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Study Organization

- Sponsor: Veterans Education and Research Association of Northern New England (VERANNE)
  - Principal Investigator: Yinong Young-Xu, ScD.

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- Funding: Sanofi Pasteur

Analysis of Relative Effectiveness of High-Dose versus Standard-Dose Influenza Vaccines Using an Instrumental Variable Method

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Study Population

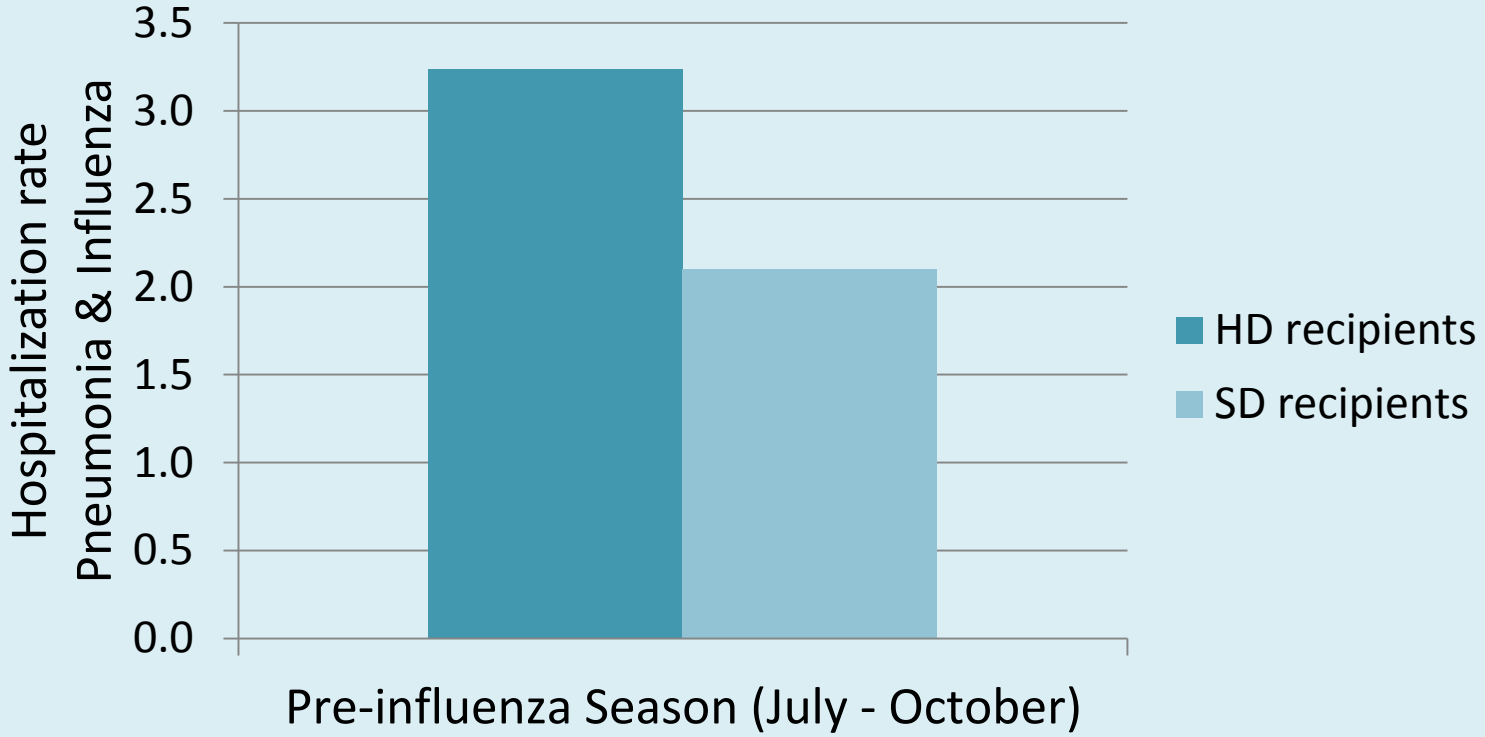
- The Veterans Health Administration (VHA) is the single largest integrated health care system in the United States
- 144 medical centers and 1,203 community-based outpatient clinics: integrated electronic medical record (EMR)
- About 3 million patients 65 years and older

Background

- Two randomized trials have shown high-dose (IIV3-HD) influenza vaccine was more efficacious in preventing hospitalizations than the standard-dose (IIV3) vaccine.[1,2]

- However, findings of observational studies utilizing matching and multivariate modeling have been inconsistent.[3,4,5]

The Challenge



Why use Instrumental Variable (IV)?

- IV acts as a randomizer of unmeasured confounders like "frailty"

- Same types of patients have different probabilities to receive HD in a VHA facility, because each VHA has an independent and unique vaccine "preference"

- Wong et al. estimated the association between influenza vaccination and all-cause mortality in Ontario using an IV.[6]

Methods

Study Design

Retrospective, longitudinal, observational cohort study over 5 influenza seasons (2010-2011 to 2014-2015)

Inclusion criteria

- Received HD or SD vaccine at VHA facility
- At least one inpatient or two outpatient visit to VHA facility in prior year

Methods, cont.

Baseline period

Baseline characteristics were measured from beginning of July until vaccination date

Observation period

Study outcomes were observed beginning two weeks after vaccination until the end of June of the next calendar year

Methods, cont.

Study Outcomes in VHA and non-VHA facilities

Hospitalizations with a principal discharge diagnosis of:

1. Cardiorespiratory disease (ICD-9: 390-519)
2. Influenza- or pneumonia (ICD-9: 480-488)
3. Urinary tract infection (ICD-9: 599) *as a falsification test*
4. Any (All-cause)

Methods, cont.

Data Analysis

- IV Poisson regression model; IV = VHA facility vaccine preference in a given season, or "HD-proportion" (HD/HD+SD)
- Independent variables include age, gender, race, geographic location, and comorbidity status

Data Sources

VHA electronic medical records and Medicare administrative files

Results

	High Dose		Standard Dose	
	N	%	N	%
Number of person-seasons	158,636	4%	3,480,288	96%
Comorbidities				
1. Any malignancy	24,188	15%	441,466	13%
2. Congestive heart failure	13,538	9%	233,461	7%
3. Chronic pulmonary disease	30,026	19%	561,231	16%
4. Cerebrovascular disease	12,591	8%	225,186	6%
5. Diabetes without chronic complications	68,075	43%	1,393,512	40%

Results, cont.

Observed Hospitalizations

- 1,325,366 all-cause
- 357,686 for cardiorespiratory disease
- 51,904 for influenza/pneumonia

IV-adjusted rVE estimates of HD vs. SD

Hospitalization	Observation Period
Pneumonia and Influenza	14% (6% : 22%)*
Cardio-respiratory	18% (15% : 21%)
All-cause	10% (8% : 12%)
Urinary tract infection	-5% (-34% : 18%)

*point estimate (95% confidence interval)

IV-adjusted rVE estimates of HD vs. SD

Hospitalization	Baseline Period
Pneumonia and Influenza	-5% (-21% : 10%)
Cardio-respiratory	-2% (-6% : 2%)
All-cause	1% (-2% : 4%)

Conclusions

- After IV adjustment, outcome rates during the baseline period (in absence of influenza) look similar, suggesting reduced bias

- Spanning over five seasons, our IV analysis shows that high-dose influenza vaccine is more effective than a standard-dose vaccine in protecting senior VHA patients against hospitalizations

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References

1. DiazGranados CA, Robertson CA, Talbot HK, et al. Prevention of serious events in adults 65 years of age or older: A comparison between high-dose and standard-dose inactivated influenza vaccines. Vaccine 2015. 33(38): 4988-93.
2. Gravenstein S, Davidson HE, Taljaard M, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial. Lancet Respir Med. 2017 Sep;5(9): 738-746.
3. Richardson DM, Medvedeva EL, Roberts CB, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccination in community-dwelling veterans. Clin Infect Dis 2015; 61(2): 171-6.
4. Izurieta HS, Thadani N, Shay DK, et al. Comparative effectiveness of high-dose versus standard-dose influenza vaccines in US residents aged 65 years and older from 2012 to 2013 using Medicare data: a retrospective cohort analysis. The Lancet Infectious diseases 2015; 15(3): 293-300.
5. Shay DK, Chillarige Y, Kelman J, et al. Comparative Effectiveness of High-Dose Versus Standard-Dose Influenza Vaccines Among US Medicare Beneficiaries in Preventing Postinfluenza Deaths During 2012-2013 and 2013-2014. The Journal of infectious diseases 2017; 215(4): 510-7.
6. Wong K, Campitelli MA, Stukel TA, et al. Estimating Influenza Vaccine Effectiveness in Community-Dwelling Elderly Patients Using the Instrumental Variable Analysis Method, Arch Intern Med. 2012;172(6):484-491.