Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccination in Community-Dwelling Veterans

Diane M. Richardson,1 Elina L. Medvedeva,1 Christopher B. Roberts,1 and Darren R. Linkin2,3; for the Centers for Disease Control and Prevention Epicenter Program

1Center for Health Equity Research and Promotion, Philadelphia Veterans Affairs Medical Center, 2Division of Infectious Diseases, Department of Medicine, and Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine, University of Pennsylvania, and 3Division of Infectious Diseases, Department of Medicine, Philadelphia Veterans Affairs Medical Center, Pennsylvania

Background. Influenza is a significant cause of morbidity and mortality in older adults. High-dose (HD) trivalent inactivated vaccine has increased immunogenicity in older adults compared with standard-dose (SD) vaccine. We assessed the relative effectiveness of HD influenza vaccination (vs SD influenza vaccination).

Methods. We conducted a retrospective cohort study among patients who receive primary care at Veteran Health Administration (VHA) medical centers, and who received influenza vaccine in the 2010–2011 influenza season. The primary outcome was hospitalization for influenza or pneumonia. We also conducted an analysis in subgroups defined by age.

Results. We evaluated 25,714 patients who received HD vaccine and 139,511 who received SD vaccine in 23 VHA medical centers. The rate of hospitalization for influenza or pneumonia was 0.3% in both groups in the influenza season. After accounting for patient characteristics in propensity-adjusted analyses, the risk of hospitalization for influenza or pneumonia was not significantly lower among patients receiving HD vaccine vs those receiving SD vaccine (risk ratio, 0.98; 95% confidence interval, .68–1.40). In the subgroup of patients ≥85 years of age, receiving HD (compared with SD) vaccine was associated with lower rates of hospitalization for influenza or pneumonia.

Conclusions. HD vaccine was not found to be more effective than SD vaccine in protecting against hospitalization for influenza or pneumonia; however, we found a protective effect in the oldest subgroup of patients. Additional studies are needed to evaluate the effectiveness of HD vaccine.

Keywords. influenza vaccines; influenza human; comparative effectiveness research; elderly.

Influenza-associated morbidity and mortality are high in older adults and have not declined despite increasing influenza vaccination coverage among elderly persons (≥65 years of age) [1–5]. While vaccination remains the most effective approach for preventing influenza-related hospitalizations and death, older adults respond to vaccination with lower antibody titers to influenza hemagglutinin compared with younger adults, and the effectiveness of influenza vaccination among elderly persons is poor [6–10]. The lack of a highly effective vaccine highlights the need for novel vaccine strategies for this vulnerable population [11].

A new high-dose (HD) trivalent inactivated vaccine, containing 4 times the amount of hemagglutinin antigen per strain of influenza virus compared with standard-dose (SD) vaccine, received US Food and Drug Administration accelerated approval in December 2009 [12] based on its superior immunogenicity response compared with SD vaccine [13]. Results of a large-scale, multicenter efficacy trial in the elderly show superior incremental protection against influenza infection for HD vaccine relative to SD, but results for hospitalization and other important
clinical outcomes are less conclusive [14], and the public health impact on the elderly population is not known.

The Centers for Disease Control and Prevention and the Advisory Committee on Immunization Practices continue to not state a preference for either HD or SD vaccine for elderly persons [15]. Consequently, there is no formal guidance, and few published data on clinical outcomes to support decisions about which vaccine to recommend for elderly patients. In addition, the relative effectiveness of the HD vaccine compared with that of the SD vaccine in the more diverse population typically seen in the real-world setting is not known.

To address this gap, we determined rates of hospitalization for influenza or pneumonia, and evaluated the relative effectiveness of HD compared to that of SD vaccination in preventing hospitalizations for pneumonia and influenza among elderly persons in the Veterans Health Administration (VHA).

METHODS

Design Overview and Data Sources
We conducted a retrospective cohort study to compare clinical outcomes of receiving HD vs SD influenza vaccination among community-dwelling elderly patients in the VHA during the 2010–2011 influenza season. We evaluated rates of hospitalization for influenza or pneumonia as the primary outcome, and examined hospitalization for all causes and mortality as secondary outcomes. The VHA Statistical Analysis System (SAS) National Patient Care Database and VHA Decision Support System National Data Extracts were used to identify patients’ influenza vaccinations and to determine patient covariates and hospitalization status. These datasets consist of administrative records for all inpatient and outpatient encounters within the VA health system, and include patient age, sex, race/ethnicity, healthcare service locations and dates, diagnosis and procedure codes, and pharmacy records. Mortality was determined using the VHA Vital Status File, which combines multiple VA and non-VA data sources and contains dates of death for Veterans who since 2002 have received care, compensation, or pension benefits from the VHA, or are enrolled in the VHA [16].

Setting and Participants
The VHA is a national network of 152 acute care medical centers and associated outpatient clinics. Patients were included if they met all the following criteria: received a single dose of inactivated influenza vaccine as an outpatient between 1 August 2010 and the end of the 2010–2011 regional influenza season, were aged ≥65 years at the time of vaccination, and had ≥1 primary care visit in the VHA in the year prior to vaccination. We included patients from facilities in which at least 50 patients received HD vaccine. The study received institutional review board approval from the Philadelphia VA Medical Center (VAMC) and the University of Pennsylvania.

Influenza Vaccination Exposure
The primary exposure of interest was receipt of either HD or SD inactivated trivalent influenza vaccine in the VHA. Individual medical centers purchased Fluzone HD and Fluzone (SD) influenza vaccine (Sanofi Pasteur, Bridgewater, New Jersey) through a national VHA contract.

Influenza vaccination was identified using Current Procedural Terminology (CPT) codes. Receipt of SD vaccination was identified by CPT codes 90658, Q2035, Q2036, Q2037, Q2038, and Q2039; HD vaccination was identified based on the presence of code 90662 [17]. We excluded patients who received >1 dose of influenza vaccine or who received live attenuated inactivated vaccine.

Influenza and Preinfluenza Seasons
To improve the specificity of our outcomes, we defined a regional influenza season for each VAMC, based on Centers for Disease Control and Prevention multistate reporting regions [18]. For each VAMC, we assigned season start and end dates based on influenza activity reported for that region. Using weekly reports of the percentage of positive influenza tests among all influenza tests performed in each region, we defined the regional influenza season as the weeks when the percentage of positive tests was ≥10% [19]. We also defined a preinfluenza season as the period between 1 June 2010 and 31 August 2010, when the percentage of positive influenza tests was <10% nationally [20].

Outcomes and Follow-up
The primary outcome was hospitalization for pneumonia or influenza, which was defined based on the presence of an inpatient record having International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes 480–487 [8] as the primary diagnosis. We also examined hospitalization for any cause and death for any cause as secondary outcomes. Outcomes were included if they occurred at least 2 weeks after vaccination [21], and in the period of the regional influenza season.

Baseline Characteristics
We examined patient age (continuous, and grouped as 65–74, 75–84, and ≥85 years), sex, and race (white, black, and other). Using data from the year prior to vaccination, we defined indicators for receipt of any immunosuppressive medication, presence of human immunodeficiency virus (HIV) infection, and (separately) receipt of the monovalent pH1N1 (pandemic) vaccine and/or the trivalent influenza vaccine during the 2009–2010 (prior) influenza season. Comorbidity was defined using the Elixhauser comorbidity score [22]. To assess potential bias due to unmeasured non-influenza activity related factors associated with selection of vaccine type, we also examined hospitalization for influenza or pneumonia during the preinfluenza season [23].
Statistical Analysis
For baseline characteristics, we report frequencies and percentages for categorical variables and means and standard deviations for continuous variables for patients receiving HD and SD vaccines. We compared baseline characteristics by vaccine group using χ² tests for categorical variables and t tests for continuous variables. We also compared preinfluenza season hospitalization for influenza or pneumonia to detect differences between groups in the period before the onset of the influenza activity when the true difference between similar groups of patients should be zero. This comparison allowed us to determine whether the 2 groups differed with respect to characteristics, observed or unobserved, associated with risk of the study outcome [23]. For example, potential bias due to differences between vaccine groups in the prevalence of severe illness and frailty, which may not be fully captured by ICD-9 codes, is estimated in this comparison, and can thus be controlled in subsequent analyses.

Receipt of HD or SD vaccine was not randomly assigned, and if there were systematic differences in observed baseline characteristics between patients who received HD and SD vaccine, estimates of the relative effectiveness of the 2 vaccines could be biased. We conducted a propensity score analysis to reduce this potential bias. The propensity score has been called a “balancing score”: Within strata or blocks defined based on the true propensity score, patient baseline characteristics in different treatment groups are similar [24]. Stratifying on the quintiles of the estimated propensity score has been shown to eliminate approximately 90% of the bias due to observed confounders [25].

We developed a logistic regression model for the probability of receiving HD vaccine—the propensity score. In this model, receipt of HD vaccine was the outcome variable, and patient age, sex, race, Elixhauser comorbidity score, preinfluenza season hospitalization for influenza, prior year pH1N1 vaccination, prior year trivalent influenza vaccination, HIV infection, and use of immunosuppressive medication were included as predictors. Using the resulting model, we estimated each patient’s propensity to receive HD vaccination. We assessed the effectiveness of this estimated propensity score in balancing patient characteristics by comparing the standardized differences in means for baseline characteristics between HD and SD vaccination groups within strata defined by quintiles of the propensity score. The standardized difference compares the difference in means between groups in units of the pooled standard deviation, and provides a measure that is not dependent on sample size [24].

We used Poisson regression (to account for person-time at risk) to model the association between the primary study outcome and receipt of HD vaccine, stratified by propensity quintile, and used a robust variance estimator clustered at the VAMC level. We included preinfluenza season hospitalization for influenza or pneumonia [26] as an adjustment variable, and combined results across propensity strata to estimate the relative risk (RR) of the primary outcome, among patients vaccinated with HD vs SD vaccine. Secondary outcomes (ie, all-cause hospitalization, mortality) were analyzed in the same way. In a sensitivity analysis for hospitalization outcomes, we repeated the analyses including only patients who did not die.

In view of the increased immunosenescence and reduced vaccine effectiveness of the SD vaccine among older patients, we hypothesized that the relative effectiveness of HD vs SD vaccine would be greater among older Veterans. We tested for effect modification by age by including an interaction term for (continuous) patient age and the type of vaccine in the model for hospitalization for influenza or pneumonia. We then estimated the relative risk of hospitalization for influenza or pneumonia within subgroups of patients aged 65–74, 75–84, and ≥85 years [27]. In these age-stratified analyses, we used propensity score quintile as a covariate, instead of stratifying, to avoid having strata with no outcome events. We then repeated the analysis including preinfluenza season hospitalization for influenza or pneumonia as an adjustment variable. SAS software version 9.3 (SAS Institute, Cary, North Carolina) was used for all analyses.

RESULTS
We identified 26 566 patients who received HD vaccine and 266 335 who received SD vaccine in 48 VA medical centers nationally. After restricting the sample to those facilities where at least 50 patients received HD vaccine, there were 25 714 patients who received HD vaccine and 139 511 who received SD vaccine in 23 VA Medical Centers. Among these patients, 2419 (1.5%) had missing data on 1 or more covariates, and were excluded from the propensity score analyses.

The patient population was predominately male. Those who received HD vaccine (vs those who received SD vaccine) were slightly older, more likely to be black, had higher Elixhauser comorbidity score, and were more likely to have HIV and exposure to immunosuppressive drugs. Patients who received HD vaccine were also more likely to have been vaccinated with the 2009–2010 trivalent vaccine and less likely to have received the pH1N1 vaccine for influenza in the previous influenza season, compared with patients who received SD vaccine. In the preinfluenza season, patients who received HD vaccine did not differ from those who received SD vaccine with respect to either hospitalization for influenza or pneumonia or hospitalization for other reasons (Table 1).

Table 2 summarizes hospitalization and mortality outcomes for the influenza season. In the influenza season, 0.3% of patients in both groups were hospitalized for influenza or pneumonia.

We confirmed that propensity stratification resulted in strata or blocks of patients having similar baseline characteristics: The
mean and maximum absolute standardized differences before propensity stratification were 0.026 and 0.06, and after propensity stratification they were 0.018 and 0.05, suggesting that the propensity model was adequately specified.

In the propensity-stratified analysis of influenza season hospitalization for influenza or pneumonia, there was no significant difference between those who received HD and SD vaccine (RR, 0.98; 95% confidence interval [CI], .68–1.40; P = .92). There were no significant differences in hospitalization for all causes and mortality between the 2 groups (Table 2). The results of the hospitalization outcomes were nearly identical when excluding subjects who died during the study period.

In subgroup analysis, we found that age modified the effect of HD vaccination compared with SD vaccination on hospitalization for pneumonia or influenza, based on the significance of the age–vaccine type interaction term (P = .002). Among patients aged ≥85 years, those who received HD vaccine had lower hospitalization rates for influenza and pneumonia than those who received SD vaccine—0.30% and 0.66%, respectively (RR, 0.52; 95% CI, 0.29–0.92). Patients 65–84 years of age who were vaccinated with HD did not have lower adjusted hospitalization

### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Vaccination Type</th>
<th></th>
<th></th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High Dose (n = 25,714)</td>
<td>Standard Dose (n = 139,511)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>4660</td>
<td>18.1</td>
<td>18,943</td>
<td>13.6</td>
</tr>
<tr>
<td>Other</td>
<td>2553</td>
<td>9.9</td>
<td>17,619</td>
<td>12.6</td>
</tr>
<tr>
<td>White</td>
<td>18,501</td>
<td>71.9</td>
<td>102,949</td>
<td>73.8</td>
</tr>
<tr>
<td>Male sex</td>
<td>25,316</td>
<td>98.5</td>
<td>136,945</td>
<td>98.2</td>
</tr>
<tr>
<td>Age, mean and SD</td>
<td>75.5</td>
<td>7.45</td>
<td>75.0</td>
<td>7.43</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–74</td>
<td>12,318</td>
<td>47.9</td>
<td>70,160</td>
<td>50.3</td>
</tr>
<tr>
<td>75–84</td>
<td>9,782</td>
<td>38.0</td>
<td>51,139</td>
<td>36.7</td>
</tr>
<tr>
<td>≥85</td>
<td>3,614</td>
<td>14.1</td>
<td>18,212</td>
<td>13.1</td>
</tr>
<tr>
<td>Elixhauser score, mean and SD</td>
<td>2.1</td>
<td>5.00</td>
<td>1.9</td>
<td>4.85</td>
</tr>
<tr>
<td>HIV</td>
<td>86</td>
<td>0.3</td>
<td>302</td>
<td>0.2</td>
</tr>
<tr>
<td>Immunosuppressive drugs</td>
<td>2,144</td>
<td>8.3</td>
<td>10,508</td>
<td>7.5</td>
</tr>
<tr>
<td>Monovalent pH1N1 influenza vaccination</td>
<td>5,467</td>
<td>21.3</td>
<td>32,314</td>
<td>23.2</td>
</tr>
<tr>
<td>Trivalent influenza vaccination</td>
<td>17,606</td>
<td>68.5</td>
<td>89,752</td>
<td>64.3</td>
</tr>
<tr>
<td>Preinfluenza season hospitalization for pneumonia or influenza</td>
<td>40</td>
<td>0.16</td>
<td>211</td>
<td>0.15</td>
</tr>
<tr>
<td>Preinfluenza season hospitalization for other reasons</td>
<td>858</td>
<td>3.34</td>
<td>4,442</td>
<td>3.18</td>
</tr>
</tbody>
</table>

Abbreviations: HIV, human immunodeficiency virus; pH1N1, pandemic H1N1; SD, standard deviation.

* For the (prior year) 2009–2010 influenza season.

### Table 2. Hospitalization and Mortality for Patients Receiving High-Dose Versus Standard-Dose Influenza Vaccine

<table>
<thead>
<tr>
<th>Mortality</th>
<th>High-Dose Recipients (n = 25,714), No. (%)</th>
<th>Standard-Dose Recipients (n = 139,511), No. (%)</th>
<th>RR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Influenza season</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalized for pneumonia or influenza</td>
<td>83 (0.3)</td>
<td>454 (0.3)</td>
<td>0.98 (0.68–1.40)</td>
<td>.92</td>
</tr>
<tr>
<td>Hospitalized for any cause</td>
<td>1,263 (4.9)</td>
<td>6,443 (4.6)</td>
<td>0.99 (0.86–1.16)</td>
<td>.94</td>
</tr>
<tr>
<td>Death</td>
<td>429 (1.7)</td>
<td>2,054 (1.5)</td>
<td>1.05 (0.87–1.26)</td>
<td>.61</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

* Propensity score analysis.
patients receiving high-dose versus standard-dose influenza vaccine

Table 3. Hospitalization for Pneumonia or Influenza, by Age, for Patients Receiving High-Dose Versus Standard-Dose Influenza Vaccine

<table>
<thead>
<tr>
<th>Age Category</th>
<th>High Dose, No. (%)</th>
<th>Standard Dose, No. (%)</th>
<th>RR* (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>65–74 y</td>
<td>27/12 318 (0.22)</td>
<td>151/70 160 (0.22)</td>
<td>1.16 (.71–1.88)</td>
<td>.55</td>
</tr>
<tr>
<td>75–84 y</td>
<td>45/9782 (0.46)</td>
<td>183/51 139 (0.36)</td>
<td>1.44 (.82–2.52)</td>
<td>.20</td>
</tr>
<tr>
<td>≥85 y</td>
<td>11/3614 (0.30)</td>
<td>120/18 212 (0.66)</td>
<td>0.52 (.29–.92)</td>
<td>.02</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.
*Adjusted for propensity score quintile.

Results of our subgroup analysis indicate a significant relative benefit of the HD vaccine for reducing hospitalizations for pneumonia or influenza among patients aged ≥85 years, compared with SD vaccine. It is possible that the effect of SD vaccine is lower in older subgroups, whereas the effect of HD vaccine is more stable as age increases. Further study is needed to evaluate this hypothesis.

Strengths of our study include use of a large national sample from a diverse population receiving care within a real-world setting. Our study evaluated complications of influenza with substantial public health impact. Including preinfluenza season hospitalization for influenza or pneumonia in our analysis adds strength because it serves as an indicator of the presence of unmeasured confounders such as frailty and severe illness. We accounted for observed confounders using propensity score stratification, and were able to confirm that our propensity score approach resulted in within-strata comparisons among patients who were similar with respect to baseline characteristics. Thus, despite the observational nature of our study, we were able to address and adjust for potential bias due to both observed and unobserved preinfluenza season confounders.

Our study has several limitations. First, because our data on admitted patients did not include results of laboratory confirmation for influenza infection for admitted patients, our primary hospitalization outcome may have identified patients with respiratory conditions that are not influenza related, and missed admitted patients with influenza not coded as having influenza or pneumonia [31]. Restricting our analysis to periods of significant influenza activity reduces (but does not eliminate) this potential nondifferential misclassification that may bias the results toward not finding a difference. Second, our comparative effectiveness study was observational, and treatment allocation was not randomized, so the potential for residual confounding by indication or confounding by unmeasured covariates cannot be eliminated. Third, patients aged ≥65 years are eligible for Medicare, and may have received services, including hospitalization, outside the VA health system. We limited our study to patients receiving ongoing care in the VA system but also do not have reason to suspect that hospitalization outside of the VA would be more likely among patients receiving HD vs SD vaccine. Fourth, although our sample size was very large, only 0.3% of patients had our study outcome, reducing power to detect all but a moderately large effect. In addition, as with any study of influenza vaccination, ours is only generalizable to influenza seasons with similar levels of preexisting immunity and an excellent match of the vaccine to circulating influenza strains.

In conclusion, in this large nationwide sample of community-dwelling older adults vaccinated for influenza in the 2010–2011 influenza season, we did not find that HD vaccine resulted in lower rates of hospitalization for influenza or pneumonia.
compared to SD vaccine. We found similar results for the secondary outcomes of all-cause hospitalization or death. However, in the subpopulation of patients aged ≥85 years, we did find that HD vaccine was protective relative to SD vaccine.

Further studies are needed to evaluate the potential clinical benefit of the new HD vaccine, as well as to continue to explore alternative routes to increasing immunogenicity of influenza vaccine in older adults.

Notes

Acknowledgments. We thank Arwin M. Thomasson, PhD, for assistance in refining the analysis plan, and Ebbing Lautenbach, MD, MPH, MSCE, for comments that greatly improved the manuscript.

Disclaimer. The funding source approved the funding of the investigator-proposed research, but had no role in the design, execution, or decision to publish the study.

Financial support. This work was supported by the Veterans Integrated Service Network 4 Competitive Pilot Project Fund. The study was also supported in part by the Centers for Disease Control and Prevention Epicenters Program (US4-CK000163 [Ebbing Lautenbach]).

Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References