Impact of High-Dose vs Standard-Dose Influenza Vaccine on Respiratory-Related Hospitalizations: A Fuzzy Regression Discontinuity Design

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Introduction

Influenza causes significant morbidity and mortality in the US.[1] The high-dose (HD) vaccine has 4x more antigen than the standard-dose (SD) vaccine and is approved for adults ages ≥65. The HD vaccine decreased influenza infections and hospitalizations in clinical trials.[2] The HD vaccine is twice the cost of the SD vaccine, but several studies have demonstrated this use is cost-effective.[3-4] Off-label use of the HD vaccine occurs, but outcomes haven't been described.[6] The objective of this study was to determine if the HD vaccine has similar clinical benefits in adults <65 vs older adults.

Methods

Study Design - Fuzzy Regression Discontinuity Design: This was a retrospective cohort study of patients who received the SD vs HD influenza vaccine. A fuzzy regression discontinuity design estimated the causal effect of the HD vaccine on influenza and respiratory hospitalizations. This design takes advantage of the discontinuity in likelihood of receiving the HD vaccine at age 65 to compare the outcomes of adults immediately above and below age 65.

Data Source: This study used the IQVIA PharMetrics® Plus for Academics, which is provides access to ~10 million patients in a nationally representative claims database. Vaccines were identified using CPT or GPI codes, and outcomes and covariates were identified using ICD9/ICD10 codes.

Setting and Definitions: Each influenza season was defined as September 1 – May 31. Influenza seasons from 2012-2018 were included, thus one individual could be in this dataset up to 7 times. Individuals were followed for outcomes from the date of vaccination to the end of the season (May 31).

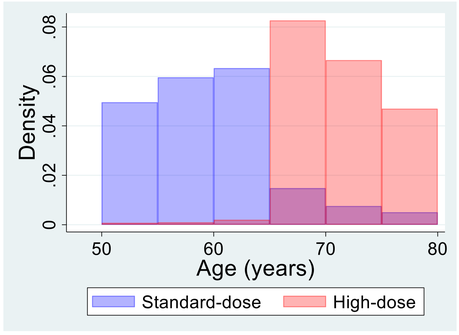
Inclusion Criteria	Exclusion Criteria
• ≥50 years old • Vaccinated from Sept 1 – Dec 31 • Continuous enrollment from June 1 to the end of the season.	• >1 influenza vaccine in a season • Vaccinated during a hospital stay • Hospitalization from June 1 until vaccination

Outcomes: The primary outcome was influenza- or respiratory-related hospitalization. Secondary outcomes were all-cause hospitalization, ER visits, flu infections, oseltamivir (Tamiflu®) use.

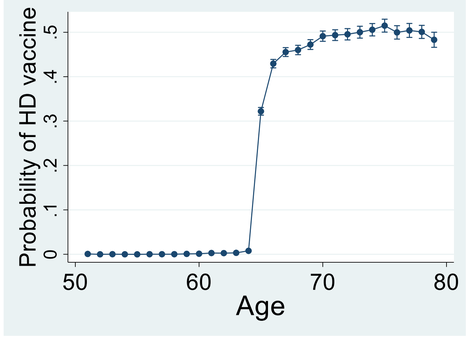
Analysis: The age threshold is an instrumental variable (IV) for receipt of the HD flu vaccine. This model was estimated using Two-Stage Residual Inclusion (2SRI) equations.

Results

Use of the HD vaccine is more common in older adults.



The marginal effect of age on the adjusted probability of receiving the HD vaccine jumps at age 65.



Checking instrument validity: Age 65 is an appropriate instrumental variable. (F>20 indicates a strong instrument)

First-stage regression summary statistics

Variable	R-sq.	Adjusted R-sq.	Partial R-sq.	Robust F(1,220178)	Prob > F
vaxtype	0.4707	0.4707	0.1112	12502.3	0.0000

Table 1. Demographics and outcomes by age-group

	Ages 50-64 (n=288,696)	Ages 65-80 (n=95,484)	Difference (65+ - <65)
Influenza/ Respiratory Hospitalization, %	1	3	2
HD vaccine, %	0.3	52	51
Age, years, mean	57	71	14
Male, %	43	45	3
Region, %			
• East	28	33	5
• Midwest	30	26	(4)
• South	21	9	(11)
• West	21	33	12
Payer type, %			
Commercial	86	40	(46)
Medicaid	11	3	(8)
Medicare	1	55	(54)
Unknown	3	1	(2)
CCI, median	0	1	1
CLD, %	6	7	1
DM, %	16	22	6
CVD, %	29	45	16

All results statistically significant at <0.001. HD = high-dose CCI = Charlson Comorbidity Index; CLD = Chronic lung disease; DM = Diabetes mellitus; CVD = Cardiovascular disease.

Table 2. Marginal Effects of Covariates on Influenza/ Respiratory Hospitalization[a]

Covariates	Average marginal effect (SE)	P-value	95% CI
HD vaccine	-0.005 (0.002)[c]	0.003	-0.005, -0.002
Age	0.001 (0.000)	<0.001	0.001, 0.002
CLD	0.022 (0.001)	<0.001	0.021, 0.023
DM	-0.001 (0.001)	0.015	-0.002, -0.001
CVD	0.005 (0.001)	<0.001	0.004, 0.006
CCI	0.004 (0.000)	<0.001	0.004, 0.005
Male	0.002 (0.001)	<0.001	0.001, 0.003
Payer type[b]			
• Medicaid	0.011 (0.001)	<0.001	0.009, 0.012
• Medicare	0.005 (0.001)	<0.001	0.004, 0.007
• Unknown	0.001 (0.001)	0.780	-0.002, 0.003
Residual	0.004 (0.002)	0.020	0.001, 0.008

[a] Model additionally controlled for year and region. [b] Reference group is commercial. [C] SE for primary outcome calculated via bootstrapping. SE = standard error; CI = Confidence interval

Strengths & Limitations

- The primary model was robust to various sensitivity checks including different specifications of the relationship between the running variable and the primary outcome.
- This data was originally collected for insurance claims purposes, and thus some information may be inaccurate due to errors in the billing process
- Additional data variables were unavailable from this data source including death records, race, and medications administered while inpatient.

Conclusions

- The results of this study demonstrate that the HD vaccine reduces the probability of an influenza or respiratory hospitalization by 0.5% points compared to the SD vaccine for adults who received the HD vaccine because of their age group.
- HD influenza vaccine my similarly improve outcomes in young adults
- Insurance companies should consider expanding coverage of the HD vaccine to adults ages 50-64, especially those with comorbid conditions
- Future research is needed to establish the most cost-effective approach to influenza vaccination among adults younger than 65.

References: 1. Centers for Disease Control and Prevention. Influenza (Flu). (2020). Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention. https://www.cdc.gov/flu/index.htm. 2. DiazGranados CA, Dunning AJ, Kimmel M, et al. Efficacy of high-dose versus standard-dose influenza vaccine in older adults. New England Journal of Medicine. 2014;371(7):635-645. 3. Raviotta JM et al. Cost-effectiveness and public health effect of influenza vaccine strategies for US Elderly Adults. 2016. 4. Raviotta JM et al. Cost-effectiveness and public health impact of alternative influenza vaccination strategies in high-risk adults. 2017. 5. McGrath LJ, Brookhart MA. On-label and off-label use of high-dose influenza vaccine in the United States, 2010-2012. Hum Vaccin Immunother. 2015;11(3):537-544.