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Comparing the impact of high-dose versus standard dose influenza vaccines on hospitalization cost for cardiovascular and respiratory diseases: Economic assessment in the US Veteran population during 5 respiratory seasons using an instrumental variable method ☆

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ABSTRACT

Objectives: Cost savings associated with high-dose (HD) as compared to standard-dose (SD) influenza vaccination in the United States (US) Veteran's Health Administration (VHA) population have been attributed to better protection against hospitalization for cardiac and respiratory diseases. The relative contribution of each of these disease categories to the reported savings remains to be explored.
Methods: During a recently completed study of HD versus SD vaccine effectiveness (conducted in the VHA over five respiratory seasons from 2010/11 through 2014/15), we collected cost data for all healthcare services provided at both VHA and Medicare-funded facilities. In that analysis, we compared the costs of vaccination and hospital care for patients admitted with either cardiovascular or respiratory disease. Treatment selection bias and other confounding factors were adjusted using an instrumental variable (IV) method. In this brief report we use the same study cohort and methods to stratify the results by patients admitted for cardiovascular disease (CVD) and those admitted for respiratory disease.
Results: We analyzed 3.5 million SD and 0.16 million HD person-seasons. The IV-adjusted rVEs were 14% (7–20%) against hospitalizations for CVD and 15% (5–25%) against respiratory hospitalizations. Net cost savings per HD recipient were $138 ($66–$200) for CVD related hospitalizations and $62 ($10–$107) for respiratory disease related hospitalizations.
Conclusions: In the US VHA population, the reduction in hospitalizations for CVD over five respiratory seasons contributed twice the cost savings (per HD recipient) of the reduction in hospitalizations for respiratory disease.

1. Background

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

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over five respiratory seasons (2010/11 through 2014/15) to be between 24 and 34 million US dollars [2]. 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 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 protection, in seniors [3]. In a recent study [4] we estimated that, with an average HD coverage rate of 4.4% of all influenza vaccines administered to seniors seeking care at VHA facilities during this five season period, HD was associated with a 14% (95% CI: 8–19%) additional reduction in hospitalizations for either cardiovascular (CVD) or respiratory disease as compared to SD. As a result of the reduced hospitalizations, we estimated that the US taxpayer achieved averaged annual net cost savings of 6.4 million US dollars (95% CI: $3.6–$8.8 million); however, the relative contribution of each of the disease categories to the reported savings remains to be explored. While the literature is quite decisive on the causal relationship between influenza vaccination and prevention of respiratory complications, evidence for this relationship on especially the *magnitude* of the prevention of CVD is still developing [5,6]. The objective of this brief report is, to assess the relative contribution of CVD and respiratory diseases to the aggregate vaccine effectiveness and cost savings.

2. Methods

2.1. Study Design, population and data sources

The Van Aalst et al. (2019) study [4], 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. We used the same population and methods of Van Aalst 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 [7], and VA priority group, a surrogate measure for socio-economic status (Appendix 1) [8]. In addition, the same instrumental variable (IV), a facility's preference for HD use 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 (Appendix 12) [4,9].

For the cost of vaccination in VA facilities, we obtained data from the National Acquisition Center Contract Catalog Search Tool [10]. 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 necessary reflect true costs for the healthcare provider [11]. 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 outcomes were an acute hospitalization for CVD, defined by its principal discharge diagnosis (International Classification of Diseases, Ninth Revision, [ICD-9]: 390–459) and acute hospitalizations for respiratory disease (ICD-9: 460–519, Appendix 2). For ease of comparison, we report the earlier published aggregated outcome, a hospitalization for either CVD or respiratory disease (ICD-9: 390–519). Additionally, we explored stratification of outcomes by more specific disease groups (e.g. hospitalizations for pneumonia, acute myocardial infarction, Appendix 11). To adjust for measured and unmeasured confounding, crude rVEs for each outcome were adjusted using an instrumental variable (IV) analysis (Appendix 12)."

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 applied the model described by Van Aalst et al. (2019) and included the same sensitivity analyses (Appendix 6–10). In summary, the total observed number of hospitalizations were assigned to the HD and SD recipients using the IV-adjusted rVE. 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 rate in the SD cohort. The multiplicative inverse of ARR results in the number needed to vaccinate (NNV = 1/ARR): the number of patients that need to be vaccinated with HD instead of SD to prevent one additional hospitalization. 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 NNV minus the average cost difference of administering the two vaccines. Vaccine cost included the cost of the vaccine itself as well as the cost of administrating it; ascertained by their current procedural terminology (CPT) code (Appendix 3). We calculated the total realized cost savings by multiplying the total number of HD recipients by the cost savings per patient. The potential savings were calculated under the assumption that 10% of the study population had received HD (assuming a continuation of the upward trend: 3.3% in 2013/14 and 7.7% in 2014/15, Appendix 4).

3. Results

During the five-season study period, we analyzed 3.6 million person-seasons (Table 1). We observed 314,014 hospitalizations for CVD in our study cohort. We estimated the rVE (HD vs SD) for acute CVD hospitalizations at 14% (95% CI: 7–20%). In each study season HD was associated with reduced hospitalizations for CVD (Appendix 4). IV-adjusted hospitalization rates (per person-season) were 0.087 (95% CI: 0.087 – 0.087) for SD recipients and 0.075 (95% CI: 0.070 – 0.080) for HD recipients. Based on these rates, we calculated an NNV with HD instead of SD of 84 (95% CI: 59 – 160) to prevent one additional hospitalization for CVD. We observed 164,948 hospitalizations for respiratory disease – about half the number of those hospitalized for CVD (Table 1). We estimated an rVE for hospitalizations for respiratory disease of 15% (95% CI: 5–25%) and an NNV of 144 (95% CI: 89 – 473) to prevent one additional hospitalization for respiratory disease.

Table 1
Number of influenza vaccinations, hospitalization rates for cardiovascular, respiratory and either cardiovascular or respiratory disease, and number needed to vaccinate (NNV) to prevent one additional 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%		
	Cardiovascular		Respiratory	Either*
Observed hospitalizations	314,014		164,948	478,962
Applied rVE	14% (7–20%)		15% (5–25%)	14% (8–19%)
Hospitalization incidence rates				
Rate among HD recipients	0.075 (0.070–0.080)		0.039 (0.035–0.0433)	0.114 (0.108–0.121)
Rate among SD recipients	0.087 (0.087–0.087)		0.046 (0.046–0.0454)	0.132 (0.132–0.133)
Vaccine effect				
Number needed to vaccinate (NNV)	84 (59–160)		144 (89–473)	55 (40–93)

* Data in the 'Either' column has been published previously [4], and is added for ease of comparing the stratified results with the aggregate.

The average cost for SD recipients of a VA hospitalization was $16,523 (95% CI: $16,269–$16,781) for CVD and $15,497 (95% CI: $15,136–$15,872) for respiratory disease (Table 2). Average CMS reimbursement to a non-VA facility was $10,320 (95% CI: $10,231–$10,411) per hospitalization for CVD and $8,720 (95% CI: $8,636–$8,803) for respiratory disease.

We estimated the savings per HD-vaccinated VHA patient to be $138 (95% CI: $66–$200, Table 3) due to reduced hospitalizations for CVD. Estimated total savings were $138 × 158,636 HD recipients = $22 million (95% CI: $11–$32 million) based on an HD coverage rate of 4.4%. Estimated potential savings under the assumption that 10% of the study population had received HD are $138 × 363,892 HD recipients = $50 million (95% CI: $24–$73 million). Reduced hospitalizations for CVD contributed for 69% to the cost savings due to reduced hospitalizations for either CVD or respiratory disease. The remaining 31% of cost savings were realized by reduced hospitalizations for respiratory disease. Where the rVEs for hospitalizations related to CVD ranged from 10% in seasons 2011/13 to 15% in season 2013/14, the rVEs for hospitalizations related to respiratory disease ranged from 3% in 2011/12 (not statistically significant) to 23% in 2012/13 (Appendix 4). As a result, vaccination with HD instead of SD was cost saving in each of the five seasons in our study as a result of reduced hospitalizations for CVD (Appendix 5). In contrast, vaccination with HD instead of SD was cost saving in some seasons and on average over five seasons due to reduced hospitalizations for respiratory disease. In the seasons HD was not cost saving, the net savings per patient were positive but not statistically significant.

4. Discussion

We estimated the average rVE (HD vs SD) over five years for prevention of acute CVD hospitalizations at 14% (95% CI: 7–20%), Table 1. Although the rVEs of HD vs SD for prevention of CVD and respiratory disease hospitalizations were similar, the average cost savings due to prevented hospitalizations for CVD were significantly higher than the average cost savings due to prevented hospitalizations for respiratory disease. Net savings per vaccinated patient (HD instead of SD) were $138 (95% CI: $66–$200) for CVD hospitalizations compared to $62 (95% CI: $10–$107) for

Table 2
Mean cost and reimbursement per hospitalization, in US dollars, for cardiovascular, respiratory and either cardiovascular or respiratory disease among vaccinated VHA enrollees during the 2010/11 through 2014/15 respiratory seasons.

	Cardiovascular		Respiratory		Either*	
Hospitalization	Mean (95% CI)	Wt.[1]	Mean (95% CI)	Wt.[1]	Mean (95% CI)	Wt.[1]
VHA cost	16,523 (16,269–16,781)	35%	15,497 (15,136–15,872)	26%	16,220 (16,009–16,430)	32%
CMS reimbursement	10,320 (10,231–10,411)	65%	8,720 (8,636–8,803)	74%	9,716 (9,652–9,781)	68%
Average cost[2]	12,490 (12,343–12,639)		10,499 (10,342–10,659)		11,796 (11,685–11,907)	

[1] wt(Wt) is based on observed hospitalizations in VHA and non-VHA facilities incurred by HD and SD recipients. [2]Average cost of one hospitalization is the weighted average of the VHA cost and CMS reimbursements for an SD recipient.
* Data in the 'Either' column has been published previously [4], and is added for ease of comparing the stratified results with the aggregate.

Table 3
Estimation of realized and potential net cost savings, in US dollars, among vaccinated VHA enrollees due to reduced hospitalizations for cardiovascular, respiratory and either cardiovascular or respiratory disease during the 2010/11 through 2014/15 respiratory seasons.

Net cost savings	Cardiovascular Mean (95% CI)	Respiratory Mean (95% CI)	Either* Mean (95% CI)
Per patient SD → HD	138 (66–200)	62 (10–107)	202 (115–280)
Total	22 M (11 M–32 M)	10 M (2 M–17 M)	32 M (18 M–44 M)
Potential VHA	18 M (8.4 M–26 M)	5.7 M (1.0 M–10 M)	23 M (13 M–33 M)
Potential Medicare	32 M (16 M–47 M)	16 M (3.0 M–29 M)	50 M (29 M–69 M)
Potential Total	50 M (24 M–73 M)	22 M (4 M–39 M)	73 M (42 M–102 M)
Contribution	69%	31%	100%

* The data in the 'Either' column has been published previously [4], and is added for ease of comparing the stratified results with the aggregate.

hospitalizations for respiratory disease. This difference was mainly due to the higher incidence rate of CVD hospitalizations, which was almost twice as high as the incidence rate of hospitalizations for respiratory disease (Table 1).

As previously reported, the average costs of an HD and SD vaccination during this period were $23.48 (95% CI: $21.29–$25.85) and $12.21 (95% CI: $11.49–$13.00) per vaccinated patient, respectively [4]. We compared the actual cost of the HD and SD vaccines in each of the five seasons with the avoided costs due to hospitalizations prevented in each season (Appendix 5) and calculated the weighted averages for the cost analysis over five seasons. Assuming a linear cost increase, the half-way point of the study (2012/13 season) can be considered as the base year of the costs presented in Table 2.

We observed that a significantly higher proportion of hospitalizations for CVD took place in VA-facilities compared to hospitalizations for respiratory disease: 35% of all hospitalizations for CVD took place in VA facilities (65% in non-VA facilities) compared to 26% of all hospitalizations for respiratory disease (74% in non-VA facilities). In other words, VHA pays for a greater share of the more expensive CVD admissions compared to the Medicare-funded non-VA admissions. In this context, preventing one admission for CVD by vaccinating 84 patients with HD instead of SD leads to significant cost savings, for VHA especially. If HD uptake was to increase from 4.4% to 10%, and assuming that increased HD vaccination will not significantly change a patient's propensity of being hospitalized in a VH versus non-VA facility, we estimate annual net cost savings of 3.5 million for VHA (18 M/5 years). Under similar assumptions, another annual 1.1 million would be saved by reduced hospitalizations for respiratory disease (5.7 M/5 years). Although the literature has traditionally focused on the cost-effectiveness of influenza vaccination due to reduced respiratory complications, our study suggests that the majority of the cost savings are associated with the reduction of cardiovascular complications. Evidence for a causal relationship between influenza vaccination and the magnitude of the prevention of CVD is still developing [5,6]. Our study suggests an association between influenza vaccination (HD versus SD) and reduced hospitalizations for CVD of the same magnitude as the reduction of hospitalizations for respiratory disease. The association of HD with reduced hospitalizations for Acute Myocardial Infarction (AMI) was even higher (rVE of 21% [13–29%], Appendix 11), suggesting HD to have a stronger treatment effect on a more influenza specific CVD outcome [12]. Caution must be exercised when interpreting our findings. Although we used an instrument (IV) that fulfills the underlying assumptions based on accepted analytical methods (Appendix 12), some residual bias caused by treatment selection bias cannot be ruled out. Like in any retrospective study relying on routinely collected data, misclassification of treatment, outcomes and baseline characteristics (Appendix 1) and missing data (information bias) cannot be ruled out [13]. We classified outcomes using the principal discharge diagnosis, defined as the 'condition established after study to be chiefly responsible for occasioning the admission of the patient to the hospital for care' [14]. This does not rule out the possibility that some patients might have received treatment for both cardiovascular and respiratory disease during a hospitalization that we classified as Cardiovascular (or Respiratory).

Because HD rVE estimates highly depend on specificity and severity of the outcome, seasonal heterogeneity of viral activity and vaccine strain match, population under observation, and choice of comparator vaccine, comparing our results with other studies is challenging. A recent study comparing HD with a trivalent adjuvanted SD vaccine (aIIV3) in the 2016/17 and 2017/18 seasons reported a pooled rVE of 12.0% (95% CI: 3.3–20%) against hospitalizations for respiratory disease and 5.7% (0.3–11%) against hospitalizations for cardiovascular disease [15]. Izurieta and colleagues reported that HD was associated with lower hospitalization rates for probable influenza (hospitalization with an administrative ICD-10 code of 489 on any position on the claim) when compared to aIIV3, with an rVE of 7.7%, (5.1–10.2%) in the 2017/18 season [16]. Compared with the standard of care, a quadrivalent SD vaccine (IIV4-SD), the rVE of HD was estimated to be 10.0% (7.8–12.3%) against hospitalization for probable influenza. These recent studies add to the substantial body of evidence demonstrating that HD is more effective in the prevention of influenza associated outcomes than trivalent SD [17], and are likely to be repeated when quadrivalent HD becomes available in the 2020/21 season for the U.S. population.

Strengths and limitations of the methods, including rVE estimation, have been discussed in detail elsewhere [4,9]. Briefly, strengths include the size and longitudinal observation of the cohort over multiple seasons. Seasonal variation in influenza viral activity and vaccine efficacy 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. IV estimation can adjust for selection bias caused by measured and unmeasured preferential treatment based on patient characteristics such as "frailty". To achieve that, IV estimation requires an instrument that satisfies the several assumptions including that the instrument is not associated with the outcome. 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. Although we can't identify these "marginal patients" in the study population, it is likely that the estimates apply to the majority of the study population. Another limitation is that 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. This is, however, the population that has the biggest impact on VHA's resources, and thus, most interesting from a policy perspective. Because VHA stopped offering HD to its patient population after the 2016/17 season, we were unable to estimate cost savings for this population in recent influenza seasons.

5. Conclusion

In the US VHA population, the reduction in hospitalizations for CVD over five respiratory seasons contributed twice the cost savings (per HD recipient) of the reduction in hospitalizations for respiratory disease.

CRediT authorship contribution statement

Robertus van Aalst: Conceptualization, Formal analysis, Writing - original draft. **Ellyn M. Russo:** Writing - review & editing. **Nabin Neupane:** Data curation, Formal analysis, Software, Writing - review & editing. **Salaheddin M. Mahmud:** Writing - review & editing. **Jan Wilschut:** Writing - review & editing. **Sandrine I. Samson:** Conceptualization, Writing - review & editing. **Ayman Chit:** Writing - review & editing. **Maarten Postma:** Writing - review & editing. **Yinong Young-Xu:** Formal analysis, Software, Writing - review & editing.

Declaration of Competing Interest

This study was funded by Sanofi Pasteur RVA, SS and AC are employees of Sanofi Pasteur. YYX and ER report grants from Sanofi Pasteur during the conduct of the study. SMM has received unrestricted research grants from Merck, GlaxoSmithKline, Sanofi

Pasteur, Pfizer and Roche-Assurex for unrelated studies. SMM has received fees as an advisory board member for Sanofi Pasteur. MP received grants and honoraria from various pharmaceutical companies, inclusive those developing, producing and marketing influenza vaccines (in particular GSK, Astra Zeneca, Seqirus and Sanofi Pasteur) NN and JW report no conflict of interest.

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Appendix A. Supplementary material

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