Comparative Safety of High-Dose Versus Standard-Dose Influenza Vaccination in Patients With End-Stage Renal Disease

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DISCLOSURES

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BACKGROUND

- Patients with end-stage renal disease (ESRD) are at high risk of influenza-associated morbidity and mortality.
- The use of high-dose influenza vaccine (HDV) has increased among patients with ESRD since its approval in 2009 by the United States (US) Food and Drug Administration for use by persons aged ≥ 65 years.
- HDV has been associated with higher rates of mild or moderate injection site and systemic reactions in the general population of older adults.
- Patients with ESRD have decreased immunocompetence, which may result in a different vaccination safety profile than that in the general population of older adults.

OBJECTIVE

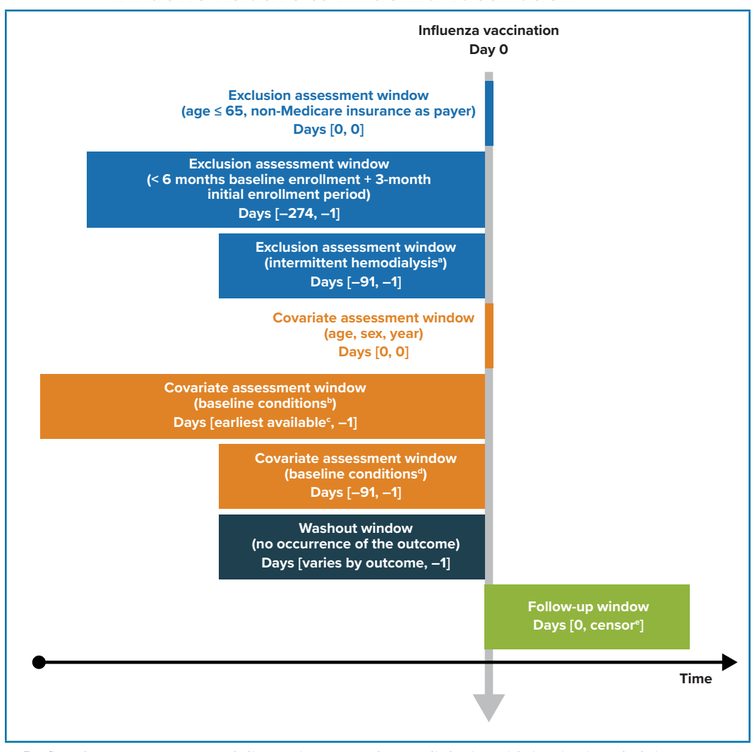
- To compare the risk of adverse events following vaccination with HDV versus standard-dose influenza vaccine (SDV) among patients aged ≥ 65 years receiving maintenance hemodialysis in the US.

METHODS

Setting and Population

- We used data from the US Renal Data System (USRDS) from 2010 to 2016.
  - The USRDS is a national registry of patients with ESRD with Medicare insurance and contains data on enrollment, cause of ESRD, death, and Medicare administrative billing claims for procedure, diagnosis, and pharmacy medication dispensing claims.
- We identified individuals on maintenance hemodialysis aged ≥ 65 years at their first SDV or HDV in each influenza season (from August 1 to the Centers for Disease Control and Prevention–defined end of the influenza season) from the 2010-2011 season to the 2016-2017 season (data ending on December 31, 2016) (Figure 1).
  - A patient could be included once in each yearly cohort.
- Patients were excluded from outcome-specific cohorts if they experienced the outcome during prevaccination washout windows (Table 1).

Figure 1. Study Design Schematic and Variable Assessment Windows Relative to Influenza Vaccination



[a] Defined as treatment modality as in-center hemodialysis, with institutional claims covering at least 67% of enrolled days.

[b] Baseline conditions included chronic comorbidities.

[c] The earliest available date of enrollment in the USRDS occurring after the latest of January 1, 2008, or 91 days after dialysis initiation.

[d] Baseline conditions included frailty markers, acute events, and screening/preventive health care utilization.

[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, or receipt of a kidney transplant.

Note: Figure template available at http://www.repeatinitiative.org.

Exposure and Outcomes

- Influenza vaccinations were identified using procedure codes.
  - **Exposure:** high-dose, trivalent influenza vaccines (HDV)
  - **Comparator:** standard-dose, trivalent or quadrivalent, nonadjuvanted, egg-based, inactivated influenza vaccines (SDV)
- Outcomes were identified with diagnosis coding, and outcome-specific washout and ascertainment periods are shown in Table 1.

Approach

- We estimated incidence rates and 95% confidence intervals (CI) by treatment group separately for each outcome in outcome-specific cohorts.
- We compared rates among HDV recipients with rates among SDV recipients using standardized mortality ratio (SMR) weighted Cox proportional hazards models, estimating hazard ratios (HRs) and 95% CIs.
  - We estimated CIs with robust sandwich covariance matrix estimates to account for the potential within-person correlation.
- Subgroup analyses were performed by yearly influenza season, age group, and time on dialysis.

Table 1. Outcome-Specific Follow-up Periods and Prevaccination Washout Periods

Outcome	Follow-up Window[a]	Prevaccination Washout Window
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 diagnoses of Guillain-Barré syndrome or CIDP)
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 (inpatient or outpatient) in 42 days
Hospitalized nausea and vomiting	8 days	Any nausea and vomiting (inpatient or outpatient) in 42 days
Hospitalized diarrhea	8 days	Any diarrhea (inpatient or outpatient) in 42 days
Composite hypersensitivity	8 days	6 months
Composite gastrointestinal	8 days	42 days

CIDP = chronic inflammatory demyelinating polyradiculoneuropathy.

[a] Inclusive of the vaccination date.

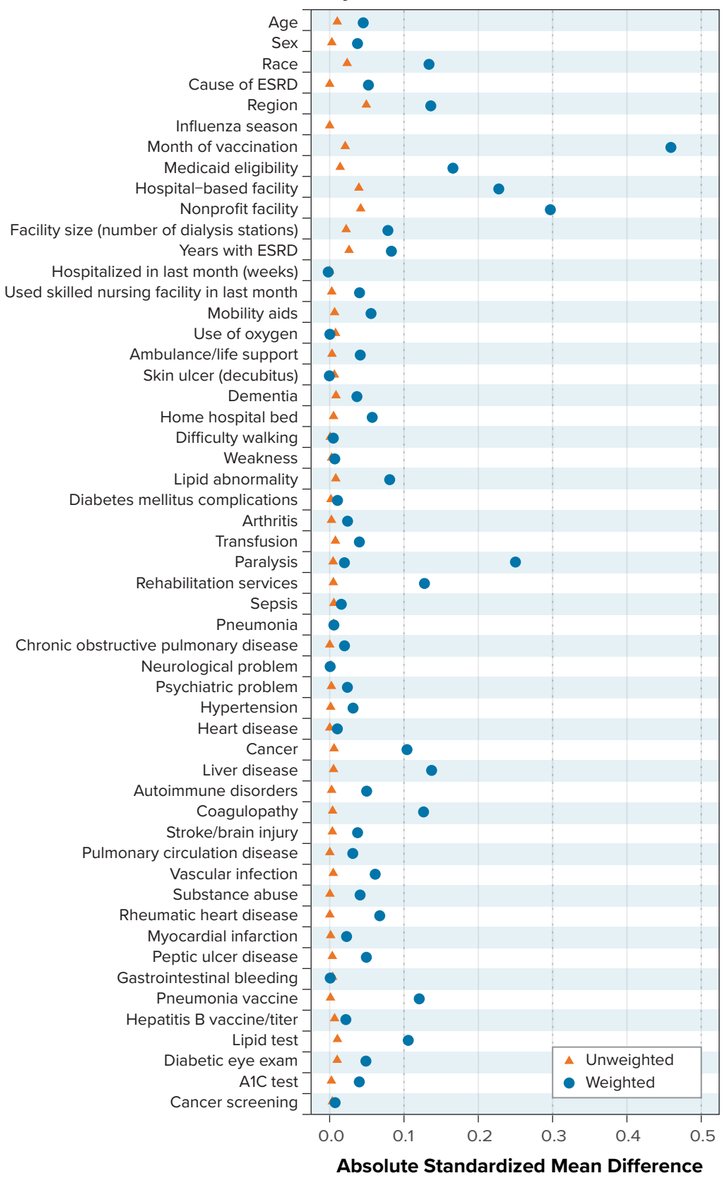
Table 2. Selected Characteristics of Patients With ESRD Receiving Maintnance Hemodialysis Who Received Seasonal Influenza Vaccination in the United States, 2010-2015

Characteristic	Total N = 520,876	HDV N = 38,441	SDV N = 482,435
Age in years, mean (SD)	74.7 (7.0)	75.0 (7.0)	74.7 (7.0)
Male sex, %	50.5	52.3	50.3
Race, n (%)			
White	63.2	69.2	62.7
Black	30.5	25.1	30.9
Other	6.3	5.6	6.4
Influenza season year[a], n (%)			
2010-2011	13.1	1.5	14.0
2011-2012	13.2	3.7	13.9
2012-2013	14.1	4.8	14.8
2013-2014	14.3	6.1	15.0
2014-2015	15.1	8.7	15.6
2015-2016	15.2	10.9	15.5
2016	15.1	64.4	11.1
Month of vaccination			
August-September	59.8	38.6	61.5
October	36.5	55.3	35.0
November	2.6	4.6	2.5
December	0.6	1.1	0.6
January or later	0.5	0.4	0.5

SD = standard deviation.

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

Figure 2. Balance of Covariates Between Patients With ESRD Receiving HDV or SDV for Unweighted and Weighted Cohorts for the Mortality Outcome



RESULTS

- We identified 520,876 eligible index vaccinations from 216,843 unique patients during the study period.
  - 38,441 (7.4%) of the observed vaccinations were HDV (Table 2).
- Most clinical characteristics were well balanced between exposure groups in the crude, unweighted cohort. Other imbalances were resolved after SMR weighting (Figure 2)
- Incidence rates of most serious outcomes were low after vaccination, including anaphylaxis, angioedema, and Guillain-Barré syndrome (Table 3).
- Weighted HRs for some milder events were elevated (Table 3).
  - This pattern was consistent across most subgroups.

Table 3. Association of HDV With Adverse Events Compared With SDV Among Patients With ESRD

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

NE = not estimable due to small case counts; PY = person-years.

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

[b] Including diarrhea, nausea, and vomiting.

DISCUSSION

- Vaccination with HDV was not associated with increased risks of serious adverse events in patients with ESRD receiving dialysis compared with SDV.
- Rates of some milder outcomes were higher in patients receiving HDV than in those receiving SDV, consistent with clinical trials results in the general population of older adults.

CONCLUSIONS

- Older patients with ESRD and their providers should consider the benefits and risks of routine influenza vaccination with HDV.

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