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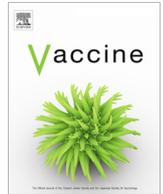
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Economic assessment of a high-dose versus a standard-dose influenza vaccine in the US Veteran population: Estimating the impact on hospitalization cost for cardio-respiratory disease



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ABSTRACT

Objective: To compare the economic impact of high-dose trivalent (HD) versus standard-dose trivalent (SD) influenza vaccination on direct medical costs for cardio-respiratory hospitalizations in adults aged 65 years or older enrolled in the United States (US) Veteran's Health Administration (VHA).

Methods: Leveraging a relative vaccine effectiveness study of HD versus SD over five respiratory seasons (2010/11 through 2014/15), we collected cost data for healthcare provided to the same study population both at VHA and through Medicare services. Our economic assessment compared the costs of vaccination and hospital care for patients experiencing acute cardio-vascular or respiratory illness.

Results: We analyzed 3.5 million SD and 158,636 HD person-seasons. The average cost of HD and SD vaccination was \$23.48 (95% CI: \$21.29 - \$25.85) and \$12.21 (95% CI: \$11.49 - \$13.00) per recipient, respectively, while the hospitalization rates for cardio-respiratory disease in HD and SD recipients were 0.114 (95% CI: 0.108–0.121) and 0.132 (95% CI: 0.132–0.133) per person-season, respectively. Attributing the average cost per hospitalization of \$11,796 (95% CI: \$11,685 - \$11,907) to the difference in hospitalization rates, we estimated savings attributable to HD to be \$202 (95% CI: \$115 - \$280) per vaccinated recipient. **Conclusions:** For the five-season period of 2010/11 through 2014/15, HD influenza vaccination was associated with net cost savings due to fewer hospitalizations, and therefore lower direct medical costs, for cardio-respiratory disease as compared to SD influenza vaccination in the senior US VHA population.

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1. Introduction

Adults 65 years and older (hereinafter referred to as seniors) are at an increased risk for complications caused or triggered by an influenza infection [1]. Young-Xu and colleagues estimated the range of annual direct medical costs of influenza-attributable

hospitalizations at Department of Veterans Affairs (VA) Medical Centers for senior Veterans Health Administration (VHA) enrollees over five respiratory seasons (2010/11 through 2014/15) to be between 24 and 34 million US dollars [2]. Given this substantial cost, a health economic analysis of the various influenza vaccination strategies for this age group is pertinent.

One of the vaccination options available to the VHA during this period was the injectable high-dose inactivated trivalent influenza vaccine (Fluzone[®] High-Dose, Sanofi Pasteur, PA, US, licensed in the US in 2009 for people aged 65 years and older; hereinafter referred

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to as the high-dose vaccine (HD)). HD contains four times more influenza hemagglutinin antigen than standard-dose trivalent influenza (SD) vaccines (60 µg vs. 15 µg per strain), improving immune response and therefore protection, in seniors. Young-Xu et al. [3] reported a relative vaccine effectiveness (rVE), or additional reduction, of HD versus SD of 10% (95% CI, 8%–12%) for all-cause hospitalization; 18% (95% CI, 15%–21%) for cardio-respiratory-associated hospitalization; and 14% (95% CI, 6%–22%) for influenza/pneumonia-associated hospitalizations during five respiratory seasons (2010/11 through 2014/15).

Various features of the Young-Xu et al. (2019) study enable us to assess the contribution of HD in lowering the direct medical cost of influenza-attributable hospitalizations, thereby improving the accuracy of economic burden estimations. First, the study included hospitalizations in non-VA medical centers. The majority of senior Veterans are “dual users” and receive care in both VA and non-VA facilities paid for by Medicare [4,5]. Second, the study captured five rather than one single respiratory season. Incorporating seasonal variation in influenza viral circulation and vaccine effectiveness increases the confidence in our economic assessment as an average economic effect. Third, the study used a statistical method to adjust for observable and unobservable differences between the HD and SD recipients.

In this paper, we will assess the economic impact of HD versus SD vaccination on cost of hospitalization for cardio-respiratory disease in the population analyzed by Young-Xu et al. (2019). In addition, we estimate the economic impact in a scenario where 10% of the study population had received HD and 90% SD.

2. Methods

2.1. Study Design, population and data sources

The Young-Xu et al. [3] study, a retrospective cohort study with approximately 700,000 patients included in each of the five respiratory seasons, compared hospitalizations between those who received HD versus SD at a VA facility. Patients were included when they were at least 65 years old at vaccination, had received only one HD or SD vaccine in the seasons of interest, and had sought medical care at a VA facility in the six months before vaccination. This resulted in a study population of 3.5 million SD and 158,636 HD person-seasons. We used the same population and methods of Young-Xu et al. (2019) to calculate rVEs for the present study. In summary, for each study participant at each season, the baseline period (during which baseline characteristics were measured) was defined from the beginning of each respiratory season in week 27 (beginning of July) until his or her influenza vaccination date. The observation period (during which study outcomes were measured) was defined from two weeks after vaccination until the end of the respiratory season in week 26 (end of June). Crude rVE rates were adjusted for treatment selection bias (confounding by indication) using differences in observable baseline characteristics between the cohorts that included demographics, comorbidities adapted from the Deyo-Charlson comorbidity score [6], and VA priority group, a surrogate measure for socio-economic status (Appendix 1) [7]. In addition, an instrumental variable (IV) based on the facility's treatment preference for HD, defined as the proportion of HD recipients at a certain facility in a given respiratory season, was used to act as a pseudo-randomizer of unobservable differences [3].

VHA is the largest integrated health care system in the US, providing care at 1,240 health care facilities, including 170 VA Medical Centers and 1,061 outpatient sites of care of varying complexity (VA outpatient clinics) to over nine million Veterans enrolled in healthcare through VA [8]. Admissions to VA hospitals were

derived from its unified electronic medical record system (EMR) that contains information about inpatient, outpatient, and emergency department (ED) visits.

For the cost of vaccination in VA facilities, we obtained data from the National Acquisition Center Contract Catalog Search Tool [9]. Hospitalizations, and their reimbursement costs, of VHA enrollees that occurred in non-VA facilities were obtained from the Centers for Medicare and Medicaid Services (CMS) administrative fee-for-service claims. These records supplement those in the VHA database as many patients seek healthcare outside VA once eligible for CMS benefits. While VHA applies a system of cost allocation, costs of non-VA hospitalizations are based on insurance reimbursements, which do not necessarily reflect true costs for the healthcare provider [10].

The study received institutional review board approval from the Veteran's Institutional Review Board of Northern New England at the White River Junction VA Medical Center.

2.2. Outcomes and IV-adjusted rVEs

Our primary outcome of interest was an acute hospitalization for cardio-respiratory disease, defined by its principal discharge diagnosis (International Classification of Diseases, Ninth Revision, ICD-9: 390-519, Appendix 2). Because this definition is less inclusive than the definition by Young-Xu et al. (2019) that included both acute hospitalizations and nursing home admissions, we recalculated rVEs using the same statistical model for cardio-respiratory disease. We assessed HD's impact on cost of acute hospitalization for pneumonia or influenza (P&I) as well. Because expected underreporting of these hospitalizations introduced significant bias in the estimation of incidence rates, we refer for the results to Appendices 3 and 4 [11–13]. In addition, we report HD's impact on a more sensitive outcome, all-cause hospitalizations, in these appendices.

2.3. Economic assessment

The need to adjust the crude rVE for treatment selection bias prevented us from a straight comparison of costs incurred by the HD recipients to those incurred by the SD recipients. We used a model based on the incidence rate ratio (RR) derived from the IV-adjusted rVE (1) and applied the RR to the total number of outcomes (Y_T , adjusted for number of HD and SD recipients (N_{HD} and N_{SD} , respectively), to estimate the number of outcomes in the SD cohort (2).

$$rVE = (1 - RR) \times 100\%; RR = \frac{Y_{HD}/N_{HD}}{Y_{SD}/N_{SD}} \quad (1)$$

$$\hat{Y}_{SD} = \frac{Y_T}{1 + RR \frac{N_{HD}}{N_{SD}}} \quad (2)$$

$$\text{Hospitalizationrate}_{SD} = \frac{\hat{Y}_{SD}}{N_{SD}} \quad (3)$$

Where N_T is the study population size in a given respiratory season and consisting of all vaccine recipients ($N_T = N_{HD} + N_{SD}$); Y_T is the total number of *observed* outcomes (e.g. hospitalizations for cardio-respiratory disease) in the study population; \hat{Y}_{SD} and \hat{Y}_{HD} are the number of outcomes *attributed* to the SD and HD recipients ($Y_T = \hat{Y}_{SD} + \hat{Y}_{HD}$); RR is the IV-adjusted incidence rate ratio; and $\text{Hospitalizationrate}_{SD}$ is the hospitalization rate of outcome \hat{Y}_{SD} in the group of SD recipients.

After adjusting the observed outcomes with the season and outcome-specific rVE, we calculated the absolute risk reduction

[ARR] by subtracting the incidence rate in the HD cohort from the SD cohort. The multiplicative inverse of ARR results in the number needed to treat (NNT = 1/ARR): the number of patients that need to be switched over from SD to HD to prevent one hospitalization. For cost of vaccination, we averaged season specific vaccine and administration costs. To increase the accuracy of the economic assessment and reduce the impact of data entry errors and rare-but-extreme values, we removed the top and bottom two percentiles equivalent to at least two standard deviations in a normal distribution of the observed hospitalization costs, as was done by Young-Xu et al. (2017), retaining 96% of observations in the cost-analysis [2,14]. Because variation in vaccination cost was small, we included all observations. We used random sampling with replacement bootstrapping to calculate 95% confidence intervals (CI).

To evaluate cost-savings of HD vaccination, we estimated the difference in costs per SD recipient as if they had received HD instead. This was calculated as the average cost of a hospitalization for an SD recipient divided by the number needed to treat (NNT) minus the average cost difference of administering the two vaccines. The cost of administering a vaccine included the cost of the vaccine itself as well as the cost of the administration process (vaccine injection and record keeping). We calculated the total realized cost-savings by multiplying the total number of HD recipients by the cost-savings per patient. The maximum (potential) savings were calculated by dividing the total savings by the HD proportion minus the number of HD recipients divided by the sum of HD and SD recipients.

$$\text{Savings}_{\text{SD} \rightarrow \text{HD}} = \frac{\frac{1}{Y_{\text{SD}}} \sum \text{Cost}Y_{\text{SD}}}{\text{NNT}} - \left(\frac{1}{N_{\text{HD}}} \sum \text{Cost}N_{\text{HD}} - \frac{1}{N_{\text{SD}}} \sum \text{Cost}N_{\text{SD}} \right) \quad (4)$$

Where Y_{SD} is the number of observed outcomes in the SD cohort, $\text{Cost}Y_{\text{SD}}$ are the total costs of these outcomes, N_{HD} the number of HD recipients, Cost_{HD} the total cost of vaccinating the HD cohort, N_{SD} the number of SD recipients, and Cost_{SD} the total cost of vaccinating the SD cohort. $\text{Savings}_{\text{SD} \rightarrow \text{HD}}$ are the estimated savings per SD recipient if they had received an HD vaccination instead.

The lower limit of the CI for cost-savings is based on the lower limit of the CI for the rVE, the upper limit for incremental costs of vaccination, and the lower limit of hospitalization costs. We applied the opposite limits of the ones used to calculate the lower limit for the upper limit. The variation in VHA costs and Medicare reimbursements, as well as variation in the cost of vaccination, are reflected in their CI.

We first calculated season-specific NNTs and cost-savings using season-specific numbers of HD and SD recipients, observed hospitalizations and costs, for which the results are presented in Appendices 3 and 4. We then analyzed combined data from all five seasons longitudinally, accounting for repeated measures from patients appearing in multiple seasons, to provide one summary measure of NNT and cost-savings.

2.4. Sensitivity analysis

We performed three sensitivity analyses to test the robustness of our findings. First, our economic assessment reassigns the observed total number of outcomes to the HD and SD cohorts using the IV-adjusted rVE. We assume that the true proportion of outcomes in VHA-hospitals does not change after this reassignment. To explore the sensitivity of the cost-savings to potential changes of the true proportion, we varied the observed proportion of hospitalizations with underlying cardio-respiratory disease by 25 percentage points in either direction. This allowed us to model a

best/worst case scenario without negative hospitalizations in any of the five respiratory seasons (Appendix 6). Second, we report a historical cost-assessment that will change if underlying costs change. To explore the sensitivity of the historical cost savings to changes in the incremental cost of vaccination – the average cost difference of administering the two vaccines – we explored a scenario in which the incremental cost of vaccination is doubled, aligning it more closely to the values of \$19.75 and \$20.00 reported in other studies, with and without a 5 percentage point increase of the cost of hospitalization (Appendix 7) [15–17]. We recognize that VHA cost and CMS reimbursement are imperfect proxies of the true cost of a hospitalization. The VHA system of cost-allocation may allow for cost inefficiency, whereas CMS reimbursements do not always cover true costs incurred by a facility or healthcare provider [10,18]. In other words, VHA cost may be an overestimation of true cost, while the CMS reimbursements may be an underestimation. We therefore performed a sensitivity analysis in which VHA costs were reduced by 10 and 20 percentage points, while increasing CMS reimbursement were increased by 10 and 20 percentage points (Appendices 8 and 9). Last, we explored the effect of removal of outliers on our results. We repeated the main analysis including all cost data (Appendix 10).

3. Results

During the five-year study period, we analyzed 3.6 million person-seasons (Table 1). The overall HD proportion has more than doubled from 3.1% in 2010–11 to 7.7% in 2014–15 (Appendix 2). We observed 478,982 hospitalizations for cardio-respiratory disease in our study cohort. We estimated the rVE (HD vs SD) for acute hospitalizations with underlying cardio-respiratory disease to be 14% (95% CI: 8% – 19%). IV-adjusted hospitalization rates (outcomes per person-year) were 0.132 (95% CI: 0.132–0.133) for SD recipients and 0.114 (95% CI: 0.108–0.121) for HD recipients. Based on these rates, we calculated a number needed to treat (NNT) of 55 (95% CI: 40–93) to prevent one hospitalization for cardio-respiratory disease.

The average cost of a VA hospitalization for cardio-respiratory disease for SD recipients was \$16,220 (95% CI: \$16,009–\$16,430, Table 2). Average CMS reimbursement to a non-VA facility was \$9,716 (95% CI: \$9,652–\$9,781) per hospitalization. Of all observed hospitalizations for cardio-respiratory disease, 32% were seen in a VA facility, while 68% were observed in a non-VA facility. Average costs of an HD and SD vaccination were \$23.48 (95% CI: \$21.29–\$25.85) and \$12.21 (95% CI: \$11.49–\$13.00) per vaccinated patient, respectively.

We estimated the savings per HD-vaccinated VHA patient to be \$202 (95% CI: \$115–\$280, Table 3). Estimated total savings were

Table 1
Number of influenza vaccinations, hospitalization rates for cardio-respiratory disease, and number needed to treat (NNT) to prevent one hospitalization for VHA enrollees vaccinated during respiratory seasons 2010–11 through 2014–15.

Study cohort	3,638,924	
HD recipients	158,636	4.4%
SD recipients	3,480,288	95.6%
Observed hospitalizations	478,982	
Applied rVE	14% (8–19%)	
Hospitalization incidence rates		
Rate HD recipients	0.114 (0.108–0.121)	
Rate SD recipients	0.132 (0.132–0.133)	
Treatment effect		
Number Needed to Treat	55 (40–93)	

Table 2

Mean cost and reimbursement per hospitalization for cardio-respiratory disease and vaccination among vaccinated VHA enrollees during the 2010–11 through 2014–15 respiratory seasons in US dollars.

Hospitalization	Mean (95% CI)	Weight	Value
SD recipients			
VHA cost	16,220 (16,009–16,430)	32%	11,796 (11,685–11,907)
CMS reimbursement	9,716 (9,652–9,781)	68%	
Vaccination			
Mean (95% CI)			
VHA cost		Incremental cost	
HD recipients	23.48 (21.29–25.85)		11.27 (9.81–12.86)
SD recipients	12.21 (11.49–13.00)		

Table 3

Estimation of realized and potential savings for hospitalizations among vaccinated VHA enrollees for cardio-respiratory disease in US dollars).

Savings	Mean (USD)	95% CI	
		Lower	Upper
Per patient SD→HD	202	115	280
Total	32M	18M	44M
Potential	73M	42M	102M

$\$202 \times 158,636$ HD recipients = \$32 million (95% CI: \$18–\$44 million) based on an HD proportion of 4.4%. Estimated potential savings under the assumption that 10% of the study population had received HD are $\$202 \times 363,892$ HD recipients = \$74 million (95% CI: \$42–\$102 million). HD remained cost-saving in all sensitivity analyses performed for hospitalizations with underlying cardio-respiratory disease.

4. Discussion

We compared the cost of influenza vaccination and acute hospitalization for cardio-respiratory disease of 158,636 HD and 3.6 million SD recipients during five respiratory seasons and found that HD vaccination resulted in average savings of \$202 (95% CI: \$115–\$280) per recipient. These savings were achieved by a reduced number of hospitalizations based on HD's IV-adjusted rVE of 14% (95% CI: 8% – 19%) for cardio-respiratory disease-associated acute hospitalizations.

Our outcome definitions were less inclusive than the definitions used by Young-Xu et al. (2019) that included both acute hospitalizations and nursing home admissions. Limiting the outcome definition as such allowed for a more precise comparison of the observed mean cost of a hospitalization with external sources and reduced likelihood of overestimation. We estimated the rVE for acute hospitalizations with underlying cardio-respiratory disease to be 14% (95% CI: 8% – 19%), about 22% lower than the 18% (95% CI, 15%–21%) estimated by Young-Xu and colleagues for the same study cohort [3].

Although we estimated substantial savings of \$32 million (95% CI: \$18–\$44 million) over a five-year period, we feel confident these are not an overestimation of the true savings for several reasons. First, we did not consider outpatient visits, nursing home admissions, lost income because of illness, or reductions in quality of life. Second, the rVE we applied was recalculated for the outcome of interest: acute hospitalizations with underlying cardio-respiratory disease. Moreover, the rVE we used is consistent with a meta-analysis of existing studies of the rVE of HD vs. SD, showing a 10.4% (95% CI, 1.6% – 18.5%) additional reduction of all-cause hospitalizations and a 27.3% (95% CI, 15.3%–37.6%) additional

reduction of pneumonia-associated hospitalizations [19]. Last, the average Medicare reimbursements of \$9,716 we observed (Appendix 3, season 2012/13) are in the range reported by Moore et al. (\$8,500–\$22,500) for 2012 [20].

VHA funding is appropriated by Congress as a global budget and distributed to its 23 Veterans Integrated Service Networks (VISNs) via a form of (risk-adjusted) capitation such that, in general, a VA hospital does not receive additional money for an additional hospitalization. VHA's electronic Managerial Cost Accounting system captures the cost of healthcare services, which are not based on insurance claims, reimbursements or billing data; rather, they are the aggregate of actual expenses (e.g. salaries, equipment, buildings, energy, negotiated drug prices, materials) attributed to a specific healthcare encounter. Although an additional hospitalization in a VA hospital does not result in an immediate additional cost – due to the capitated payment model – to those ultimately responsible for the costs, US taxpayers, we believe that the allocated expenses should be considered as opportunity costs: all resources needed to care for a potentially vaccine-preventable hospitalization could have been used for another admission.

Because our objective is not to compare cost of care between VA and non-VA facilities, but to estimate cost to the US taxpayer, we consider differences in VHA costs and Medicare reimbursement data to be acceptable.

Our cost-saving estimate of \$202 per patient is between the net savings of \$91 Chit and colleagues calculated in a randomized controlled trial (RCT) for cardio-respiratory hospitalizations, and the \$262 per patient Shireman et al. estimated for acute hospitalizations in the US nursing home population [15,16]. RCT participants were drawn from the general, relatively healthy population. The Veteran patient population, in contrast, is on average older, predominantly male, has a higher prevalence of comorbid conditions and poorer health status than the general population [21]. If patients with a poorer health status benefit more from HD than healthy patients, it is logical that the estimated savings found in our study are closer to the savings observed for nursing home residents than to those in the general population.

Strengths and limitations of the study cohort and the statistical method of IV estimation we used in our calculations have been reported elsewhere [3]. Additional strengths include the size and longitudinal observation of the cohort over multiple seasons. Seasonal variation in influenza viral activity and vaccine efficacy caused by a better or worse match between circulating strains and those included in the vaccine portends seasonal variation in the severity of influenza; therefore, incorporating multiple seasons in this analysis increases confidence in our assessment as an average economic effect. During the span of our study we observed two seasons with a high severity (2012/13 and 2014/15), two with moderate (2010/11 and 2013/14), and one with a low (2011/12) severity [22]. The predominant circulating strain in the two high severity seasons was H3N2, while 2012/13 saw additional B strain circulation. As the Food and Drug Administration decides which strains must be included in vaccines sold in the US, the HD and SD vaccines contain similar strains in a given season. In the 2012/13 seasons, the vaccines were a good match with the circulating strains, while the vaccines in 2014/15 were not well matched [23]. Notably, HD rVEs and costs did not significantly vary over the course of the five seasons, resulting in relatively consistent savings.

In addition, IV estimation can adjust for selection bias caused by preferential treatment based on patient characteristics that are not visible to researchers. An example of a patient characteristic that is visible to a VA health care provider, but not captured in our data set is “frailty”. However, in order to adequately adjust for unmeasured confounders, IV estimation requires an instrument that satisfies the underlying assumptions of the method. Only then does

the instrument works as a randomizer. An important assumption – that the instrument is not associated with the outcome – can never be entirely ruled out. Our instrument, a facility's treatment preference for HD, targets patients who would have received a different vaccine if they had gone to a different VA facility. It is impossible to identify these “marginal patients” in the study population.

The value of a prevented hospitalization is the weighted average of the cost of a VA hospitalization and the reimbursement of a non-VA hospitalization. The weights were based on the proportion of observed hospitalizations in VA and non-VA facilities. Because VHA costs are almost twice the value of Medicare reimbursements, this proportion has a big impact on the value of a prevented hospitalization. We used the observed proportion to estimate savings under the assumption that HD prevents the same percentage of hospitalizations in VA and non-VA facilities. We cannot verify this assumption with our current data set. However, HD remained cost saving in the sensitivity analysis for which the observed proportion was altered by 25 percentage points in either direction (Appendix 6).

Furthermore, we did not include costs of healthcare utilization associated with vaccine side effects. Safety data from the RCT showed increased rates of local reactogenicity observed in HD recipients; however, injection site symptoms were generally not severe and resolved quickly, and overall rates of systemic complaints were comparable to those of the SD recipients [24].

Our study population is not representative of the general VHA-enrolled population: we included patients who had sought medical care at a VA facility in the six months before vaccination, which excluded approximately 30% of enrollees who received an HD or SD vaccine in a VA facility.

5. Conclusion

We estimate that offering the HD vaccine instead of SD to this Veteran study population has saved the US taxpayer \$32 million (95% CI: \$18 – \$44 million) over a five-year period as a result of fewer hospitalizations due to underlying cardio-respiratory disease. Although we believe that switching more senior patients from SD to HD will result in higher total net savings – our findings show a 5.6% increase in vaccination coverage can result in savings of \$73 million (95% CI: \$42 – \$104 million) – additional analysis is necessary to confirm this hypothesis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: RVA and AC are employees of Sanofi Pasteur. SMM has received research funding from Assurex, GSK, Merck, Pfizer, Roche and Sanofi, and is/was a member of advisory boards for GSK and Sanofi. VM has received research funding from Sanofi-Pasteur, is Chair of the Independent Quality Committee at HCR Manor Care, and Chair of the Scientific Advisory Board and consultant at NaviHealth, Inc., as well as former Director of PointRight, Inc., where he holds less than 1% equity. YYX has received research funding from Sanofi, AstraZeneca, Roche, Pfizer, and Janssen

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.06.066>.

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