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Analysis of relative effectiveness of high-dose versus standard-dose influenza vaccines using an instrumental variable method



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ABSTRACT

Background: Observational studies of the relative effectiveness of influenza vaccines are essential for public health decision making. Their estimates, however, are subject to bias due to unmeasured confounders. Instrumental variable (IV) methods can control for observed and unobserved confounders.

Methods: We used linked electronic medical record databases in the Veterans Health Administration (VHA) as well as Medicare administrative files to examine the relative vaccine effectiveness (rVE) of high-dose influenza vaccine (HD) versus standard-dose influenza vaccines (SD) in preventing hospitalizations among VHA-enrolled Veterans ≥ 65 years of age during 5 influenza seasons (2010–2011 through 2014–2015). Using multivariable IV Poisson regression modeling to address unmeasured confounding and bias, we analyzed the data by each season and through longitudinal analysis of all five seasons.

Findings: We included 3,638,924 person–influenza seasons of observation where 158,636 (4%) were among HD vaccine recipients and 3,480,288 (96%) were among SD vaccine recipients. Of the 1,728,562 Veterans, 1,702,824 (98.5%) were male and 1,299,412 (75%) were non-Hispanic white. Based on the longitudinal analysis of all five seasons, the IV-adjusted rVE estimate of HD vs. SD was 10% (95% CI, 8–12%) against all-cause hospitalization; 18% (95% CI, 15–21%) against cardiorespiratory-associated hospitalization; and 14% (95% CI, 6–22%) against influenza/pneumonia-associated hospitalization. The findings by season were similar.

Interpretation: Our analysis of VHA clinical data collected from approximately 1.7 million Veterans 65 years and older during five seasons demonstrates that high-dose influenza vaccine is more effective than standard-dose influenza vaccines in preventing influenza- or pneumonia-associated hospitalizations, cardiorespiratory hospitalizations, and all-cause hospitalizations.

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1. Introduction

Seasonal influenza epidemics result in a substantial annual health burden. In the United States (US), more than 200,000 people are hospitalized and upwards of 23,000 people are estimated to die annually from respiratory and circulatory complications associated with seasonal influenza infections [1–3]. Serious medical complications leading to hospitalizations and deaths are greatest and the efficacy of influenza vaccination is less among persons aged 65 years and older (hereinafter referred to as seniors) [4,5]. In

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2009, the US Food and Drug Administration (FDA) licensed an injectable high-dose inactivated trivalent influenza vaccine (HD; Fluzone® High-Dose, Sanofi Pasteur, PA, US). HD contains four times more influenza hemagglutinin antigen than standard-dose influenza vaccines (SD; 60 µg vs. 15 µg per strain), designed to provide improved protection in seniors.

Clinical trials have shown that HD was 7% (95% CI, 0.5–12.8%) and 8% (95% CI, 0.3–14%) more effective than SD influenza vaccine in preventing all-cause hospital admissions in ambulatory and nursing home seniors, respectively [6,7], as influenza may “trigger exacerbation of pre-existing conditions,” [6] including those that are not respiratory [7]. This has led to the suggestion that more attention should be paid to those hospitalizations due to respiratory conditions, as direct prevention by influenza vaccines might be expected [8]. While findings from randomized control trials (RCT) have shown greater relative vaccine effectiveness (rVE) of HD compared to SD [6,9], the findings of observational studies that utilized matching and multivariate modeling have been mixed. Notably, a study by Richardson et al. did not find any additional benefit of HD over SD in preventing pneumonia admissions in a population of US Veterans in the 2010–2011 season [10], while a study with a different design, by Young-Xu and colleagues, found a significant benefit of HD over SD in a similar US Veterans population during the 2015–2016 season using a similarly defined outcome [11]. Izurieta et al. found that HD provided an rVE of 22% versus SD in preventing hospitalizations with an admission diagnosis of influenza in the 2012–2013 season [12]. In a follow-up study by the same investigators, the benefit of HD over SD in the 2013–2014 season was about half what it was in the 2012–2013 season (12.7% vs. 22.1%) [13]. The heterogeneity in the observational literature could be due to differences between influenza seasons in circulating strains, specific products used, and varying degrees of success in controlling for confounding.

Confounding by indication can arise from the fact that patients who are prescribed a medication are inherently different from those who do not take the drug because they are taking the specific drug for a reason, i.e., an “indication” for use. For example, the use of HD may appear to be associated with an increased risk of hospitalization because it was given to patients who were sicker and thus at higher risk for hospitalization. In observational studies of treatment effectiveness, confounding by indication is well recognized but challenging to rectify. This is especially so when valid negative controls are lacking and when the confounders are difficult to quantify and measure [14]. Furthermore, conventional analytical strategies such as stratification, matching, and multivariate regression analysis cannot adequately adjust for unobserved confounders [15]. One such confounder, in this case, is frailty – a condition characterized by an increased risk of catastrophic declines in health and function most often found among older adults [16,17].

In this work, we employed an econometric technique – the Instrumental Variable (IV) method – to adjust for bias from measured and unmeasured confounders and estimate the rVE of HD versus SD influenza vaccine in preventing hospital admissions, overall and due to common diseases of importance to public health, in a cohort of senior US Veterans over five influenza seasons.

2. Methods

2.1. Design and data sources

We conducted a retrospective cohort study to compare hospital admissions among HD and SD influenza vaccine recipients over a period of five influenza seasons (2010–2011 through 2014–2015). We examined four outcomes (1) All-cause hospitalizations

(2) Hospitalizations primarily caused by a cardiorespiratory event (International Classification of Diseases, Ninth Revision, (ICD-9): 390–519); (3) Influenza- or pneumonia-associated hospitalizations (ICD-9: 480–488); all have been studied in either clinical trials or observational studies thus available for comparison; and, as a falsification test, [18] (4) Hospitalizations primarily caused by urinary tract infection (UTI, ICD-9: 599).

The Veterans Health Administration (VHA) of the Department of Veterans Affairs (VA) is the single largest integrated healthcare system in the US and provides clinical care to military Veterans at 144 medical centers and 1,203 community-based outpatient clinics. As of 2015, there were over six million patients with healthcare service records in the VHA. An integrated and unified electronic medical record (EMR) system stores information regarding all inpatient, emergency, and outpatient visits as well as laboratory tests and prescriptions at the VHA. Each patient is assigned a unique identification number that allows for longitudinal follow-up. We also obtained administrative health records for VHA enrollees from Centers for Medicare and Medicaid (Medicare) administrative fee-for-service files. These records supplement the VHA database as many VHA patients seek healthcare outside the VHA system once they turn 65 and thus qualify for Medicare benefits.

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

2.2. Study population and influenza vaccination

The study population included all VHA-enrolled patients aged 66 years and older at the beginning of each season and maintained their enrollment until the end of the 2014–2015 season or death, whichever occurred earlier. This restriction improves the probability of capturing all comorbidities and healthcare encounters prior to the study period. Influenza vaccination was identified using Current Procedural Terminology (CPT) codes (SD vaccine CPT codes: 90655–90659 and Q2034–Q2039; HD vaccine CPT code: 90662). We applied two exclusion criteria to reduce the chances of misclassification and to ensure valid comparison. First, Veterans who self-reported vaccination status were excluded, as HD and SD vaccines are similar in presentation and administration, thus making them challenging to distinguish by recipients. Second, we excluded all Veterans who had received more than one influenza vaccine at the VHA in the same season.

2.3. Baseline and observation periods

For each participant at each season, the baseline period (during which baseline characteristics were measured) began at the end of each previous respiratory season in week 27 (beginning of July) and ran until his or her influenza vaccination date. The observation period (during which study outcomes were measured) began two weeks after vaccination and ran until the end of the respiratory season in week 26 (end of June).

2.4. Baseline characteristics

Characteristics measured during the baseline period included demographics, comorbidities, and healthcare utilization. Demographics comprised age, sex, race, US geographic region, and priority level of VHA care. Priority level of VHA care serves as a surrogate measure for socioeconomic status because it is partially based on income and the capacity for gainful employment [19]. Significant comorbidities were defined according to an adaptation of Deyo-Charlson comorbidity score [20]. The comorbidities of interest were chronic health conditions such as cancer, cardiovascular disease, and respiratory disease that may put individuals

at elevated risk for complications owing to influenza, as identified by Mullooly and colleagues [21]. Healthcare utilization was measured by the number of outpatient visits and all-cause hospitalizations during the baseline period. Because the presence of comorbidities was captured from diagnosis codes recorded during visits, this information was collected during the six months prior to vaccination date. These are clinical diagnosis codes recorded in the VHA EMR for healthcare encounters, and are not administrative codes based on billing data. All baseline characteristics were included as covariates in the statistical models.

2.5. Statistical analysis

We organized our data in panel format over five influenza seasons from 2010–2011 through 2014–2015 using patient-season as the unit of analysis. In addition to estimating rVE for each season separately, data from all five seasons were combined and analyzed longitudinally, accounting for repeated measures from patients appearing in multiple seasons, to provide one summary measure of rVE over the multiple seasons for each outcome. In the dataset combining all five seasons, all variables, including outcomes, exposure, potential confounders, and our study instrumental variable – the proportion of HD recipients at facilities – were assessed for each season.

This study employed an IV approach, a widely used econometric method for removing the effects of unobserved confounders in observational studies by creating a “natural experiment” [22,23]. In the VHA, medical centers have autonomy over their seasonal influenza vaccination policy, and thus choice of vaccination and rules for administration differ across centers. Because of the varied availability and policies at the VHA, the instrument used in this study was the proportion of HD recipients at each of the 1,347 VHA facilities during each influenza season, defined as the number of HD recipients divided by the total number of both HD and SD recipients in that season at each VHA facility. VHA facilities manage relatively comparable groups of patients (similar socioeconomic background and health status), and at any given facility, the choice of vaccine policy is unlikely to be driven by unique characteristics of the patient population relative to other facilities. This feature allows us to exploit the heterogeneity in facilities’ propensity to use HD as an IV because the decision to provide HD was dependent upon facility policies and practices and not solely on patient characteristics such as underlying health status. In particular, while an older and frailer patient may be more likely to receive HD at any facility, the same patient is more likely to receive HD at a facility with a high HD proportion, making the facility HD proportion a quasi-randomization device.

Because our outcomes are count variables, we performed IV analysis using multivariable Poisson models. For each influenza season, we estimated the IV-adjusted incidence rate ratio (IRR) of each outcome. Also using the IV method but combining data from all five seasons in the study period, we conducted longitudinal analyses to better adjust for time varying covariates such as age and comorbidity and to estimate overall rVEs for the entire study period. We performed statistical analyses using SAS 9.4 [Cary, North Carolina], and STATA 15 [College Station, Texas]. All tests were two-tailed, and 0.05 was the level of statistical significance.

To be valid, an IV must satisfy two requirements: (1) it must be correlated with the treatment, and (2) it must not influence the outcome except through its influence on the likelihood of receiving the treatment (exclusion restriction). To test the correlation requirement, we estimated the F statistics of our selection equation (receipt of HD as a function of HD proportion and the covariates). To test the exclusion restriction, we compared characteristics of facilities with high versus low HD proportional use. To the extent that facilities with high and low HD proportion are similar

on observed dimensions, it gives us greater confidence that they are also similar on unobserved dimensions [24]. We conducted a falsification test to examine the effect of HD versus SD on UTI hospitalizations, where we would not expect a protective effect of HD. A second falsification test was also conducted where we performed the IV analysis during the baseline period with little to no circulating influenza.

2.6. Conventional analysis

A conventional analysis using a multivariable Poisson model, adjusting for the above-mentioned measured confounders, was performed to better understand the impact of the IV-based regression. We used the same data, exposures and outcomes, and included the same variables in the standard Poisson model with the exception of the IV used to control for the endogeneity of the vaccine assignment (HD versus SD). We accounted for clustering at both the patient and facility levels. For the five-season longitudinal analysis, a Generalized Estimating Equations (GEE) analysis was performed based on Poisson distribution [25], and an autoregressive of first order correlation structure was applied to the repeated measures on patients appearing in multiple seasons. Relative risk estimates were obtained from these models and 95% confidence intervals (CI) were calculated using a robust covariance estimator for the estimated effects.

3. Results

Over five influenza seasons, we analyzed data of approximately 700,000 patients each season, totaling 3,638,924 person-influenza seasons of observation (Table 1). We observed 1,325,366 all-cause hospitalizations, 357,686 cardiorespiratory-associated hospitalizations, and 51,904 influenza/pneumonia-associated hospitalizations during this period. Prior to vaccination, HD recipients tended to have a higher prevalence of recorded comorbidities (Table 2), a finding consistent with our hypothesis that HD recipients might be frailer or considered at higher-risk by their practitioners.

HD influenza vaccine proportion ranged from 0% to 99% across VHA facilities. The partial F statistics from the first-stage IV regression models were greater than 1,000, suggesting the instrument is highly correlated with the explanatory variable of interest – in this case, provision of HD [23]. Using the median HD proportion at 4.7%, we divided the facilities into two groups – those that administered the HD to $\leq 4.7\%$ of their patients and those that administered more. Although there were small differences in specific patient risk factors, the distribution of the risk factors between the two groups were similar and consistent across all influenza seasons. The balance in the distribution of the measured risk factors across facilities provides reasonable evidence to support to facility-level influenza vaccine coverage being a valid IV (Appendix A, Table A1).

Our study population included 1,728,562 VHA patients who were vaccinated at 1,347 VHA facilities (medical centers and community-based outpatient clinics) during the study period; 1,702,824 (98.5%) were of male gender, and 1,299,412 (75%) were of non-Hispanic white race. Of the 3,638,924 person-influenza-seasons of observation, 158,636 person-seasons (4%) were among HD vaccine recipients, while 3,480,288 (96%) were among SD vaccine recipients. In the overall longitudinal five-season analysis, IV-adjusted rVE estimate of HD versus SD was 10% (95% CI, 8–12%) against all-cause hospitalization; 18% (95% CI, 15–21%) against cardiorespiratory-associated hospitalization; and 14% (95% CI, 6–22%) against influenza/pneumonia-associated hospitalization. The rVE against UTI-associated hospitalization was –5% (95% CI, –34% to 18%). The contrasts among the estimates were similar across individual seasons, with larger positive rVEs for

Table 1
Study population disease burden by influenza season and vaccine type.

	Hospitalizations (rate) ^a /seasons	2010–2011	2011–2012	2012–2013	2013–2014	2014–2015
HD	All-cause	8503 (624)	12,000 (626)	10,584 (601)	9983 (577)	22,234 (555)
	Cardiorespiratory	2204 (162)	2787 (145)	2417 (137)	2141 (124)	4796 (120)
	Influenza/Pneumonia	372 (27)	428 (22)	399 (23)	329 (19)	699 (17)
	Urinary Tract Infection	106 (8)	136 (7)	139 (8)	108 (6)	204 (5)
	Number of Patients	20,878	27,561	25,354	25,307	59,536
SD	All-cause	251,404 (546)	256,198 (533)	256,071 (505)	254,410 (474)	243,979 (478)
	Cardiorespiratory	73,618 (160)	71,448 (149)	70,445 (139)	64,684 (121)	63,146 (124)
	Influenza/Pneumonia	10,467 (23)	10,049 (21)	10,582 (21)	8815 (16)	9764 (19)
	Urinary Tract Infection	3062 (7)	3163 (7)	2911 (6)	2831 (5)	2467 (5)
	Number of Patients	657,449	658,786	711,283	740,503	712,267
ALL	All-cause	259,907 (548)	268,198 (537)	266,655 (508)	264,393 (477)	266,213 (483)
	Cardiorespiratory	75,822 (160)	74,235 (149)	72,862 (139)	66,825 (121)	67,942 (123)
	Influenza/Pneumonia	10,839 (23)	10,477 (21)	10,981 (21)	9144 (17)	10,463 (19)
	Urinary Tract Infection	3168 (7)	3299 (7)	3050 (6)	2939 (5)	2671 (5)
	Number of Patients	678,327	686,347	736,637	765,810	771,803

^a Based on primary diagnoses; rate in unit of per 1000 person-years.

cardiorespiratory- or influenza/pneumonia-associated hospitalizations and negligible negative rVEs for UTI-associated hospitalizations and smaller, but still positive rVEs for all-cause hospitalizations in between. The heterogeneity that we observed in published literature regarding the benefit of HD over SD from season to season is also apparent when we look at the estimates for the same outcome from different seasons. For example, in the case of influenza/pneumonia-associated hospitalizations, the estimated rVEs ranged from a low of 10% (95% CI, –3% to 21%) in the 2012–2013 season to a high of 18% (95% CI, 4–30%) in the 2014–2015 season (Table 3). Again, these could be due to differences between influenza seasons in circulating strains, specific products used, and to varying degrees of success in controlling for confounding.

In the conventional analysis, we found that the overall adjusted rVE estimate of HD was –2% (95% CI, –3% to 0%) against all-cause hospitalization; –3% (95% CI, –8% to 3%) against cardiorespiratory-associated hospitalization; and 5% (95% CI, 0% to 10%) against influenza/pneumonia-associated hospitalization. The adjusted rVE against UTI-associated hospitalization was 7% (95% CI, –7% to 19%; Appendix B, Table B2). Among rVEs estimated during each season, most were slightly associated with an increased risk of hospitalization with two exceptions in the 2014–2015 season, for which rVEs of 6% (95% CI, 2–10%) against cardiorespiratory-associated hospitalization and 18% (95% CI, 12–24%) against influenza/pneumonia-associated hospitalization were found (Appendix B, Table B2).

4. Discussion

In an analysis that spanned five influenza seasons, we found HD influenza vaccination of senior Veterans to be associated with 10% additional reduction in all-cause hospitalizations beyond that attained by SD influenza vaccination, 18% incremental benefit against cardiorespiratory-associated hospitalizations, and 14% against the composite of influenza/pneumonia-associated hospitalizations. The additional benefit of HD was evident in each season. We observed no protective effect against UTI in the analysis, which is reassuring as we do not expect an effect of influenza vaccine on the prevention of UTIs. To our knowledge, our study is the first longitudinal multi-season comparative effectiveness analysis of HD versus SD vaccine. These results are consistent with a meta-analysis of existing studies, that included randomized clinical trials, of the rVE of HD versus 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 [26].

Richardson et al. studied a similar cohort of senior Veterans, and reported that the rVE was 2% (95% CI, –40% to 32%) against influenza-related and pneumonia-attributed hospitalizations and 1% (95% CI, –16% to 14%) against all-cause hospitalizations [10]. These results, which were entirely based on a standard multivariable Poisson approach, and were reproduced by our conventional analysis, did not fully address confounding by indication induced by unmeasured variables.

Several studies have attempted to address the issue of confounding by indication induced by unmeasured variables. Izurieta and colleagues focused on individuals who received their vaccination at outpatient pharmacies, because compared to physicians, pharmacists are more likely to base product choice on inventory and pharmacy policy than on clinical considerations. Further, the authors matched HD and SD recipients by the time and the location of vaccination and found an rVE against influenza-attributed hospitalizations or emergency department visits of 22% (95% CI, 16–27%) in the 2012–2013 season [12]. Young-Xu et al., using a difference-in-differences design, found an rVE of 25% (95% CI: 2–43%) against influenza- or pneumonia-associated hospitalization in the 2015–2016 season [11]. In a cluster-randomized, prospective relative efficacy trial in an elderly nursing home population, Gravenstein and colleagues found HD vaccine to be more effective than SD vaccine in reducing both respiratory illness-associated hospitalizations (12.7%, 95% CI, 1.8–22.4%) and all-cause hospital admissions (6.7%, 95% CI, 1.5–11.6%) in the 2013–2014 season, also consistent with our findings [7].

HD was given to a small fraction of patients, 3–4% during the first four seasons, and 8% during the last season of our study period, which may suggest an increase in the chance that this was due to an indication(s). The contrast between the findings based on the standard multivariable Poisson analysis (as in Richardson et al. and our conventional analysis) and the findings that were based on analyses that addressed unmeasured confounding to varying degrees of success, indicate the existence of one or more unmeasured confounders, e.g., frailty, that are associated with both HD uptake and increased risk of hospitalizations related to influenza.

4.1. Strengths

Our study had several notable strengths in addition to the application of the IV method. We analyzed more than 3.6 million person-influenza-seasons of observation, making our study one

Table 2
Patient characteristics during study period by vaccine type.

	HD	SD	Total
Number of Person-Seasons	158,636 (4%)	3,480,288 (96%)	3,638,924 (100%)
Age			
65–69	53,646 (34%)	1,130,630 (32%)	1,184,276 (33%)
70–74	29,004 (18%)	645,611 (19%)	674,615 (19%)
75–79	27,740 (17%)	643,189 (18%)	670,929 (18%)
80–84	25,379 (16%)	566,571 (16%)	591,950 (16%)
85+	22,867 (14%)	494,287 (14%)	517,154 (14%)
Male	156,378 (99%)	3,427,402 (98%)	3,583,780 (98%)
Race			
Black	24,456 (15%)	328,621 (9%)	353,077 (10%)
Hispanic	7611 (5%)	149,218 (4%)	156,829 (4%)
Other	2563 (2%)	57,943 (2%)	60,506 (2%)
White	114,538 (72%)	2,652,463 (76%)	2,767,001 (76%)
Unknown	9468 (6%)	292,043 (8%)	301,511 (8%)
Region			
Northeast	28,062 (18%)	440,419 (13%)	468,481 (13%)
Midwest	27,169 (17%)	570,764 (16%)	597,933 (16%)
South	48,956 (31%)	1,140,606 (33%)	1,189,562 (33%)
West	15,479 (10%)	509,927 (15%)	525,406 (14%)
Unknown	38,970 (25%)	818,572 (24%)	857,542 (24%)
Priority			
Level 1	41,068 (26%)	782,576 (22%)	823,644 (23%)
Level 2	10,594 (7%)	212,977 (6%)	223,571 (6%)
Level 3	18,888 (12%)	360,781 (10%)	379,669 (10%)
Level 4	4996 (3%)	127,520 (4%)	132,516 (4%)
Level 5	61,921 (39%)	1,390,391 (40%)	1,452,312 (40%)
Level 6–8	21,169 (13%)	606,043 (17%)	627,212 (17%)
Comorbidity			
Any malignancy	24,188 (15%)	441,466 (13%)	465,654 (13%)
Metastatic solid tumor	1165 (1%)	19,448 (1%)	20,613 (1%)
Congestive heart failure	13,538 (9%)	233,461 (7%)	246,999 (7%)
Chronic pulmonary disease	30,026 (19%)	561,231 (16%)	591,257 (16%)
Cerebrovascular disease	12,591 (8%)	225,186 (6%)	237,777 (7%)
Dementia	3393 (2%)	50,679 (1%)	54,072 (1%)
Diabetes with complications	12,460 (8%)	235,526 (7%)	247,986 (7%)
Diabetes without complications	68,075 (43%)	1,393,512 (40%)	1,461,587 (40%)
HIV/AIDS	945 (0.6%)	9394 (0.3%)	10,339 (0.3%)
Mild liver disease	3442 (2.2%)	46,183 (1.3%)	49,625 (1.4%)
Moderate/severe liver disease	375 (0.2%)	5607 (0.2%)	5982 (0.2%)
Myocardial infarction	2102 (1.3%)	43,722 (1.3%)	45,824 (1.3%)
Hemiplegia/paraplegia	1131 (0.7%)	19,748 (0.6%)	20,879 (0.6%)
Peptic ulcer disease	1114 (0.7%)	20,006 (0.6%)	21,120 (0.6%)
Peripheral vascular disease	12,277 (8%)	233,269 (7%)	245,546 (7%)
Rheumatoid disease	2815 (2%)	53,870 (2%)	56,685 (2%)
Renal disease	16,510 (10%)	316,305 (9%)	332,815 (9%)

of the largest ever conducted to assess influenza rVE. The large sample allowed us to adjust for more confounding variables without compromising statistical power. We excluded patients who self-reported vaccination status so as to reduce the chances for misclassification. We used data from VHA EMR records as studies have shown that EMR data are more likely to be complete in capturing medical conditions and have a lower risk of up-coding [27,28]. We included Medicare claims data in order to have as complete a record as possible of all healthcare encounters that occurred for our study population. Our use of the IV method in longitudinal analysis over multiple seasons was a first and provided a comparison not only between SD and HD recipients, but also the same patient over multiple seasons, further adjusting for fixed, but unmeasured confounders such as those related to genetics and other causes of predisposition. Because vaccine effectiveness is season-dependent, the overall assessment resulting from these longitudinal analyses can provide a succinct appraisal of HD's relative effectiveness over SD. We covered a wide range of outcomes, methodically moving from the more general to the more specific that one would expect to be associated with influenza. Hospitalizations with UTI as the primary discharge diagnosis were unlikely to be associated with influenza vaccines, and therefore served as a fal-

sification test. To further verify this, we estimated UTI rates by HD versus SD during the baseline period where there was little to no influenza circulation in the community. Then, using a Poisson regression, we were able to calculate an IRR between the two groups of 0.95 (95% CI, 0.85–1.05). This lack of association between UTI and the two vaccine groups during the baseline period is reassuring. Finally, again during the baseline period when there was little to no influenza circulation in the community, we performed the same IV analysis as we did in our main analysis, using data from all five seasons, and found that the rVEs against hospitalization during the baseline period for HD were: all-cause, 1% (95% CI, –2–4%); cardiorespiratory-associated, –2% (95% CI, –6% to 2%); influenza/pneumonia-associated, –5% (95% CI, –21% to 10%). This lack of added benefit of HD receipt prior to the start of the season provides further evidence that confounding was addressed by the instrumental variable.

Because of the difficulty in adequately addressing confounding, concerns have been raised regarding the validity of observational studies of vaccine effectiveness [29–32]. In this study, in addition to IV analysis, we employed two approaches to address bias, recommended by Jackson and Simonsen [32], among others, that have shown some promising results. The first involved analyzing the

Table 3
Relative vaccine effectiveness of HD versus SD influenza vaccines using instrumental variable analysis.

Hospitalizations (Primary Diagnoses)	All-cause	Cardiorespiratory	Influenza/Pneumonia	Urinary Tract Infection
2010–2011	0.96 (0.91–1.01)	0.83 (0.76–0.91)	0.89 (0.78–1.02)	1.05 (0.85–1.30)
2011–2012	0.94 (0.90–0.98)	0.83 (0.77–0.90)	0.84 (0.67–1.05)	1.03 (0.85–1.25)
2012–2013	0.89 (0.85–0.94)	0.81 (0.74–0.90)	0.90 (0.79–1.03)	1.08 (0.86–1.36)
2013–2014	0.90 (0.85–0.95)	0.81 (0.74–0.89)	0.86 (0.66–1.13)	1.06 (0.86–1.32)
2014–2015	0.90 (0.87–0.93)	0.82 (0.77–0.88)	0.82 (0.70–0.96)	0.99 (0.84–1.17)
Longitudinal 5-season analysis	0.90 (0.88–0.92)	0.82 (0.79–0.85)	0.86 (0.78–0.94)	1.05 (0.82–1.34)

pre-influenza or baseline periods as we have done in our second falsification analysis. The second was to include a range of outcomes from the general to the specific and compare the strengths of their associated effectiveness with the overall guideline that effectiveness should rise as outcomes become more specific which we adopted in our main analysis.

4.2. Limitations

VHA has a unique population – it is 98% male as shown in the results and tends to have greater disease burden than the general population [33]. Even with the combined data from the VHA and Medicare, a relatively small amount of missing data may remain for those who enrolled in Medicare Advantage plans. In addition, although our study does not rely on them, ICD codes from claims data have been shown to inadequately capture comorbidity and functional status [34]. Moreover, no diagnosis codes, whether parts of medical or billing records, can capture conditions that are difficult to measure or are unmeasured; however, this is the benefit of utilizing an IV analysis, with its ability to mimic a randomized study. Past studies have used IV to examine the effectiveness of vaccine, although not to compare HD to SD [35,36]. These studies share the inherent limitation of IV analysis: in an exactly-identified model (one endogenous variable, receipt of HD; and one instrument, HD proportion) it cannot be definitively proven that the exclusion restriction has been satisfied [23,37]. We, nevertheless, believe that our validity tests (Appendix A) provided evidence consistent with the appropriateness of our instrument choice. Lastly, due to our interest in the impact on the overall healthcare utilization (e.g. all-cause hospitalizations) during the entire influenza season, we did not restrict our analyses to periods of peak influenza activity as some past studies have done. One consequence of using the broader period is that bias can potentially arise from misclassification. Combined with a lack of specificity of our study outcomes, such as all-cause hospitalizations, and thus potential bias, we observed less than expected variations in individual-season estimations of rVEs. Because of this, we compared our rVEs for all-cause hospitalization to those from the RCT conducted by DiazGranados and colleagues [6] season by season: for 2011–2012, we estimated the rVE to be 6% (95% CI, 2–10%), while it was 0% (95% CI, –10% to 9%) in the RCT; for 2012–2013, our estimate was 11% (95% CI, 6–15%) and it was 14% (95% CI, 5–21%) in the RCT (Table 3). Despite differences between the study populations, for which 98% of ours was male and 56–57% of the RCT was female, and in the collection of outcomes, for which we evaluated hospitalization events recorded in EMR as opposed to clinical trial monitoring and adjudication in the RCT, these findings appear to be consistent, with a small to negligible difference observed between the HD and SD groups during the 2011–2012 season, a much larger one during the 2012–2013 season, and with overlapping confidence intervals in both seasons. When it comes to our most specific outcome – influenza/pneumonia-associated hospitalizations – the estimated rVEs ranged from a low of 10% (95% CI, –3% to 21%) in the 2012–2013 season to a high of 18% (95% CI, 4–30%) in the 2014–2015 season (Table 3). This range, again, is

similar to the results reported by DiazGranados et al. from their RCT, where rVEs for pneumonia events differed by 12 percentage-points from one year to the next [6]. Vaccine effectiveness (or relative effectiveness) could be impacted by the season-dependent match between the vaccine and the predominant circulating strain and the severity of the influenza season [13,23]. Additional analysis of more seasons, perhaps through a cluster-randomized, prospective study design, may shed light on the consistency of HD's relative effectiveness. One observation study is likely to be limited in its ability to fully address the issue of confounding, especially unmeasured confounding. We believe that a body of evidence, one that includes observational studies conducted by other researchers, on different populations, using different research mythologies, along with clinical trials, can examine this issue satisfactorily.

4.3. Conclusion

Using an IV approach, we provided estimates of relative influenza vaccine effectiveness in the senior VHA patient population. We found that HD is more effective than a SD in protecting against influenza- or pneumonia-associated hospitalization, cardiorespiratory-associated hospitalization, and all-cause hospitalization.

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Declaration of Authors Competing Interests.

RVA, JKL, EWT, DPG and AC are employees of Sanofi Pasteur. JTS is an employee and holds equity in Precision Health Economics, which provides consulting services to the life sciences industry. YYX received research funding from 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.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.vaccine.2019.01.063>.

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