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- **Declaration of Author's Competing Interests**
  - I am an employee of Sanofi Pasteur

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Economic Assessment of High-Dose versus Standard-Dose Influenza Vaccine in the US Veteran Population: Estimating the Impact on Hospitalization Cost for Cardiovascular and Respiratory Disease

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High-dose vaccine increases protection

against influenza infection and its complications

- Standard-dose (SD) vaccines contain 15µg of hemagglutinin per strain
- High-dose vaccine increases immune response, contains 60µg per strain
- Developed for seniors 65 years and older with natural, age-reduced immune response: **Immunosenescence**
- Trivalent high dose (HD-IIV3) licensed in the US since 2009, but not available in Europe

Our study population uses VHA health care

- 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

Why this study?

- Superior protection of HD-IIV3 versus SD-IIV3 vaccines reported in large randomized and observational studies for variety of outcomes[1]
- Relative vaccine effectiveness is outcome specific: impact of HD-IIV3 on cardiovascular hospitalizations has not been reported yet
- Is incremental cost of HD-IIV3 cost-effective?

1. Jason K. H. Lee, Gary K. L. Lam, Thomas Shin, Jiyeon Kim, Anish Krishnan, David P. Greenberg & Ayman Chit (2018) Efficacy and effectiveness of high-dose versus standard-dose influenza vaccination for older adults: a systematic review and meta-analysis, Expert Review of Vaccines, 17:5, 435-443, DOI: 10.1080/14760584.2018.1471989

Cohort observed over 5 influenza seasons

- 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 outpatient visit to VHA facility in six months prior to vaccination

Outcomes observed until end of June

- 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
  - Cardiovascular complications can trail an (influenza) infection longer than previously assumed[1]

1. Musher DM, Abers MS, Corrales-Medina VF. Acute infection and myocardial infarction. New England Journal of Medicine. 2019 Jan 10;380(2):171-6.

Outcomes ascertained with diagnostic codes

- Hospitalizations counted in both VHA and non-VHA facilities

- Hospitalizations with a principal discharge diagnosis of:
  1. Cardiovascular disease (ICD-9: 390-459; ICD10: I)
  2. Respiratory disease (ICD-9: 460-519; ICD 10: J)
  3. Either cardiovascular or respiratory disease (ICD-9: 390-519; ICD10: I-J)
  4. Urinary tract infection (ICD-9: 599; ICD-10: N39) *as a falsification test*

Residual bias adjusted with Instrumental Variable (IV)

- 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

Baseline characteristics look similar

	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%

High-dose associated with reduced hospitalizations

compared to standard-dose

Hospitalization	IV adjusted rVE[1]	ARR[2]
Cardiovascular	14% (7% - 20%)	0.012
Respiratory	15% (5% - 25%)	0.007
Either cardio or respiratory	14% (8% - 19%)	0.018
Urinary tract infection	-5% (-34% : 18%)	

1. rVE: relative vaccine effectiveness; point estimate and 95% confidence interval
2. ARR: absolute risk reduction; point estimate

High-dose associated with net cost savings

compared to standard-dose

Hospitalization	Cost[1]	NNS[2]	Net Savings[3]
Cardiovascular	12,490	84 (59 - 160)	22M (11M - 32M)
Respiratory	10,499	144 (89 - 473)	10M (2M - 17M)
Either cardio or respiratory	11,796	55 (40 - 93)	32M (18M - 44M)

1. Cost of one hospitalization; average
2. NNS: number needed to switch from SD-IIV3 to HD-IIV3 to prevent one hospitalization; point estimate and 95% confidence interval
3. Net savings: cost avoided due to hospitalizations prevented - incremental cost of HD-IIV3 vaccine (over 5 influenza seasons in millions of US dollars)

Limitations

- VHA cost and Medicare reimbursed insurance claims have a different cost-basis and are difficult to reconcile
- Limited generalizability: VHA population is predominantly male, is older and has more comorbid conditions than the average US population
- IV adjustment assumes no direct association between instrument and outcome, which can't be directly observed in the data. Result of falsification test suggests IV is specified correctly.

Conclusions

- In the US VHA population, a reduction in hospitalizations for CVD over five influenza seasons contributed more cost savings (per high-dose recipient) than the reduction in hospitalizations for respiratory disease
- Similar to other (randomized) studies, high-dose influenza vaccine is associated with cost savings due to additional prevented hospitalizations compared to standard-dose vaccine

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