to day 3 postimmunization side effects diary. Injection site reactions were more frequent in the full-dose group for red-

ness and/or swelling greater than 2 in (5.08 cm) in diameter (13.4% vs 8.6%; \( P = .006 \)). Although injection site pain was greater for full vs half dose (19.9% vs 14.4%; \( P = .01 \)), when analyzed for clinically significant pain levels (VAS, \( \geq 3 \) of 5), significant sex- but not dose-dependent pain differences were identified. Table 4 summarizes dose and sex comparisons of clinically significant side effects, symptoms of ILI, and medical events (eg, hospitalizations and unscheduled medical visits) during the serum collection period. Joint and/or muscle pain (VAS, \( \geq 3 \) of 5) were significantly different (\( P = .02 \) and \( P = .03 \), respectively) for dose and sex; headache, other pains, impact of fatigue, and overall side effects were significantly greater in women (\( P < .001 \), \( P = .002 \), \( P = .02 \), and \( P = .05 \), respectively). No other adverse event differed significantly by dose, and there was no evidence of ILI symptom differences by sex or dose during the 21 days after immunizations. There were 3 hospitalizations for medically unrelated events, with 1 prior to the postvaccination serum collection resulting in exclusion from serologic analyses.

For the period of November 1, 2004, through March 31, 2005, analysis of the DMSS search for ILI and complications identified no significant differences in the frequency of respiratory illness–associated, cardiovascular, or unrelated medical visits. Visits for mental health and genitourinary problems were not reviewed. There were no deaths in the study population during the study. Emergency department visits cannot be distinguished from outpatient clinic visits in the DMSS database. No other significant adverse events related to immunization were identified during the follow-up period.

Table 5 summarizes analyses of outcomes based on the number of medical visits documented within each age group by vaccine dose, for previously vaccinated participants. There were no significant differences between vaccine doses for either age group or between sex subsets. The 95% CIs show that for half vs full dose, true ILI rates are unlikely to be more than 1.46-fold higher among the younger group and 2.2-fold higher among the older group. The substantially lower total number of visits documented for the subjects aged 50 to 64 years may reflect that the group includes predominantly nonactive duty beneficiaries who have a lower priority for primary care appointments within the MHS and who often have alternative health insurance for which medical visits are not recorded within the DMSS.

The results of this study are consistent with a similar report for the 2001-2002 influenza vaccine.9 Results from the 2 studies using different TIV formulations confirm that substantially inferior immune responses following 50% vaccine dose reduction in healthy adults younger than 50 years would be unlikely. The study by Kramer et al14 with a half-dose influenza vaccine, although with a smaller population, is consistent with the conclusions of this study. Given the benefits of immunizing healthy working adults4 and caregivers,14,15 these data support the validity of a dose reduction strategy in the setting of vacc-i

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**Figure 3.** Postvaccination serum hemagglutination inhibition antibody titer differences (full- minus half-dose groups) and 95% confidence intervals (CIs) for previously vaccinated subjects by age group, compared with the results of Treanor et al (2001-2002 trivalent inactivated vaccine formulation). The bottom scale is for arithmetic difference in percentages, with 95% CIs. The area between 2 dashed lines represents no substantial differences, with the area outside dashed lines representing substantially diminished response range. A, Revaccinees aged 18 to 49 years (present study); B, revaccinees aged 18 to 49 years (Treanor et al9, 2001-2002 trivalent inactivated vaccine formulation). The results of this study are consistent with a similar report for the 2001-2002 influenza vaccine.9 Results from the 2 studies using different TIV formulations confirm that substantially inferior immune responses following 50% vaccine dose reduction in healthy adults younger than 50 years would be unlikely. The study by Kramer et al14 with a half-dose influenza vaccine, although with a smaller population, is consistent with the conclusions of this study. Given the benefits of immunizing healthy working adults4 and caregivers,14,15 these data support the validity of a dose reduction strategy in the setting of vac-
...responses to vaccines are limited,16 women have higher antibody responses among women given a half dose of TIV were similar to or greater in magnitude when compared with responses among men given a full dose. These findings suggest that guidelines for vaccine use during shortages should take sex as well as age into consideration. Although data on sex differences in immune responses to vaccines are limited,16 women have higher absolute CD4+ lymphocyte counts18 and production of Th1 cytokines after immunization19 as well as more sustained responses to antigenic challenge.20

Our data support the use of a half dose of TIV in healthy persons up to age 50 years based on serum antibody responses; data for the older age group suggest similar findings and merit further study. Reduced dosing could have a significant impact on the response to vaccine shortages, particularly at a local level when faced with considerable delays in vaccine supply delivery. In view of the trend toward reduced side effects, reducing the dose may improve vaccine acceptability in some populations. Studies related to reduced vaccine dosing and optimal c...
ria (eg, sex, age ranges) are limited; further investigation is merited, particularly in those up to age 60 years and with increased focus on relevant differences between previously vaccinated and unvaccinated subjects.26

In the present study, the overall response to the A/H1N1 component of the vaccine was rather weak and lower than that reported by Treanor et al. However, antibody avidity and potential efficacy may increase after immunization, even in the absence of increases in antibody levels. Some recent publications suggest that A/H1N1 strains may be less well covered by the TIV in some seasons. However, we observed no evidence of increased ILI outcomes in the half- vs full-dose groups, regardless of age group. Public health surveillance did not detect evidence of vaccine failure, as described for the 2003-2004 influenza vaccine season.24 These differences may also be explained by the fact that most of our subjects had received 2 to 3 doses of TIV in the 3-year period before the study, whereas a high proportion of subjects in the study by Treanor et al25 had been immunized at most once in recent years (oral communication, J.J.T., 2007). In addition, the subjects in the study by Treanor et al25 were younger, with a mean age of 33.5 years vs 42.3 years for our 18- to 49-year age group; 90.0% of our subjects were 35 years or older. Based on influenza season activity reports, there was no locally increased influenza activity until January 2005, well past the end of serum sample collections on December 23, 2004, and therefore unlikely to have affected study results (http://www.cdc.gov/flu/weekly/fluactivity.htm).25 Another factor that might affect immune responses is body mass index. There was a mild association of higher antibody responses with higher body mass index, but multivariate analyses showed that this effect does not explain or reduce the importance of the sex, dose, or age effects. The sex factor in relation to more local reactions and higher antibody responses to influenza vaccine has been previously described but has not been sufficiently considered in the context of vaccine supply shortages.26-28

Our observed relative risks of ILI for the half- vs full-dose vaccine are very close to 1.00 (no difference), but the 95% CIs include a fairly wide range of possible increased risk. Directly assessing modest differences in risk by dose would clearly require very large and costly studies. A recent review of influenza vaccine trials in healthy adults by the Cochrane Collaboration29 concluded that only 30% of ILI is prevented by immunization in adults. Thus, particularly when faced with a vaccine supply crisis, it is sensible to rely on serological results to guide public policy regarding dosing. This was the origin of our primary objective for assessing immunologic noninferiority with a different vaccine in a different season. Our results substantiate that the observations by Treanor et al30 of the similarity between the half- and full-dose parenteral vaccine are potentially applicable to future vaccines. On an immunologic basis, the principle of a wide dose response in healthy individuals should be applicable to any protein vaccine construct, particularly the recombinant hemagglutinin influenza vaccine.20

Although previous reports describe the use of reduced TIV doses, most involve alternative means of administration (intradermal, transdermal, or by needle-free jet injectors) not in common use and potentially requiring new training and skill sets.31-34 The present study represents the second largest study, to our knowledge, on half- vs full-dose TIV in a different season with a different vaccine formulation, supporting a reduced vaccine dosing strategy in healthy persons younger than 50 years.9,16 Our data suggest that this approach could be extended beyond age 49 years, particularly for healthy women, but further studies are required. Half-dose TIV represents a viable alternative strategy for managing supply shortages to optimize timely delivery, particularly to critical personnel such as first responders and service members. The fact that such a strategy also reduces side effects may have the added benefit of improved overall vaccine acceptability, particularly in subpopulations ex-

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Table 5. Previously Vaccinated Subjects With 1 or More Medical Visits for Influenza-like Illness (ILI) Involving the Upper or Lower Respiratory Tract During the 2004-2005 Influenza Season (Through March 31, 2005)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>No.</th>
<th>Subjects With ILI Visit, No. (%)</th>
<th>RR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 18-49 y, revaccines</td>
<td>661</td>
<td>49 (14.6)</td>
<td>1.01 (0.70-1.46)</td>
<td>Primary access to medical care through Military Health System most likely with risk of personal cost if accessed outside system</td>
</tr>
<tr>
<td>Half dose</td>
<td>336</td>
<td>47 (14.8)</td>
<td>1.07 (0.53-2.18)</td>
<td>Capture of all medical visits may be lower for this age group due to alternate medical insurance options, lower priority access for primary care</td>
</tr>
<tr>
<td>Full dose</td>
<td>325</td>
<td>15 (4.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age 50-64 y, revaccines</td>
<td>615</td>
<td>14 (4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Half dose</td>
<td>308</td>
<td>15 (4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full dose</td>
<td>307</td>
<td>14 (4.5)</td>
<td></td>
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</tbody>
</table>

Note 1: Subjects with chronic respiratory disease or other clinical risk factors for influenza vaccine illness and/or complications were not enrolled in the study. Note 2: Comparable results were found for the upper respiratory tract illness group alone and when analyzed by sex for subjects aged 18 to 49 years; numbers for those aged 50 to 64 years were too small for further meaningful analyses.

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(Reprinted) Arch Intern Med/Vol. 168 (No. 22), Dec 8/22, 2008 WWW.ARCHINTERNMED.COM

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experiencing more severe adverse effects. As recommendations for influenza immunization expand and evidence that elderly persons (men older than 60 years) may require higher doses of vaccine for optimal responses, reduced doses in healthy, younger populations may become a valuable national strategy.

Accepted for Publication: April 14, 2008.

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Author Contributions: Dr Engler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Engler, Nelson, Klimov, Keitel, and Nichol. Acquisition of data: Engler, Nelson, Klose, Cox, Klimov, Keitel, Nichol, Carr, and Treanor. Analysis and interpretation of data: Engler, Nelson, VanRaden, Huang, Cox, Klimov, Keitel, Nichol, Carr, and Treanor. Drafting of the manuscript: Engler, Nelson, VanRaden, Keitel, and Carr. Critical revision of the manuscript for important intellectual content: Engler, Nelson, Cox, VanRaden, Huang, Cox, Klimov, Keitel, Nichol, Carr, and Treanor. Statistical analysis: Engler, VanRaden, and Huang. Obtained funding: Engler, Cox, Klimov, and Carr. Administrative, technical, and material support: Engler, Nelson, Cox, Klimov, Keitel, and Carr. Study supervision: Engler, Nelson, Klose, Klimov, and Carr.

Financial Disclosure: None reported.

Funding/Support: This study was supported by the Office of the Army Surgeon General in collaboration with Walter Reed Army Medical Center (WRAMC) and Healthcare System; the North Atlantic Regional Medical Command; the US Army Medical Research and Materiel Command; the National Institute of Allergy and Infectious Diseases, National Institutes of Health; and the Influenza Branch of the Centers for Disease Control and Prevention.

Disclaimer: The views expressed in this article are those of the authors and do not reflect the official policy of the Department of the Army, Department of Defense, US government, National Institutes of Health, Centers for Disease Control and Prevention, or other federal agencies.

Walter Reed Health Care System Influenza Vaccine Consortium: Bryan L. Martin, DO (Colonel, US Army, retired); Deniece Shelton, RN, BSN; Ha Tran, BS (Captain, US Army) and the WRAMC Pathology Department; Bruce McLennathan, MD (Major, US Army); Margaret Yakovone, MD (Lieutenant Colonel, US Army); Ronald DeGuzman, MD (Lieutenant Colonel, US Army); Karla Davis, MD (Major, US Army); Cecilia Mikita, MD (Major, US Army); Ann Desoto, BA; Limone C. Collins, MD; John J. Moore, MD (Colonel, US Army, retired); and the dedicated staff of the Walter Reed Regional Vaccine Healthcare Center.

Additional Contributions: We acknowledge and give special thanks to the following individuals and organizations for the remarkable interagency rapid response and teamwork support of this research effort: developed from an idea at the National Vaccine Advisory Committee on October 10, 2004, to full-protocol approval (with the Food and Drug Administration-approved investigational new drug) and implementation by November 8, 2004: Kevin Kiley, MD (Lieutenant General, US Army, retired), the Army Office of the Surgeon General, without whom this study could never have been done; Harold Timboe, MD (Major General, US Army, retired), and Kenneth Farmer, MD (Major General, US Army, retired), as Commanders of the North Atlantic Regional Medical Command; the dedicated staff of the Walter Reed Army Medical Center Department of Clinical Investigation, particularly Maria Sjogren, MD (Colonel, US Army, retired), Susan D. Fracisco, MD (Colonel, US Army), and the investigational review board (IRB) and human use committee (HUC), Walter Reed Health Care System Influenza Vaccine Consortium; George Curlin, MD, Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health; Qian Dong, NIAID (statistics); Lester Martinez-Lopez, MD (Major General, US Army, retired); Jerome F. Pierson, PhD (Colonel, US Army, retired), Shirley Roach, and Ann Altman (Lieutenant Colonel, US Army, retired), US Army Medical Materiel Development Activity; Leon Moore and Tony Chen from Uniformed Services University of the Health Sciences for the development of the online survey questionnaire; the staff of the online survey questionnaire: John Grabenstein (Colonel, US Army, retired), Allison C. Christ (Captain, US Army), and the staff of the Military Vaccine Agency; Dale Block (Colonel, US Army), Pentagon DiLorenzo Clinic, and his staff; Walter Reed Army Institute of Research IRB; Walter Reed Department of Pathology; the dedicated nursing staff of the Allergy-Immunology Department, WRAMC, particularly Sadie H. Massey, Norma S. Veltri; Fran Lessans and the staff at Passport Health; McKesson Biosciences, Rockville, Maryland, for rapid response labeling; and Sandii Mon, Gerard Reardon, PhD, and Christina Spooner, BS, MS, from the Vaccine Healthcare Centers Network.

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