Vaccine xxx (xxxx) xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease

J. Bradley Layton [a,*], Leah J. McGrath [b], John M. Sahrmann [c], Yinjiao Ma [c], Vikas R. Dharnidharka [d], Caroline O'Neil [c], David J. Weber [e], Anne M. Butler [c,f]

[a] RTI Health Solutions, Research Triangle Park, NC, USA
[b] NoviSci, Durham, NC, USA
[c] Division of Infectious Diseases, Department of Internal Medicine, Washington University School of Medicine, St. Louis, MO, USA
[d] Division of Pediatric Nephrology, Hypertension and Pheresis, Departments of Pediatrics and Nephrology, Washington University School of Medicine, St. Louis, MO, USA
[e] Division of Infectious Diseases, Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA
[f] Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO, USA

ARTICLE INFO

Article history:
Received 14 February 2020
Received in revised form 4 June 2020
Accepted 6 June 2020
Available online xxxx

Keywords:
Adverse reactions
Hemodialysis
High-dose
Influenza vaccines
Safety

ABSTRACT

Background: High-dose influenza vaccine (HDV) is an alternative vaccination strategy in patients with end-stage renal disease (ESRD), though the safety of HDV has not been evaluated in this population. The objective of this study was to estimate the relative occurrence of adverse vaccine reactions in patients with ESRD following vaccination with HDV compared with standard-dose influenza vaccine (SDV).

Methods: Using data from the United States Renal Data System, we identified patients with ESRD aged ≥ 65 years at influenza vaccination during yearly influenza seasons from 2010 through 2016. Patients were followed after vaccination to observe serious (anaphylaxis, angioedema, seizure, encephalopathy, Guillain-Barré syndrome [GBS], and short-term, all-cause mortality) and milder (urticaria/hives, rash, pain in limb, cellulitis, myalgia/myositis, fever, nausea and vomiting, diarrhea, and syncope) adverse events. Propensity score-weighted hazard ratios (HRs) and 95% confidence intervals (CIs) for HDV versus SDV were estimated with Cox proportional hazards models.

Results: Of 520,876 vaccinations observed (mean age = 74.7 years at vaccination; 63% white race), 7.4% were HDV. For serious events, the weighted HRs were null for seizure, encephalopathy, and mortality and inestimable due to too few cases for anaphylaxis, angioedema, and GBS. For milder vaccine reactions, the weighted HRs demonstrated generally increased risks in the HDV group, including rash (HR = 1.86; 95% CI, 1.34–2.57), diarrhea (HR = 1.26; 95% CI, 1.07–1.50), pain in limb (HR = 1.23; 95% CI, 1.12–1.34), and myalgia/myositis (HR = 1.16; 95% CI, 1.04–1.30).

Conclusions: The risks of serious adverse events were low and similar between treatment groups; however, HDV recipients had increased risks of several milder adverse events compared with SDV recipients, consistent with clinical trial findings in the general population of older adults. These results add important information to inform the risk-benefit tradeoff of the use of HDV versus SDV in patients with ESRD.

1. Introduction

Patients with end-stage renal disease (ESRD) are at high risk of influenza-associated morbidity and mortality due to immunodepression and heavy comorbidity burden [1]. Influenza vaccination is recommended for patients with ESRD [2], though the United States (US) Centers for Disease Control and Prevention (CDC) recommendations do not give preference to the type of inactivated influenza vaccine administered. Despite the importance of preventing influenza in this population, the effectiveness of standard-dose influenza vaccination (SDV) has been questioned by studies suggesting that SDV is only minimally effective among patients with ESRD [3,4]. Therefore, alternative vaccination strategies have been explored to prevent influenza among these patients, including the use of high-dose influenza vaccination (HDV).

* Corresponding author at: RTI Health Solutions, 3040 Cornwallis Road, Post Office Box 12194, Research Triangle Park, NC 27709-2194, USA.
E-mail addresses: jblayton@rti.org (J.B. Layton), lmcgrath@novisci.com (L.J. McGrath), jsahrmann@wustl.edu (J.M. Sahrmann), mayinjiao@wustl.edu (Y. Ma), vikasd@wustl.edu (V.R. Dharnidharka), oneilc@wustl.edu (C. O'Neil), dweber@unch.unc.edu (D.J. Weber), anne.butler@wustl.edu (A.M. Butler).

https://doi.org/10.1016/j.vaccine.2020.06.020
0264-410X/

The use of HDV has increased among patients with ESRD [5] since its approval in 2009 by the US Food and Drug Administration (FDA) for use by persons aged ≥ 65 years. The HDV contains the same three strains as SDV, but with more antigen (60 μg versus 15 μg per strain), and it has demonstrated increased immunogenicity compared with SDV among the general population of older adults and, potentially, in immunocompromised individuals [6–11]. Studies have not suggested an increased risk of any severe adverse events associated with HDV compared with SDV in the non-ESRD population [6,8–10,12,13]. However, HDV has been associated with higher rates of mild or moderate injection site and systemic reactions in the general population of older adults [6,8–10,12–14]. Patients with ESRD have decreased immunocompetence due to altered blood chemistry and regular hemodialysis procedures [15,16], which may result in a different level of vaccination effectiveness and safety profile than that in the general population of older adults. Prior to widespread adoption of HDV in the ESRD population, a thorough evaluation of adverse event rates following HDV administration is necessary.

We aim to compare the risk of adverse events following vaccination with HDV versus SDV among patients aged ≥ 65 years receiving maintenance hemodialysis in the US.

2. Materials and methods

2.1. Setting

We used data from the US Renal Data System (USRDS) database from 2010 to 2016 [17]. The USRDS is a national registry of patients with ESRD with US federally funded Medicare insurance. It contains data on enrollment, cause of ESRD, death, administrative billing claims (including procedure and diagnosis claims), and prescription drug claims submitted to Medicare for billing.

2.2. Population

We identified individuals receiving influenza vaccinations in any of six individual influenza seasons, as influenza is a seasonal

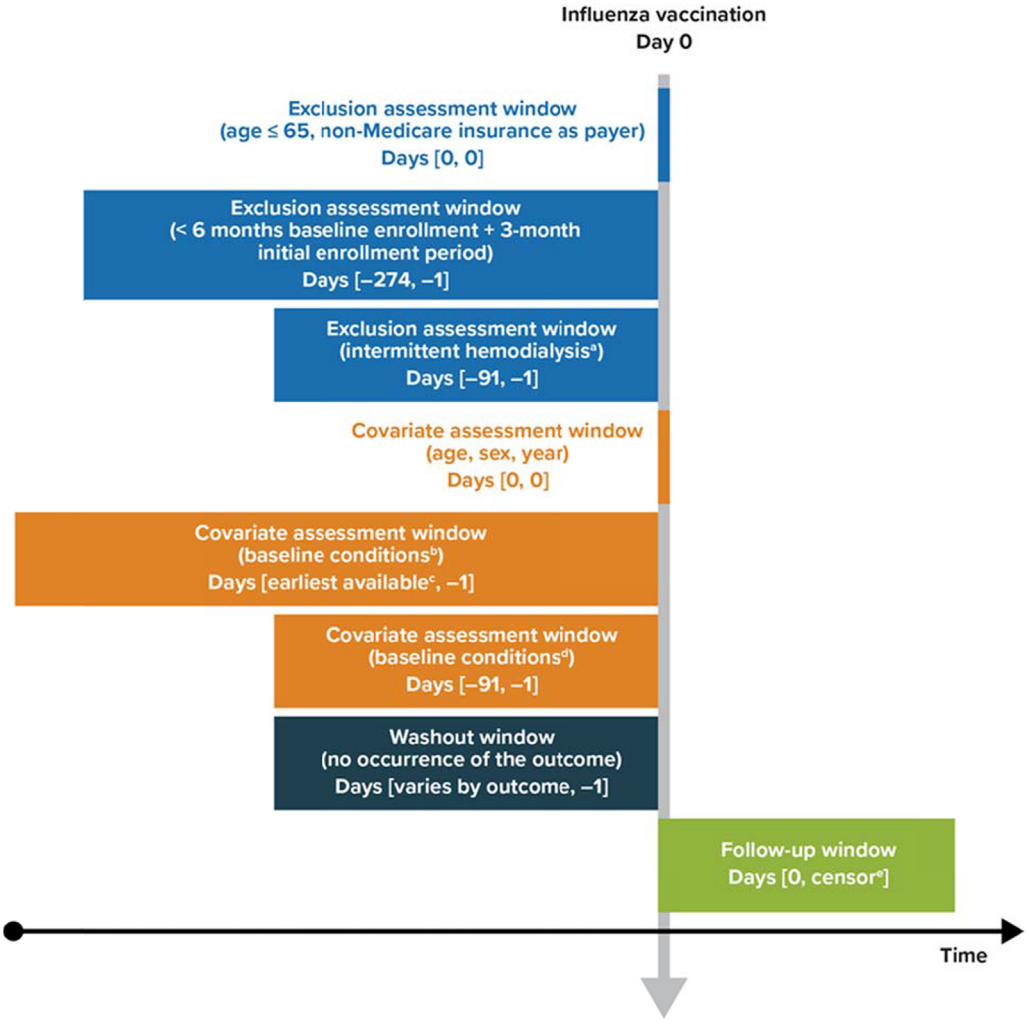

Fig. 1. Study design schematic. [a] Defined as treatment modality as in-center hemodialysis, with institutional claims covering at least 67% of enrolled days. [b] Baseline conditions included mobility aids, dementia, lipid abnormality, diabetes mellitus complications, arthritis, paralysis, chronic obstructive pulmonary disease or asthma, neurological problem, psychiatric problem, hypertension, heart disease, cancer, liver disease, autoimmune disorders, coagulopathy, stroke/brain injury, pulmonary circulation disease, rheumatic heart disease, and myocardial infarction. [c] The earliest available date of enrollment in the United States Renal Data System occurring after the latest of January 1, 2008, or 91 days after dialysis initiation. [d] Baseline conditions included use of oxygen, ambulance/life support, skin ulcer, home hospital bed, difficulty walking, weakness, transfusion, rehabilitation services, sepsis, pneumonia, vascular infection, substance abuse, peptic ulcer disease, gastrointestinal bleeding, pneumonia vaccine receipt, hepatitis B vaccine receipt, lipid test, diabetic eye exam, A1C test, and cancer screening. [e] First occurrence of one of the following events: end of outcome-specific follow-up period, death (except for the mortality analysis), disenrollment from Medicare part A or B, end of the study period (December 31, 2016), receipt of a subsequent influenza vaccine dose, switch to peritoneal dialysis, and receipt of a kidney transplant. Note: figure template available at www.repeatinitiative.org.

Please cite this article as: J. B. Layton, L. J. McGrath, J. M. Sahrmann et al., Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease, Vaccine, https://doi.org/10.1016/j.vaccine.2020.06.020

illness and influenza vaccination is recommended annually. Patients were eligible to enter each yearly cohort as early as August 1 of each year and as late as the end of the influenza season, the latter defined as the midpoint of the first week after the start of the influenza season when <10% of national influenza tests were positive for influenza, as defined by the CDC (Supplemental Table S1) [18–24]. For the 2016–2017 season, only patients who received their first influenza vaccination in 2016 were included since data availability ended on December 31, 2016.

We identified patients on the date of their first influenza vaccination during each yearly cohort; a patient could be included in multiple yearly cohorts. We included patients aged ≥ 65 years with ESRD and Medicare as the primary insurance payer at the time of vaccination. We required patients to be at least 9 months past their dialysis initiation date prior to the vaccination date, allowing for a 3-month enrollment period and a minimum of a 6-month baseline covariate assessment period. Additionally, we required patients to have a minimum of 3 months of continuous hemodialysis treatments (defined as having at least 67% of institutional claims present during the period, with hemodialysis as the treatment modality) prior to the vaccination date to ensure treatment stability (Fig. 1). Patients missing dialysis facility information were also excluded.

2.3. Exposure assessment

We identified trivalent or quadrivalent, non-adjuvanted, egg-based, inactivated influenza vaccines using Current Procedural Terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) codes in patients' billing records (Supplemental Table S2) during each influenza season. All influenza vaccine doses were categorized as either SDV or HDV, and the first date of vaccination observed during an influenza season was assigned as the index date. If multiple codes for vaccines of the same type of dose were received within a 7-day period, they were assumed to result from the same vaccination event, and the date of the earliest code was considered the index date. However, if codes from different vaccine doses were received within a 7-day period, they were assumed to be from different vaccination events, and the patient's follow-up time was censored on the date of the second vaccine in order to isolate the effects of the first vaccine. Patients receiving multiple different vaccination (e.g. pneumococcal vaccine, hepatitis B) were included.

2.4. Outcome assessment

We assessed the occurrence of the following serious outcomes: anaphylaxis, angioedema, seizure, encephalopathy, Guillain-Barré syndrome (GBS), and short-term all-cause mortality. Additionally, we assessed the occurrence of the following milder outcomes: urticaria/hives, rash, pain in limb, cellulitis, myalgia/myositis, fever, nausea and vomiting, diarrhea, and syncope. Outcomes were identified from inpatient or outpatient diagnosis codes in patient billing data resulting from routine clinical care (Supplemental Table S3). Mortality was assessed from enrollment records. Each outcome was evaluated separately in outcome-specific cohorts. To ensure identification of new-onset outcome events, we excluded individuals with diagnoses of the outcome prior to vaccination for each outcome-specific cohort (Table 1). These prevaccination washout periods ranged from 42 days for more common outcomes (e.g., fever) to ≥6 months for syncope and seizure to all-available baseline enrollment data for encephalopathy or GBS (Table 1).

Patients were followed from the vaccination date until censoring at the first of the following events: end of outcome-specific follow-up window, death (except for the mortality analysis), disenrollment from Medicare Parts A or B, end of the study period (December 31, 2016), receipt of a subsequent influenza vaccine, switch to peritoneal dialysis, or receipt of a kidney transplant. Follow-up could extend beyond the end of the influenza season. The duration of outcome-specific follow-up windows ranged from 3 days to 43 days (Table 1), depending on the anticipated onset of each outcome after vaccination. These outcome-specific ascertainment windows were consistent with clinical understanding of each outcome, as some acute outcomes such as anaphylaxis would be expected to occur much sooner after vaccination than others, such as GBS, which may manifest weeks after vaccination [25].

The primary outcomes of fever, nausea and vomiting, and diarrhea were identified in any health care setting, but secondary outcomes of hospitalized fever, nausea and vomiting, and diarrhea were limited to only those occurring during an inpatient hospitalization so that more severe events could be evaluated. Other secondary outcomes included composite hypersensitivity events (diagnoses of anaphylaxis, angioedema, urticaria/hives, adverse reactions to vaccines) and composite gastrointestinal events (nausea, vomiting, diarrhea).

Table 1
Outcome-specific follow-up periods and prevaccination washout periods.

Outcome	Follow-up period[a]	Prevaccination washout period
Serious outcomes		
Anaphylaxis	3 days	6 months
Angioedema	3 days	6 months
Seizure	15 days	6 months
Encephalopathy	43 days	All pre-index enrollment data available
Guillain-Barré Syndrome	43 days	All pre-index enrollment data available (including both ICD-9-CM[b] diagnosis code 357.0 or 357.81)
Short-term, all-cause mortality	8 days	Not applicable
Milder outcomes		
Urticaria/hives	8 days	42 days
Rash	8 days	42 days
Pain in limb	8 days	42 days
Cellulitis	8 days	42 days
Myalgia and/or myositis	8 days	42 days
Fever	8 days	42 days
Nausea and vomiting	8 days	42 days
Diarrhea	8 days	42 days
Syncope	3 days	6 months
Secondary Outcomes		
Hospitalized fever	8 days	Any fever (not just hospitalized) in past 42 days
Hospitalized nausea and vomiting	8 days	Any nausea and vomiting (not just hospitalized) in past 42 days
Hospitalized diarrhea	8 days	Any diarrhea (not just hospitalized) in past 42 days
Composite hypersensitivity	8 days	6 months
Composite gastrointestinal	8 days	42 days

ICD-9-CM = International Classification of Diseases, 9th Edition, Clinical Modification.
[a] Inclusive of the vaccination date.
[b] ICD-9-CM diagnosis codes were converted into International Classification of Diseases, 10th Edition, Clinical Modification (ICD-10-CM) using the US Centers for Medicare and Medicaid Services (CMS) forward and backward General Equivalence Mapping (GEMs) crosswalks.

2.5. Covariates

Demographic characteristics, comorbidities, screening tests and preventive services, health care utilization, and indicators of frailty

Please cite this article as: J. B. Layton, L. J. McGrath, J. M. Sahrmann et al., Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease, Vaccine, https://doi.org/10.1016/j.vaccine.2020.06.020

[26] were identified a priori from the USRDS enrollment information and billing claims. Demographic characteristics were assessed on the vaccination date; health care utilization variables, frailty indicators, and acute comorbidities were assessed in the 6 months prior to vaccination; chronic conditions were assessed using all baseline data available for each patient [27] back to January 1, 2008, or 91 days after dialysis initiation, whichever was latest (Fig. 1). These covariates were identified using diagnosis and procedure coding from inpatient and outpatient billing records (Supplemental Table S4).

2.6. Statistical analysis

We described the baseline characteristics of patients receiving vaccinations by treatment group and compared the covariate balance between HDV and SDV groups with absolute standardized mean differences (ASMDs) [28]. Patients could contribute one vaccination in each season and thus could be included in both treatment groups, potentially multiple times. Each vaccination was considered independently.

For each outcome, we estimated the incidence rate and 95% confidence interval (CI) of the outcome after vaccination for each treatment group. We compared rates among HDV recipients with rates among SDV recipients using Cox proportional hazards models, estimating hazard ratios (HRs) and 95% CIs. Because an individual could contribute an observation in multiple years, we estimated CIs with robust sandwich covariance matrix estimates to account for the potential within-person correlation.

To account for confounding resulting from imbalances of characteristics between HDV and SDV recipients, we implemented standardized mortality ratio (SMR) weighting. First, we estimated a propensity score (PS)—a predicted probability of receiving HDV based on the observed covariates—for each patient using logistic regression models in each outcome-specific cohort. We used all a priori–identified covariates as predictors and HDV receipt as the dependent variable. Second, the estimated PSs were transformed into SMR weights with the following approach: for the HDV group, SMR weight = 1; for the SDV group, SMR weight = PS/(1-PS). Lastly, the SMR weights were applied to the Cox models to estimate weighted HRs and 95% CIs.

Subgroup analyses were performed, stratifying the analysis by yearly influenza seasons, age group (65–74, 75–84, 85+ years), and by length of time on dialysis (vintage) (0, 1–2, 3–4, 5–9, 10+ years). Additionally, a sensitivity analysis restricting the SDV

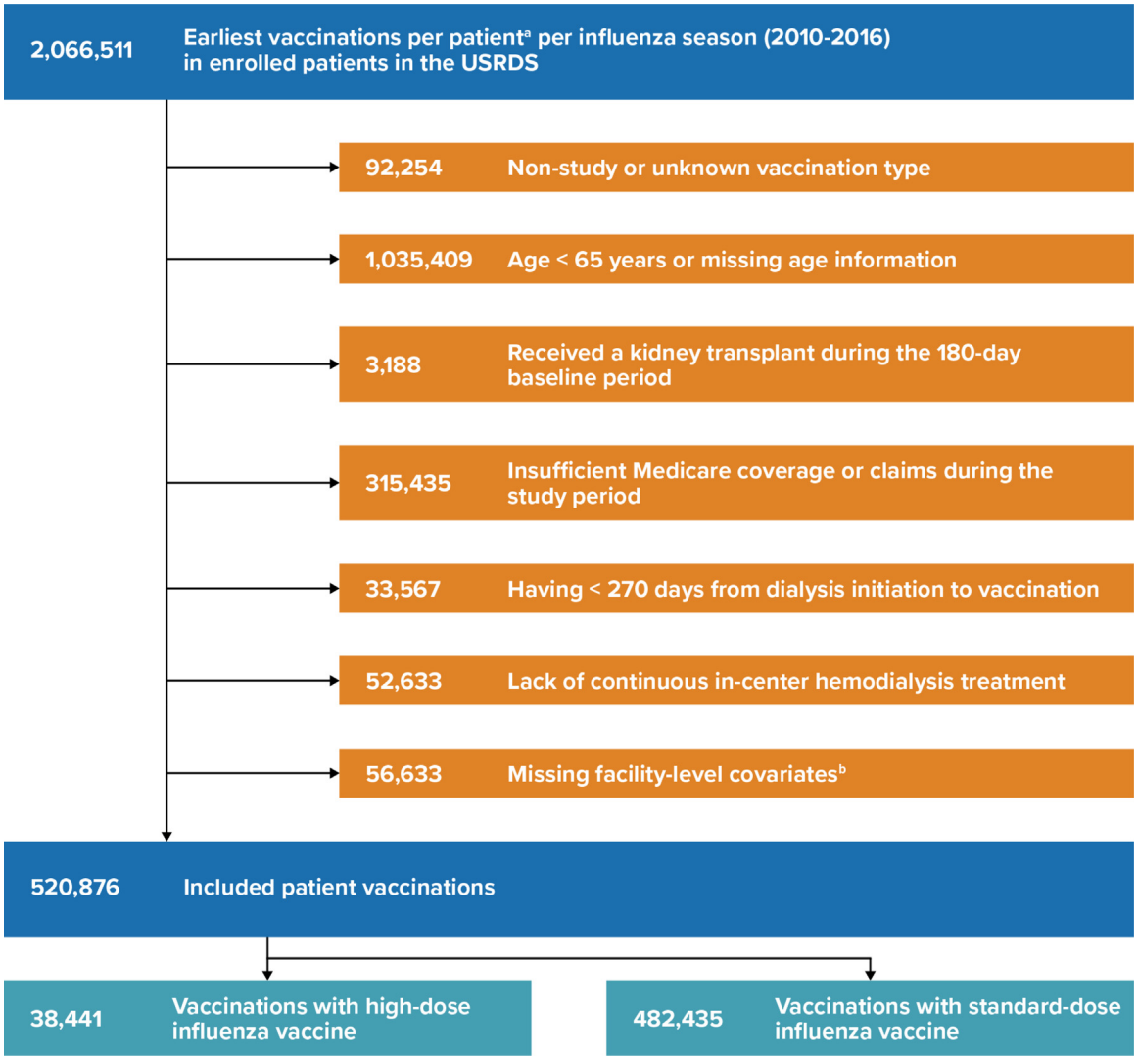

Fig. 2. Attrition due to application of eligibility criteria during cohort selection. USRDS = US Renal Data System. [a] Patients could be included once per influenza season. If patients were included in multiple seasons, exclusion criteria were applied independently at each vaccination date. [b] Covariates with the potential for missingness included geographic region, facility size, hospital-based vs. freestanding facility, profit/nonprofit facility status.

Please cite this article as: J. B. Layton, L. J. McGrath, J. M. Sahrmann et al., Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease, Vaccine, https://doi.org/10.1016/j.vaccine.2020.06.020

group to only trivalent standard-dose influenza vaccines was performed, as the HDV is also a trivalent vaccination.

This analysis of secondary, deidentified data was approved by the Institutional Review Board at . Analyses were performed with SAS Enterprise Guide 8.1 (, Inc., Cary, North Carolina) and R version 3.6 [29].

3. Results

We identified 520,876 eligible index vaccinations during the study period from 216,843 unique patients; 38,441 (7.4%) of the observed vaccinations were HDV (Fig. 2). The mean age at the time of vaccination was 74.7 years (standard deviation, 7.0), and 63.2% of vaccinations were administered to those of white race. Use of HDV was rare in the early years of the study but increased substantially in 2016; 64.4% of the HDV vaccinations occurred during the 2016 influenza season (Table 2).

3.1. Patient characteristics

There were key differences in the characteristics of patients receiving HDV versus SDV (Table 2, Supplemental Fig. S1). Patients receiving HDV were much more likely to be vaccinated in 2016, vaccinated in the month of October, and receive dialysis treatment in a hospital-based or nonprofit facility than those receiving SDV. However, most measures of frailty or other comorbidities were well-balanced between the treatment groups, even in the unweighted analyses.

3.2. Crude incidence analyses

Patients excluded from each outcome-specific cohort due to occurrence of the outcome before vaccination ranged from 0.1% of the sample for anaphylaxis or urticaria/hives to 12.8% for encephalopathy (Supplemental Table S5). Among those vaccinated with HDV, rates of the identified outcomes after vaccination varied widely, from 0 cases/10,000 person-years (py) for anaphylaxis and angioedema to 27.79 cases/10,000 py for pain in limb (Table 3). Rates of most serious outcomes were low, including anaphylaxis, angioedema, and GBS; the crude rates of encephalopathy were higher, though the rates were similar between the treatment groups (1.08 cases and 1.03 cases/10,000 py in HDV and SDV recipients, respectively). The crude rates of more minor events such as pain in limb, myalgia and/or myositis, and nausea and vomiting were high in both treatment groups (Table 3).

3.3. Weighted comparative analyses

The distributions of the PSs by treatment group were plotted for each outcome-specific cohort, and there was reasonably good overlap between the two groups, considering the much larger relative size of the SDV group as compared with the HDV group (Supplemental Fig. S2). Upon application of the SMR weights to the population, all the measured covariates were very well-balanced between the treatment groups (Supplemental Fig. S1).

Case counts were too low to estimate HRs for anaphylaxis, angioedema, and GBS. The weighted analyses of the remaining serious outcomes did not suggest increased risk associated with HDV versus SDV for seizure (HR = 1.03; 95% CI, 0.81–1.32), encephalopathy (HR = 0.94; 95% CI, 0.78–1.14), or short-term mortality (HR = 1.09; 95% CI, 0.80–1.48). However, in weighted analyses of milder adverse reactions, HDV recipients experienced increased risks of rash (HR = 1.86; 95% CI, 1.34–2.57), pain in limb (HR = 1.23; 95% CI, 1.12–1.34), myalgia and/or myositis (HR = 1.16; 95% CI, 1.04–1.30), and diarrhea (HR = 1.26; 95% CI, 1.07–1.50). The HRs for remaining milder events, including urticaria/hives, cellulitis, fever, nausea or vomiting, and syncope were null and/or imprecise.

The rate estimates for the secondary hospitalized outcomes were much lower than those of the primary outcomes identified in any setting, and the resulting HRs were much less precise because of fewer cases. While the estimate for the primary fever outcome did not suggest any increased risk, in the secondary analysis of hospitalized fever, the HR was elevated, though the small number of cases and imprecision of the estimate precluded any conclusion. The weighted HR estimate for the secondary hospitalized nausea and vomiting outcome was similarly null as the

Table 2
Characteristics of patients with end-stage renal disease receiving maintenance hemodialysis who received seasonal influenza vaccination in the United States, 2010–2015.

Characteristic	Total N = 520,876	HDV N = 38,441	SDV N = 482,435	ASMD
Age in years, mean (SD)	74.7 (7.0)	75.0 (7.0)	74.7 (7.0)	0.05
Male sex, n (%)	262,879 (50.5)	20,102 (52.3)	242,777 (50.3)	0.04
Race, n (%)				0.14
White	328,964 (63.2)	26,616 (69.2)	302,348 (62.7)	
Black	158,953 (30.5)	9,658 (25.1)	149,295 (30.9)	
Other	32,959 (6.3)	2,167 (5.6)	30,792 (6.4)	
Cause of ESRD, n (%)				0.05
Diabetes	249,596 (47.9)	17,816 (46.3)	231,780 (48)	
Hypertension	168,598 (32.4)	12,233 (31.8)	156,365 (32.4)	
Glomerulonephritis	34,700 (6.7)	2,885 (7.5)	31,815 (6.6)	
Other	67,982 (13.1)	5,507 (14.3)	62,475 (12.9)	
Region, n (%)				0.14
Northeast	89,891 (17.3)	6,909 (18.0)	82,982 (17.2)	
South	227,872 (43.7)	15,590 (40.6)	212,282 (44.0)	
West	95,324 (18.3)	6,160 (16.0)	89,164 (18.5)	
Midwest	107,789 (20.7)	9,782 (25.4)	98,007 (20.3)	
Influenza season year[a], n (%)				1.44
2010–2011	68,155 (13.1)	558 (1.5)	67,597 (14.0)	
2011–2012	68,591 (13.2)	1,417 (3.7)	67,174 (13.9)	
2012–2013	73,487 (14.1)	1,863 (4.8)	71,624 (14.8)	
2013–2014	74,518 (14.3)	2,346 (6.1)	72,172 (15.0)	
2014–2015	78,487 (15.1)	3,332 (8.7)	75,155 (15.6)	
2015–2016	79,128 (15.2)	4,181 (10.9)	74,947 (15.5)	
2016	78,510 (15.1)	24,744 (64.4)	53,766 (11.1)	

(*continued on next page*)

Please cite this article as: J. B. Layton, L. J. McGrath, J. M. Sahrmann et al., Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease, Vaccine, https://doi.org/10.1016/j.vaccine.2020.06.020

Table 2 (*continued*)

Characteristic	Total N = 520,876	HDV N = 38,441	SDV N = 482,435	ASMD
Month of vaccination				0.46
August – September	311,295 (59.8)	14,831 (38.6)	296,464 (61.5)	
October	190,272 (36.5)	21,249 (55.3)	169,023 (35.0)	
November	13,620 (2.6)	1,782 (4.6)	11,838 (2.5)	
December	3,275 (0.6)	414 (1.1)	2,861 (0.6)	
January or later	2,414 (0.5)	165 (0.4)	2,249 (0.5)	
Medicaid eligibility, n (%)	187,214 (35.9)	11,026 (28.7)	176,188 (36.5)	0.17
Hospital-based facility, n (%)	130,527 (25.1)	13,335 (34.7)	117,192 (24.3)	0.23
Nonprofit facility, n (%)	125,983 (24.2)	14,119 (36.7)	111,864 (23.2)	0.30
Facility number of dialysis stations, n (%)				0.08
0–19	256,850 (49.3)	20,564 (53.5)	236,286 (49.0)	
20–29	186,915 (35.9)	12,585 (32.7)	174,330 (36.1)	
30–80	77,111 (14.8)	5,292 (13.8)	71,819 (14.9)	
Years with ESRD, n (%)				0.09
0	26,553 (5.1)	2,348 (6.1)	24,205 (5.0)	
1–2	178,198 (34.2)	13,986 (36.4)	164,212 (34.0)	
3–4	127,153 (24.4)	8,934 (23.2)	118,219 (24.5)	
5–9	141,890 (27.2)	9,643 (25.1)	132,247 (27.4)	
≥10	47,082 (9.0)	3,530 (9.2)	43,552 (9.0)	
Hospitalized in last month, n (%)				0.00
0	458,630 (88.0)	33,983 (88.4)	424,647 (88.0)	
<1	35,752 (6.9)	2,622 (6.8)	33,130 (6.9)	
≥1	26,494 (5.1)	1,836 (4.8)	24,658 (5.1)	
Skilled nursing facility in last month, n (%)	28,799 (5.5)	1,795 (4.7)	27,004 (5.6)	0.04
Frailty indicators, n (%)				
Mobility aids[b]	193,346 (37.1)	13,286 (34.6)	180,060 (37.3)	0.06
Use of oxygen	71,913 (13.8)	5,280 (13.7)	66,633 (13.8)	0.00
Ambulance/life support	185,388 (35.6)	12,952 (33.7)	172,436 (35.7)	0.04
Skin ulcer (decubitus)	80,799 (15.5)	5,944 (15.5)	74,855 (15.5)	0.00
Dementia	163,460 (31.4)	11,430 (29.7)	152,030 (31.5)	0.04
Home hospital bed	20,623 (4.0)	1,135 (3.0)	19,488 (4.0)	0.06
Difficulty walking	126,819 (24.3)	9,463 (24.6)	117,356 (24.3)	0.01
Weakness	121,923 (23.4)	8,865 (23.1)	113,058 (23.4)	0.09
Lipid abnormality	468,618 (90.0)	35,427 (92.2)	433,191 (89.8)	0.08
Diabetes mellitus complications	364,698 (70.0)	27,119 (70.5)	337,579 (70.0)	0.01
Arthritis	385,404 (74.0)	28,846 (75.0)	356,558 (73.9)	0.03
Transfusion	48,177 (9.2)	3,134 (8.2)	45,043 (9.3)	0.04
Paralysis	63,554 (12.2)	4,439 (11.5)	59,115 (12.3)	0.02
Rehabilitation services	51,288 (9.8)	2,514 (6.5)	48,774 (10.1)	0.13
Comorbidities, n (%)				
Sepsis	50,928 (9.8)	3,574 (9.3)	47,354 (9.8)	0.02
Pneumonia	73,143 (14)	5,304 (13.8)	67,839 (14.1)	0.01
Chronic obstructive pulmonary disease	253,603 (48.7)	19,106 (49.7)	234,497 (48.6)	0.02
Neurological problem	164,342 (31.6)	12,172 (31.7)	152,170 (31.5)	0.00
Psychiatric problem	234,281 (45)	17,748 (46.2)	216,533 (44.9)	0.03
Hypertension	513,933 (98.7)	38,057 (99.0)	475,876 (98.6)	0.03
Heart disease	495,248 (95.1)	36,643 (95.3)	458,605 (95.1)	0.01
Cancer	177,159 (34.0)	14,886 (38.7)	162,273 (33.6)	0.11
Liver disease	113,950 (21.9)	10,532 (27.4)	103,418 (21.4)	0.14
Autoimmune disorders	48,825 (9.4)	4,156 (10.8)	44,669 (9.3)	0.05
Coagulopathy	152,896 (29.4)	13,409 (34.9)	139,487 (28.9)	0.13
Stroke/brain injury	168,946 (32.4)	13,131 (34.2)	155,815 (32.3)	0.04
Pulmonary circulation disease	132,826 (25.5)	10,318 (26.8)	122,508 (25.4)	0.03
Vascular infection	27,826 (5.3)	1,574 (4.1)	26,252 (5.4)	0.06
Substance abuse	34,430 (6.6)	2,933 (7.6)	31,497 (6.5)	0.04
Rheumatic heart disease	114,224 (21.9)	9,470 (24.6)	104,754 (21.7)	0.07
Myocardial infarction	97,529 (18.7)	7,544 (19.6)	89,985 (18.7)	0.02
Peptic ulcer disease	14,182 (2.7)	1,363 (3.5)	12,819 (2.7)	0.05
Gastrointestinal bleeding	92,18 (1.8)	693 (1.8)	8,525 (1.8)	0.00
Screening tests/prevention[c], n (%)				
Pneumonia vaccine	36,225 (7.0)	3,881 (10.1)	32,344 (6.7)	0.12
Hepatitis B vaccine/titer	101,088 (19.4)	7,796 (20.3)	93,292 (19.3)	0.02
Lipid test	169,594 (32.6)	14,339 (37.3)	155,255 (32.2)	0.11
Diabetic eye exam	170,505 (32.7)	13,437 (35.0)	157,068 (32.6)	0.05
Hemoglobin A1C test	308,186 (59.2)	22,011 (57.3)	286,175 (59.3)	0.04
Cancer screening	66,409 (12.7)	5,012 (13.0)	61,397 (12.7)	0.01

ASMD = absolute standardized mean difference; ESRD = end-stage renal disease; HDV = high-dose influenza vaccination; SD = standard deviation; SDV = standard-dose influenza vaccination.

Note: an individual patient may be included multiple times in either treatment group, as patients could be included up to once per influenza season

[a] Flu season year runs from August 1 to July 31; 2016 included through December 31.

[b] Defined as use of walker, wheelchair, or modified bathroom equipment.

[c] Defined during baseline period until date of influenza vaccine.

Please cite this article as: J. B. Layton, L. J. McGrath, J. M. Sahrmann et al., Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease, Vaccine, https://doi.org/10.1016/j.vaccine.2020.06.020

Table 3
Association of high-dose influenza vaccination with adverse events compared with standard-dose influenza vaccine among patients with end-stage renal disease.

Outcome	Vaccine	Count	Cases	Crude incidence rate (cases/ 10,000 py)	Crude		SMR weighted[a]	
					HR	95% CI	HR	95% CI
Serious outcomes								
Anaphylaxis	SDV	481,974	23	0.16	Reference		Reference	
	HDV	38,412	0	0.00	NE		NE	
Angioedema	SDV	481,520	12	0.08	Reference		Reference	
	HDV	38,387	0	0.00	NE		NE	
Seizure	SDV	457,914	1,088	1.59	Reference		Reference	
	HDV	36,611	97	1.78	1.12	0.91–1.38	1.03	0.81–1.32
Encephalopathy	SDV	421,039	1,838	1.03	Reference		Reference	
	HDV	33,060	150	1.08	1.05	0.89–1.24	0.94	0.78–1.14
Guillain-Barré Syndrome	SDV	480,250	N < 11	0.00	Reference		Reference	
	HDV	38,256	N < 11	0.01	NE		NE	
Short-term mortality	SDV	482,435	546	1.42	Reference		Reference	
	HDV	38,441	65	2.12	1.50	1.16–1.94	1.09	0.80–1.48
Milder outcomes								
Urticaria/hives	SDV	482,022	87	0.23	Reference		Reference	
	HDV	38,407	N < 11	0.29	1.30	0.66–2.58	1.29	0.60–2.77
Rash	SDV	479,958	474	1.24	Reference		Reference	
	HDV	38,251	65	2.13	1.72	1.33–2.24	1.86	1.34–2.57
Pain in limb	SDV	434,923	7,152	20.72	Reference		Reference	
	HDV	34,428	755	27.79	1.34	1.24–1.45	1.23	1.12–1.34
Cellulitis	SDV	474,297	1,511	3.99	Reference		Reference	
	HDV	37,834	122	4.05	1.01	0.84–1.22	0.96	0.78–1.20
Myalgia and/or myositis	SDV	436,248	4,859	14.02	Reference		Reference	
	HDV	34,723	497	18.09	1.29	1.18–1.42	1.16	1.04–1.30
Fever	SDV	468,120	2,856	7.66	Reference		Reference	
	HDV	37,370	202	6.80	0.89	0.77–1.02	0.92	0.78–1.08
Nausea and vomiting	SDV	458,563	5,645	15.53	Reference		Reference	
	HDV	36,403	514	17.86	1.15	1.05–1.26	1.07	0.96–1.19
Diarrhea	SDV	469,346	1,968	5.26	Reference		Reference	
	HDV	37,300	233	7.86	1.49	1.31–1.71	1.26	1.07–1.50
Syncope	SDV	446,450	508	3.80	Reference		Reference	
	HDV	35,430	46	4.33	1.14	0.84–1.54	1.20	0.84–1.71
Secondary outcomes								
Hospitalized fever	SDV	468,120	142	0.38	Reference		Reference	
	HDV	37,370	14	0.47	1.24	0.72–2.14	1.62	0.84–3.09
Hospitalized nausea and vomiting	SDV	458,563	218	0.59	Reference		Reference	
	HDV	36,403	24	0.83	1.39	0.91–2.12	1.04	0.63–1.72
Hospitalized diarrhea	SDV	469,346	299	0.8	Reference		Reference	
	HDV	37,300	27	0.91	1.14	0.77–1.69	0.95	0.58–1.53
Composite hypersensitivity[b]	SDV	473,139	498	1.32	Reference		Reference	
	HDV	37,785	46	1.53	1.16	0.86–1.57	1.17	0.84–1.63
Composite gastrointestinal[c]	SDV	449,025	6,926	19.48	Reference		Reference	
	HDV	35,591	676	24.10	1.23	1.14–1.34	1.12	1.02–1.23

CI = confidence interval; HDV = high-dose influenza vaccine; HR = hazard ratio; NE = not estimable due to small case counts; py = person-years; SDV = standard-dose influenza vaccine; SMR = standardized mortality ratio.

[a] Variables included in the propensity score models include age, sex, cause of end-stage renal disease, geographic region, influenza season year, month of vaccination, Medicaid eligibility, hospital-based facility, nonprofit facility, dialysis facility size, years with end-stage renal disease, hospitalizations in the last month, skilled nursing facility stay in last month, use of mobility aids, use of oxygen, use of ambulance/life support, skin ulcer (decubitus), dementia, home hospital bed, difficulty walking, weakness, lipid abnormality, diabetes mellitus complications, arthritis, transfusion, paralysis, use of rehabilitation services, sepsis, pneumonia, chronic obstructive pulmonary disease, neurological problem, psychiatric problem, hypertension, heart disease, cancer, liver disease, autoimmune disorders, coagulopathy, stroke/brain injury, pulmonary circulation disease, vascular infection, substance abuse, rheumatic heart disease, myocardial infarction, peptic ulcer disease, gastrointestinal bleeding, pneumonia vaccine, hepatitis b vaccine/titer, lipid test, diabetic eye exam, hemoglobin A1c test, and cancer screening.

[b] Including anaphylaxis, angioedema, postimmunization arthropathy, urticaria/hives, or allergy/reaction.

[c] Including diarrhea, nausea, and vomiting.

estimate for the primary outcome definition. The weighted HR for the hospitalized diarrhea outcome was attenuated, unlike the HR for the primary diarrhea outcome, which was elevated. When the composite outcomes were considered, the rates of most hypersensitivity reactions were very low, and the HRs for both composite outcomes (hypersensitivity and gastrointestinal) were similarly elevated, though the much larger number of gastrointestinal events resulted in a more precise HR estimate (Table 3).

3.4. Stratified and sensitivity analyses

When evaluating the HR estimates stratified by age, influenza season, and duration of dialysis treatment, the findings were generally consistent with the main results. The estimable risks of serious events (i.e., seizure, encephalopathy) were similar between groups, though the risks of some milder events (i.e., pain in limb, myalgia and/or myositis, rash, diarrhea, composite gastrointestinal) were increased in most levels of the stratification characteristics. However, the much smaller sample sizes in the stratified analyses resulted in wide CIs for many of the estimates (Supplemental Fig. S3).

The majority of the SDVs in the primary analysis (75.6%) were trivalent. In the sensitivity analysis restricted to HDV (which is a trivalent vaccine) versus trivalent SDV vaccinations, very similar results to the overall analyses were observed (Supplemental Table S6).

Please cite this article as: J. B. Layton, L. J. McGrath, J. M. Sahrmann et al., Comparative safety of high-dose versus standard-dose influenza vaccination in patients with end-stage renal disease, Vaccine, https://doi.org/10.1016/j.vaccine.2020.06.020

4. Discussion

In this evaluation of the safety of HDV among US patients receiving hemodialysis, no increased risks for serious adverse events (i.e., seizure, encephalopathy, short-term all-cause mortality) were observed, although there were too few cases to estimate comparative risk estimates for anaphylaxis, angioedema, or GBS. However, the risks of some milder adverse reactions (pain in limb, myalgia, rash, diarrhea) identified in any setting were consistently increased in patients receiving HDV as compared with those receiving SDV, overall and across multiple influenza seasons and patient subgroups. We did not observe evidence of increased risks of hospitalized cases of fever, nausea and vomiting, or diarrhea, potentially suggesting that HDV may be associated with increased rates of minor events, though not with more severe events. While the lack of increased risks of serious events is reassuring, older patients with ESRD receiving dialysis experience high rates of comorbidities, hospitalization, and mortality [30]; therefore, even minor adverse events may prove detrimental in this population.

The findings of the current analysis are consistent with the results of phase 2 and 3 clinical studies comparing HDV and SDV in the general population of adults, which have reported increased occurrence of adverse events such as erythema [9], localized pain [6,8,9,14], and myalgia [6,8,9] for the more immunogenic HDV; most of the reported adverse events from these studies resolved quickly with no treatment or minor treatment. Additionally, in a placebo-controlled comparison of different influenza vaccine dosages, increasing doses of influenza vaccine were associated with higher rates of injection site discomfort, redness, and swelling [10]. Similarly, an analysis of adverse event reporting to the US Vaccine Adverse Event Reporting System reported increased odds of serious cardiac or gastrointestinal events and nonserious respiratory events associated with HDV compared with SDV in the general population of older adults [13]. While patients receiving dialysis may experience compromised immunity, the increased risk of milder vaccine reactions in these patients appears similar to those observed in the general population.

There were changing dynamics in the use of HDV over the study period, with very low uptake of HDV during the early years of the study period and then a much higher occurrence of HDV vaccinations in the 2016 influenza season. These changing treatment trends and nonrandomized nature of the study may result in residual unmeasured confounding [31], where atypical patients received HDV early after its approval followed by more general acceptance of HDV among dialysis providers. When the analyses were stratified by year (Supplemental Fig. S3), the 2016 season analysis included 64% of the total HDV vaccinations in the study. While the precision of the year-stratified estimates was less than that of the overall estimates, most of the 2016 HR estimates were similar in magnitude and direction to the overall estimates, with the exceptions of myalgia and/or myositis and diarrhea, which were attenuated toward the null. This heterogeneity by year suggests potential for some confounding by changing case mix in each influenza season. To account for confounding by overall patient health status, we included a variety of proxies for health care receipt and frailty, dialysis facility characteristics, and clinical variables. After weighting, all characteristics were well-balanced. We also used an active comparator design to reduce residual confounding, as demonstrated in a previous negative control study comparing HDV to SDV and HDV to unvaccinated patients [32]. Despite our efforts, residual unmeasured confounding remains a possibility.

There are additional potential limitations of this work. This study was conducted using existing health care data that were collected for reimbursement purposes and program enrollment rather than clinical delivery or active vaccine surveillance, which may result in incomplete, missing, or misclassified information. Patients may have received vaccinations through mechanisms without billing to Medicare (e.g. self-payment), and thus, some vaccinations may not have been recorded in the data. However, most patients receiving hemodialysis obtain care at dialysis clinics multiple times a week, thus routine influenza vaccination is very likely to occur in dialysis clinics and be billed to Medicare. Additionally, not all outcomes may be medically attended and coded in reimbursement data, potentially resulting in lower outcome rates, though missingness is not likely to differ by vaccination type. Potentially, only more severe outcomes may be observed and recorded by health care providers; however, the severity of outcomes could not be evaluated in claims data, as recorded diagnoses do not differentiate between adverse event grades or contain information about disease severity. Nevertheless, secondary analyses of hospitalized fever, nausea and vomiting, and diarrhea were performed to evaluate more severe cases of these outcomes. Additionally, many of the outcomes were acute in nature, and the occurrence of outcomes was evaluated on the day of vaccination. While it was assumed that the outcomes occurring on the day of vaccination occurred after the vaccination, claims data do not record the time of health care interactions, and there is the possibility that some acute outcome preceded the vaccination and were recorded at the same visit as the vaccination.

Given the lack of serious adverse events but the increased risk of some minor adverse events observed in this study, older patients with ESRD and their providers should consider the benefits and risks of routine influenza vaccination with HDV. Previous observational studies have reported mixed results regarding the effectiveness of HDV versus SDV among patients with ESRD [33,34], and further research is necessary to clarify the effectiveness of HDV in this population. In conclusion, vaccination with HDV was not associated with increased risks of serious adverse events in patients with ESRD receiving dialysis compared with SDV. However, rates of some milder outcomes were higher in patients receiving HDV than in those receiving SDV.

5. Disclosures

The work was supported by the United States National Institutes of Health [grant number 1R21AI38385]. Data programming for this study was conducted by the Center for Administrative Data Research, which is supported in part by the Washington University Institute of Clinical and Translational Sciences grant UL1 TR002345 from the National Center for Advancing Translational Sciences (NCATS) of the National Institutes of Health (NIH) and by grant number R24 HS19455 through the Agency for Healthcare Research and Quality (AHRQ). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: JBL is an employee of RTI International, an independent, nonprofit research institute that provides research services for governmental and commercial clients, including pharmaceutical companies. LM is an employee of and owns stock in NoviSci, Inc. AMB is supported by a grant from the National Center for Advancing Translational Sciences (NCATS), NIH under award number KL2 TR002346. The other authors report no conflicts.

Acknowledgements

The data reported here have been supplied by the United States Renal Data System (USRDS). The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy or interpretation of the US government. Requests for access to the USRDS data can be made to the USRDS Coordinating Center. All authors attest they meet the ICMJE criteria for authorship.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.06.020.

References

[1] Gilbertson DT, Rothman KJ, Chertow GM, Bradbury BD, Brookhart MA, Liu J, et al. Excess deaths attributable to influenza-like illness in the ESRD population. J Am Soc Nephrol 2019;30(2):346–53.
[2] Chi C, Patel P, Pilishvili T, Moore M, Murphy T, Strikas R. Guidelines for vaccinating kidney dialysis patients and patients with chronic kidney disease. Centers for Disease Control and Prevention 2012. Available at: https://www.cdc.gov/vaccines/pubs/downloads/dialysis-guide-2012.pdf [accessed: 10 June 2019].
[3] McGrath LJ, Kshirsagar AV, Cole SR, Wang L, Weber DJ, Sturmer T, et al. Influenza vaccine effectiveness in patients on hemodialysis: an analysis of a natural experiment. Arch Intern Med 2012;172(7):548–54.
[4] McGrath LJ, Ellis AR, Brookhart MA. Controlling time-dependent confounding by health status and frailty: Restriction versus statistical adjustment. Am J Epidemiol 2015;182(1):17–25.
[5] McGrath LJ, Layton JB, Krueger WS, Kshirsagar AV, Butler AM. High-dose influenza vaccine use among patients receiving hemodialysis in the United States, 2010–2013. Vaccine 2018;36(41):6087–94.
[6] Couch RB, Winokur P, Brady R, Belshe R, Chen WH, Cate TR, et al. Safety and immunogenicity of a high dosage trivalent influenza vaccine among elderly subjects. Vaccine 2007;25(44):7656–63.
[7] DiazGranados CA, Dunning AJ, Jordanov E, Landolfi V, Denis M, Talbot HK. High-dose trivalent influenza vaccine compared to standard dose vaccine in elderly adults: safety, immunogenicity and relative efficacy during the 2009–2010 season. Vaccine 2013;31(6):861–6.
[8] DiazGranados CA, Saway W, Gouaux J, Baron M, Baker J, Denis M, et al. Safety and immunogenicity of high-dose trivalent inactivated influenza vaccine in adults 50–64 years of age. Vaccine 2015;33(51):7188–93.
[9] Falsey AR, Treanor JJ, Tornieporth N, Capellan J, Gorse GJ. Randomized, double-blind controlled phase 3 trial comparing the immunogenicity of high-dose and standard-dose influenza vaccine in adults 65 years of age and older. J Infect Dis 2009;200(2):172–80.
[10] Keitel WA, Atmar RL, Cate TR, Petersen NJ, Greenberg SB, Ruben F, et al. Safety of high doses of influenza vaccine and effect on antibody responses in elderly persons. Arch Intern Med 2006;166(10):1121–7.
[11] Samson SI, Leventhal PS, Salamand C, Meng Y, Seet BT, Landolfi V, et al. Immunogenicity of high-dose trivalent inactivated influenza vaccine: a systematic review and meta-analysis. Expert Rev Vaccines 2019;18(3):295–308.
[12] Kaka AS, Filice GA, Myllenbeck S, Nichol KL. Comparison of side effects of the 2015-2016 high-dose, inactivated, trivalent influenza vaccine and standard dose, inactivated, trivalent influenza vaccine in adults >/=65 years. Open Forum Infect Dis 2017; Winter;4(1):ofx001.
[13] Moro PL, Arana J, Cano M, Menschik D, Yue X, Lewis P, Haber P, Martin D, Broder K. postlicensure safety surveillance for high-dose trivalent inactivated influenza vaccine in the vaccine adverse event reporting system, 1 July 2010-31 December 2010. Clin Infect Dis 2012;54(11):1608–14.
[14] Volling C, Coleman BL, Katz K, Simor AE, Muller M, Powis J, et al. Immunogenicity and reactogenicity of high- vs. standard-dose trivalent inactivated influenza vaccine in healthcare workers: a pilot randomized controlled trial. Clin Microbiol Infect 2019;25(2):217–24.
[15] Labriola L, Hombrouck A, Marechal C, Van Gucht S, Brochier B, Thomas I, et al. Immunogenicity of an adjuvanted 2009 pandemic influenza A (H1N1) vaccine in haemodialysed patients. Nephrol Dial Transplant 2011;26(4):1424–8.
[16] Mastalerz-Migas A, Steciwko A, Brydak LB. Immune response to influenza vaccine in hemodialysis patients with chronic renal failure. Adv Exp Med Biol 2013;756:285–90.
[17] U.S. Renal Data System. 2019 USRDS annual data report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2019. Available at: https://www.usrds.org/adr.aspx.
[18] Update: influenza activity–United States, 2010-11 season, and composition of the 2011-12 influenza vaccine. MMWR Morb Mortal Wkly Rep 2011; 60 (21):705–12.
[19] Update: influenza activity - United States, 2011-12 season and composition of the 2012-13 influenza vaccine. MMWR Morb Mortal Wkly Rep 2012; 61 (22):414–20.
[20] Influenza activity–United States, 2012-13 season and composition of the 2013-14 influenza vaccine. MMWR Morb Mortal Wkly Rep. 2013; 62(23):473–9.
[21] Appiah GD, Blanton L, D'Mello T, Kniss K, Smith S, Mustaquim D, et al. Influenza activity - United States, 2014–15 season and composition of the 2015–16 influenza vaccine. MMWR Morb Mortal Wkly Rep 2015;64 (21):583–90.
[22] Epperson S, Blanton L, Kniss K, Mustaquim D, Steffens C, Wallis T, et al. Influenza activity - United States, 2013–14 season and composition of the 2014–15 influenza vaccines. MMWR Morb Mortal Wkly Rep 2014;63 (22):483–90.
[23] Davlin SL, Blanton L, Kniss K, Mustaquim D, Smith S, Kramer N, et al. Influenza activity - United States, 2015–16 season and composition of the 2016–17 influenza vaccine. MMWR Morb Mortal Wkly Rep 2016;65(22):567–75.
[24] Blanton L, Alabi N, Mustaquim D, Taylor C, Kniss K, Kramer N, et al. Update: Influenza activity in the United States during the 2016–17 season and composition of the 2017–18 influenza vaccine. MMWR Morb Mortal Wkly Rep 2017;66(25):668–76.
[25] Haber P, DeStefano F, Angulo FJ, Iskander J, Shadomy SV, Weintraub E, et al. Guillain-Barre syndrome following influenza vaccination. JAMA 2004;292 (20):2478–81.
[26] Faurot KR, Jonsson Funk M, Pate V, Brookhart MA, Patrick A, Hanson LC, et al. Using claims data to predict dependency in activities of daily living as a proxy for frailty. Pharmacoepidemiol Drug Saf 2015;24(1):59–66.
[27] Conover MM, Sturmer T, Poole C, Glynn RJ, Simpson Jr RJ, Pate V, et al. Classifying medical histories in US Medicare beneficiaries using fixed vs all-available look-back approaches. Pharmacoepidemiol Drug Saf 2018;27 (7):771–80.
[28] Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. Stat Med 2009;28(25):3083–107.
[29] R Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2020. Available at: http://www.R-project.org/.
[30] US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States. Am J Kidney Dis; 2019.
[31] Gagne JJ, Bykov K, Willke RJ, Kahler KH, Subedi P, Schneeweiss S. Treatment dynamics of newly marketed drugs and implications for comparative effectiveness research. Value Health 2013;16(6):1054–62.
[32] Butler AM, Layton JB, Krueger WS, Kshirsagar AV, LJ M. Assessing Residual Bias in Estimating Influenza Vaccine Effectiveness: Comparison of High-dose versus Standard Dose Vaccines. Medical Care 2019; 57(1):73–8.
[33] Butler AM, Layton JB, Dharnidharka VR, Sahrmann JM, Seamans MJ, Weber DJ, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccine among patients receiving maintenance hemodialysis. Am J Kidney Dis 2020;75(1):72–83.
[34] Miskulin DC, Weiner DE, Tighiouart H, Lacson Jr EK, Meyer KB, Dad T, et al. High-dose seasonal influenza vaccine in patients undergoing dialysis. Clin J Am Soc Nephrol 2018;13(11):1703–11.