How might a decision aid inform a real-world example?

Zostavax Vaccine Effectiveness and Duration of Effectiveness Project*

Hector S. Izurieta, MD, MPH (OBE/CBER/FDA)
On behalf of the CBER-FDA/CMS/ACUMEN team

Examining the Impact of Real-world Evidence on Medical Product Development
Workshop three, session 5
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National Academy of Sciences building, Lecture room

*Izurieta et al, CID 2017

Disclaimer

My comments and contributions are an informal communication and represent my own best judgment. These comments do not bind or obligate FDA.

Zostavax vaccine effectiveness project: Population and outcomes

- Objective:
  - Analyze Zostavax (Herpes Zoster (HZ) vaccine live) effectiveness and duration of effectiveness during 2007-14
- Study Population
  - Medicare beneficiaries vaccinated with HZ vaccine compared with unvaccinated beneficiaries
- Outcomes:
  - HZ and ophthalmic zoster medical office visits
  - Post-herpetic neuralgia (PHN)
  - HZ hospitalization

Izurieta et al, CID 2017

Analytical approach

- After matching:
  - Used Cox regression models to estimate HZ and PHN risks in vaccinees compared with the unvaccinated population
  - Adjusted for main known characteristics
  - Risk measured at different time intervals assuming duration of vaccine protection varies over time

Using the decision aid: Can we trust inference from this study?

- Clinical and epidemiologic justification
- Has the study been registered? Which regulatory agencies have examined the protocol?
- How can reporting be structured to enable replication?
- Balance after matching/weighting?
  - Display a plot of propensity score distributions
  - Justify weighting methods if used
  - Provide covariate balance tables before and after matching
- After matching, do cohorts appear to represent clinically meaningful groups ? Has utility/generalizability been sacrificed?
- Specific unmeasured confounder thought to be influential? Is there a supplemental way to measure this confounder? Can sensitivity analyses be designed to examine its influence?

Appropriate balance between cohorts?

- To achieve balance, we adopted approach by Rubin and Thomas (2000) with combination of propensity scores and Mahalanobis metric matching

- This allowed us to adjust for heterogeneity between vaccinees and controls using broad list of covariates plausibly related to herpes zoster, while generating cohorts closely matched on a subset of key covariates

Matching variables

- Broad list of variables:
  - Demographic factors
  - Socio-economic conditions
  - Healthcare utilization characteristics
  - Frailty characteristics
  - Functional immunocompromising chronic conditions
- Key covariates matched using Mahalanobis distance:
  - Age
  - Gender
  - Race
  - Low income subsidy

Matching process

- For each herpes zoster vaccinee, a set of control beneficiaries were found whose propensity scores fell within an acceptable range, or ‘caliper’ of the herpes zoster vaccine

- Among these beneficiaries, 1 herpes zoster vaccinee was matched to 1 control with the minimum Mahalanobis distance from the vaccinee

- Standardized mean difference (SMD) statistics and falsification outcomes (negative endpoints) were used to assess cohort balance

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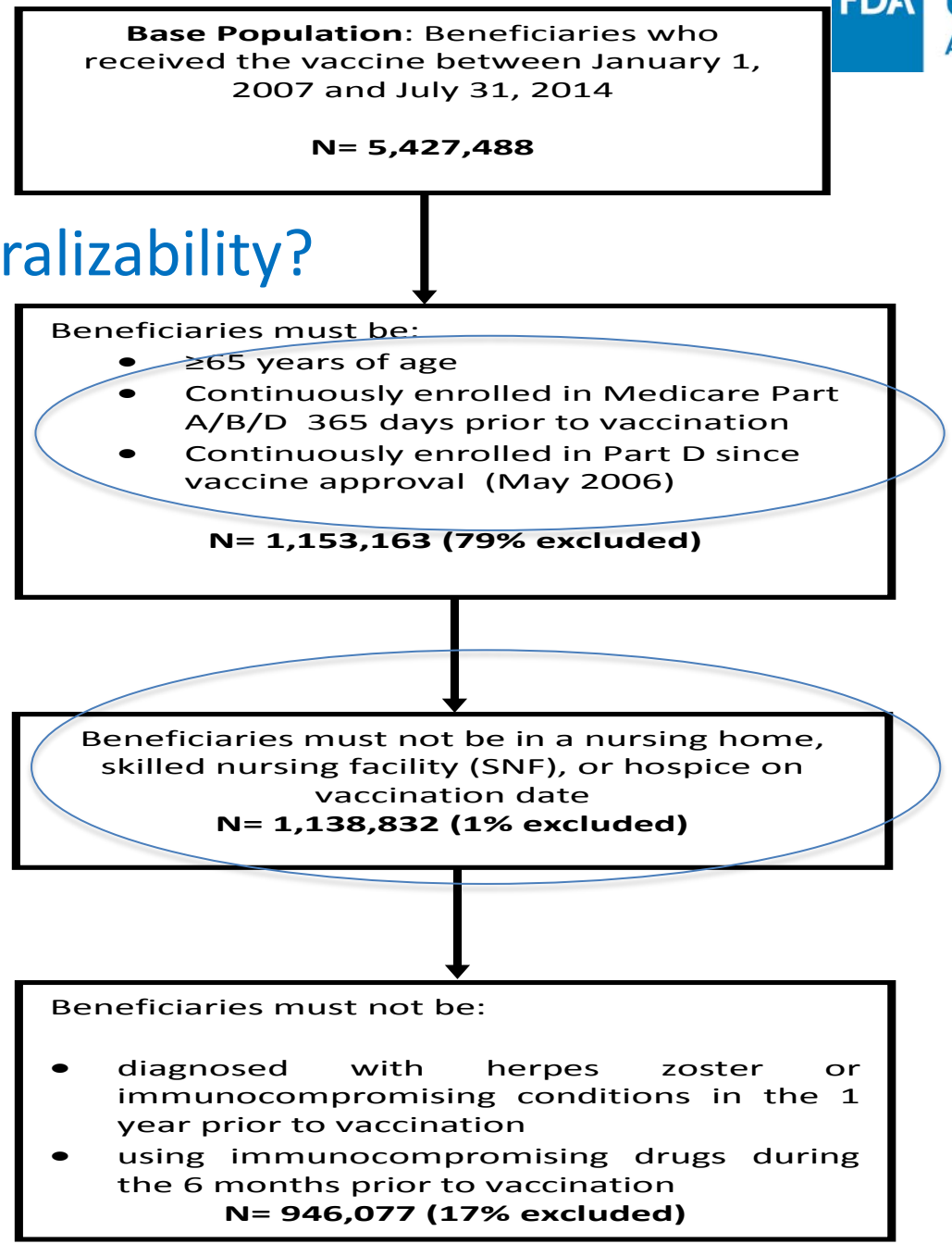
Sacrificed utility/generalizability?

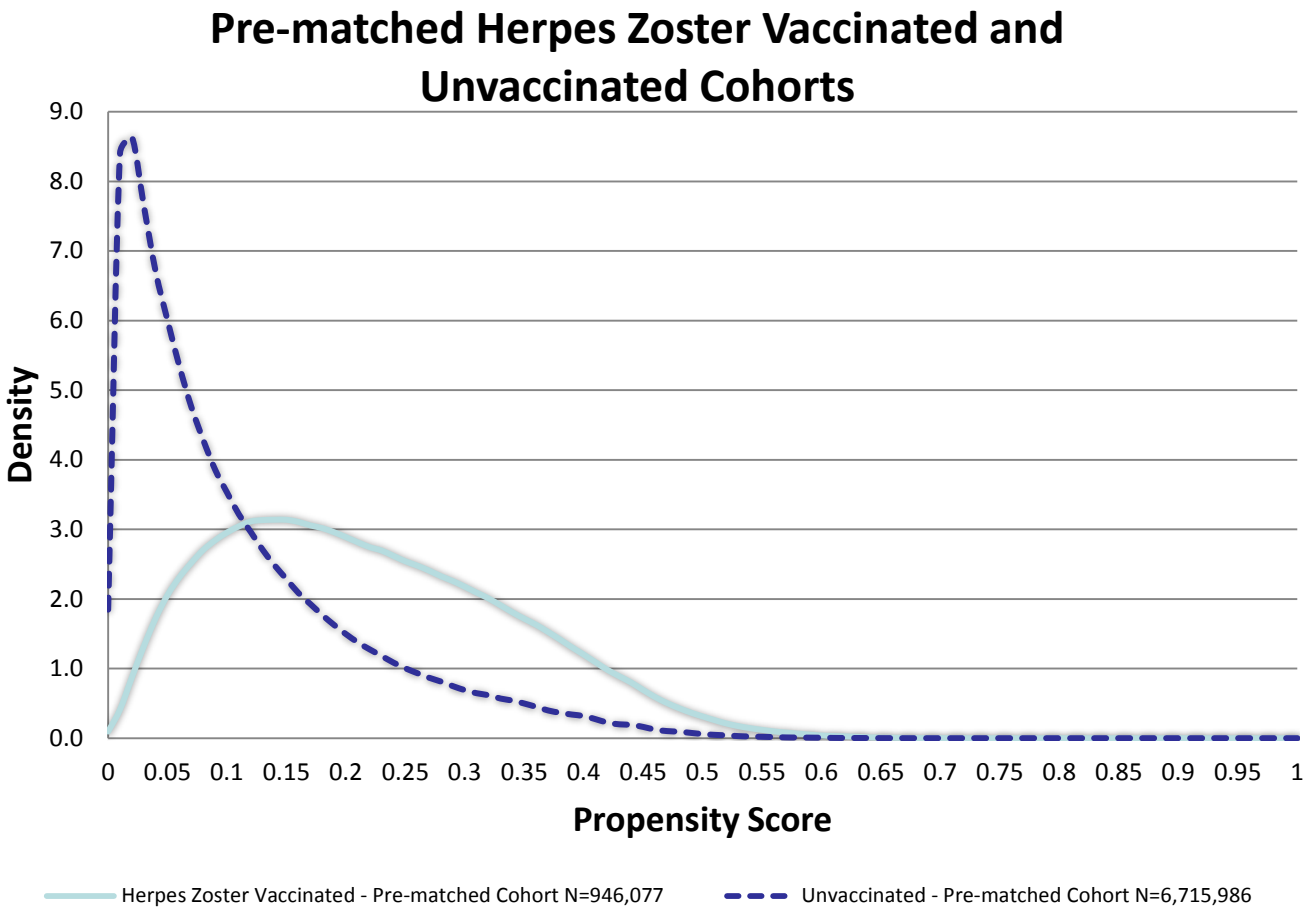


..approx. 89% of subjects ≥70 years-old..

Sacrificed utility/generalizability?

- The post-matching cohorts permit evaluation of the average treatment effect on the treated (i.e. vaccinated) population (ATT), but not the average treatment effect on the overall population (ATE)
- The number of eligible beneficiaries dropped from the study during the matching step in each cohort:
  - Vaccinated: 85 beneficiaries dropped (<1% of cohort)
  - Unvaccinated: 5,769,994 beneficiaries dropped (86% of cohort)

Propensity Score Distribution Pre-Matching

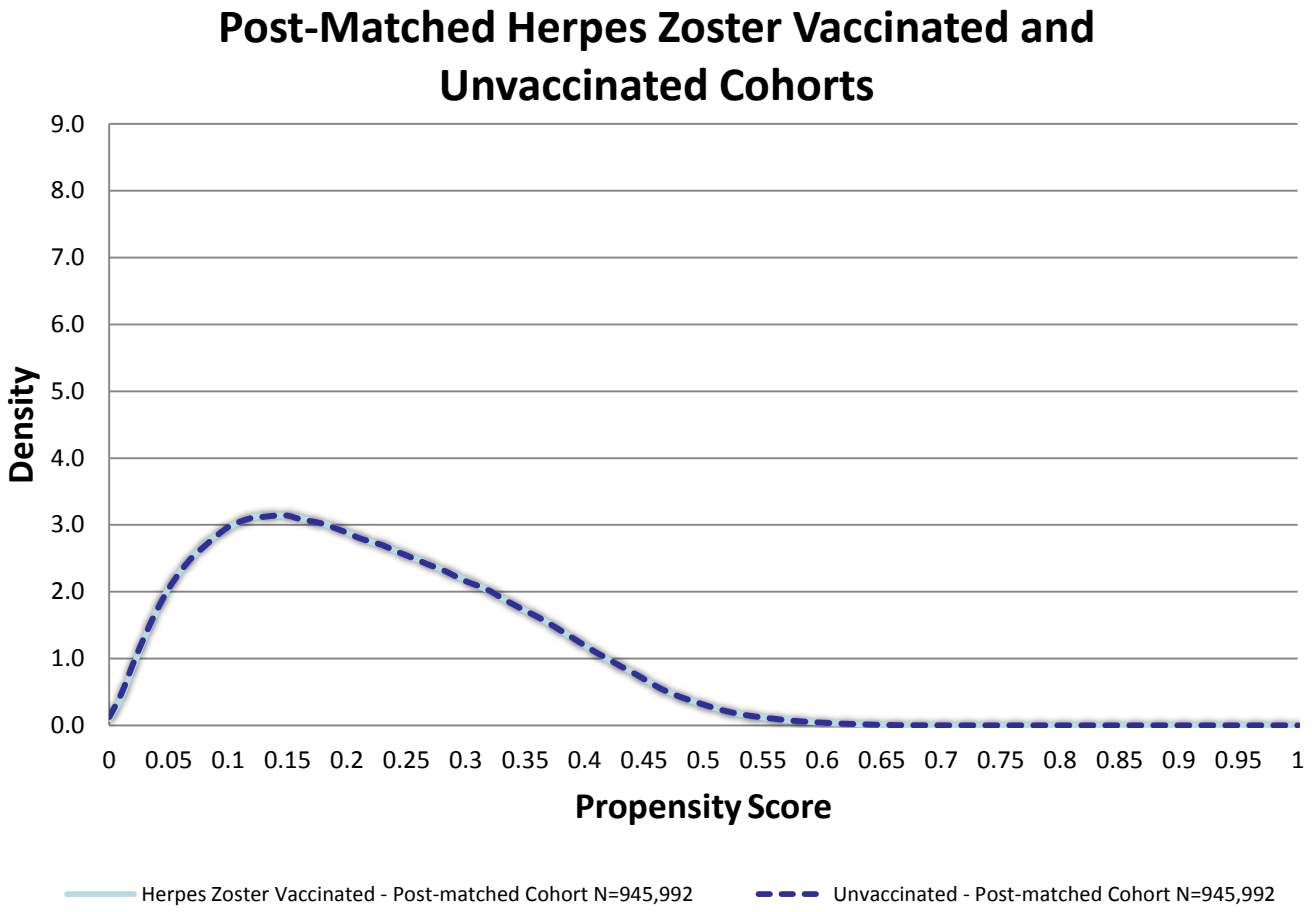


Cohort Balance Pre-Matching: Primary Population

Demographic Variables	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**946,077**	**6,715,986**	
Age (Continuous)			
Mean	76.61	78.06	0.21
SD	6.15	7.58	
Age (Categories)			
65-69	106,175 11%	923,193 14%	0.08
70-74	292,409 31%	1,574,338 23%	0.17
75-79	262,863 28%	1,508,504 22%	0.12
80-84	172,307 18%	1,275,867 19%	0.02
85-89	84,236 9%	879,397 13%	0.13
90-94	24,194 3%	420,045 6%	0.18
95-99	3,628 0%	116,978 2%	0.13
100+	265 0%	17,664 0%	0.06
Gender			
Male	316,749 33%	2,426,752 36%	0.06
Female	629,328 67%	4,289,234 64%	0.06
Race			
White	850,089 90%	5,390,931 80%	0.27
Black	22,086 2%	722,205 11%	0.35
Asian	44,649 5%	207,048 3%	0.08
Hispanic	10,905 1%	256,832 4%	0.17
Other	18,348 2%	138,970 2%	0.01
Low-Income Subsidy Status			
Receives LIS	205,438 22%	2,731,085 41%	0.42
No LIS	740,639 78%	3,984,901 59%	0.42

- Covariates were not so well balanced prior to matching

Propensity Score Distribution Post-Matching



Cohort Balance Post-Matching: Primary Population

Post-Matching Statistics

Demographic Variables	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**945,992**	**945,992**	
Age (Continuous)			
Mean	76.61	76.60	0.00
SD	6.15	6.15	
Age (Categories)			
65-69	106,167 11%	106,077 11%	0.00
70-74	292,343 31%	292,606 31%	0.00
75-79	262,853 28%	262,935 28%	0.00
80-84	172,306 18%	172,203 18%	0.00
85-89	84,236 9%	84,174 9%	0.00
90-94	24,194 3%	24,149 3%	0.00
95-99	3,628 0%	3,599 0%	0.00
100+	265 0%	249 0%	0.00
Gender			
Male	316,743 33%	316,545 33%	0.00
Female	629,249 67%	629,447 67%	0.00
Race			
White	850,032 90%	850,118 90%	0.00
Black	22,086 2%	22,068 2%	0.00
Asian	44,621 5%	44,581 5%	0.00
Hispanic	10,905 1%	10,895 1%	0.00
Other	18,348 2%	18,330 2%	0.00
Low-Income Subsidy Status			
Receives LIS	205,410 22%	205,349 22%	0.00
No LIS	740,582 78%	740,643 78%	0.00

Cohort Balance, Health variables, Post-matching

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Demographic Variables	Vaccinated		Unvaccinated[a]		Austin Std. Diff[b]
Base Population	945,992		945,992		
Hospital Visits					
1	96,593	10%	97,966	10%	0.00
2+	34,458	4%	34,559	4%	0.00
ER Visits					
0	765,417	81%	764,715	81%	0.00
1	131,875	14%	132,528	14%	0.00
2+	48,700	5%	48,749	5%	0.00
Physician Office Visits					
0-4	153,886	16%	152,646	16%	0.00
5-10	285,905	30%	287,462	30%	0.00
11-20	291,555	31%	291,723	31%	0.00
21-30	120,457	13%	120,359	13%	0.00
31+	94,189	10%	93,802	10%	0.00
Medical Conditions					
Diabetes	274,517	29%	280,717	30%	0.01
Kidney Disease	86,690	9%	88,333	9%	0.01
Heart Disease	263,650	28%	266,710	28%	0.01
Lung Disease	195,309	21%	197,762	21%	0.01
Liver Disease	14,889	2%	14,828	2%	0.00

After matching, the propensity score distributions of the vaccinated and unvaccinated cohorts were nearly identical

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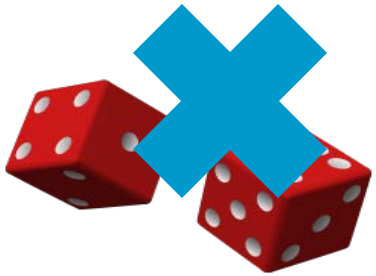
Unmeasured confounders

How we addressed them in the published study?



Addressing health seeking behavior and other bias

- HZV vaccinees might differ from non-vaccinees in their ability/desire to seek care for HZ

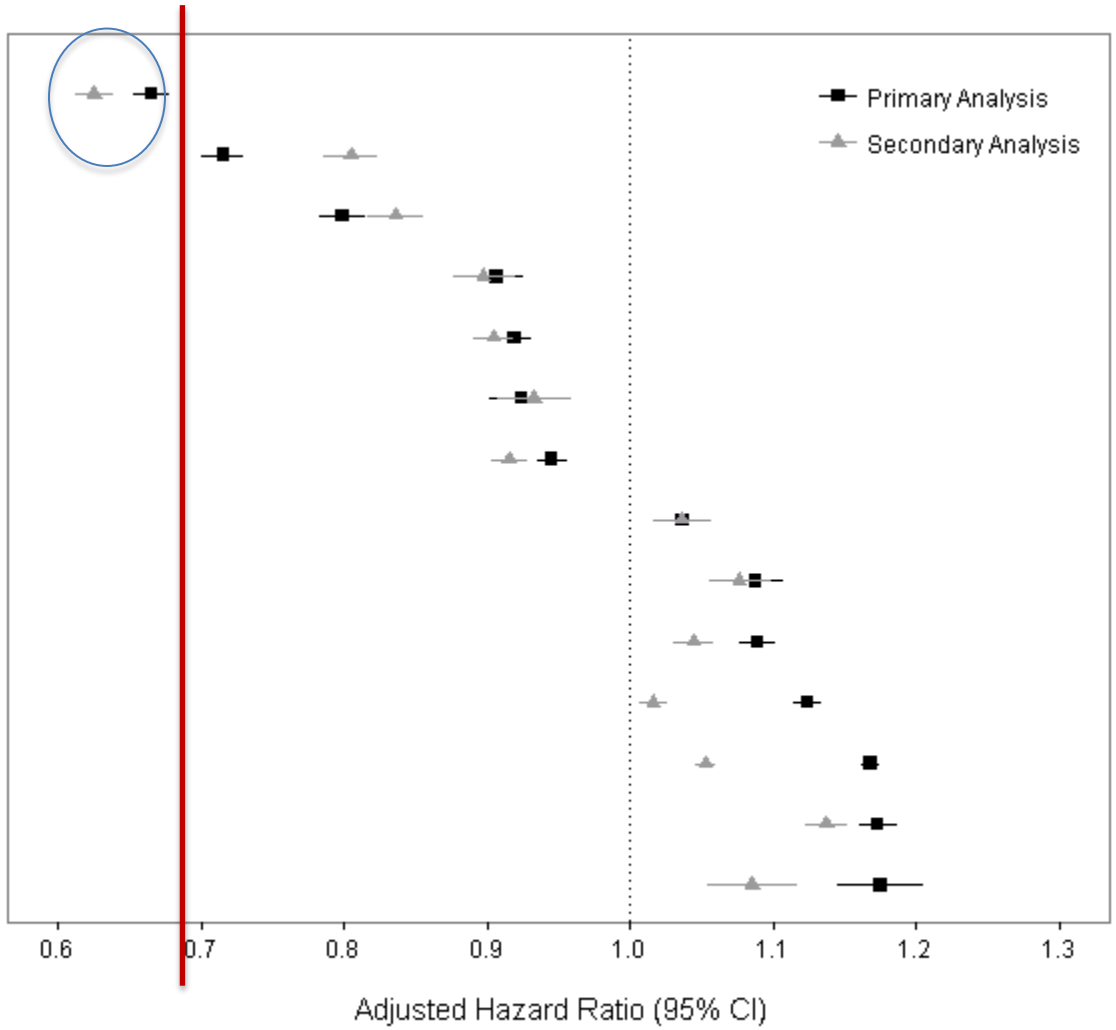
- Besides the primary analysis (comparison between HZ vaccinees and an unvaccinated cohort) we included:
  - Secondary analysis comparing HZ vaccinees with individuals who received other vaccines (pneumococcal)
  - Added a case definition requiring antiviral treatment

- As a test, we used falsification outcomes (negative endpoints) believed to be unrelated to HZ (Tseng et al, JAMA 2011)

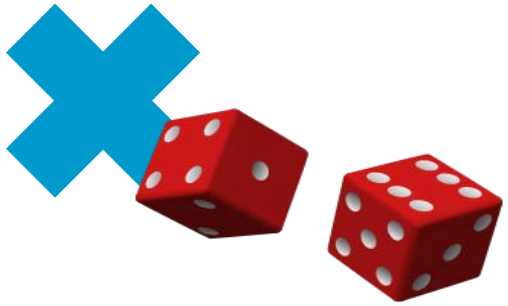
Testing balance with 13 falsification outcomes

Comparison of Adjusted Hazard Ratios of 13 Falsification Outcomes in Matched Populations

Outcome	Primary	Secondary
Outpatient Herpes Zoster*	0.67	0.63
Hip fracture	0.72	0.80
Thrombosis	0.80	0.84
Cholelithiasis and cholecystitis	0.91	0.90
Renal stone	0.92	0.90
Wrist fracture	0.92	0.93
Gout	0.95	0.92
Epistaxis	1.04	1.04
Wound of hand or finger	1.09	1.08
Ingrown nail	1.09	1.04
Hemorrhoids	1.12	1.02
Cataract	1.17	1.05
Eyelid disorder	1.17	1.14
Lipomas	1.17	1.09



Primary Analysis: This is the comparison between herpes zoster vaccinated and unvaccinated beneficiaries. Unvaccinated beneficiaries are the reference group.
Secondary Analysis: This is the comparison between herpes zoster vaccinees and pneumococcal vaccinees. Pneumococcal vaccinees are the reference group.
* The hazard ratio in the first 3 years of follow-up.



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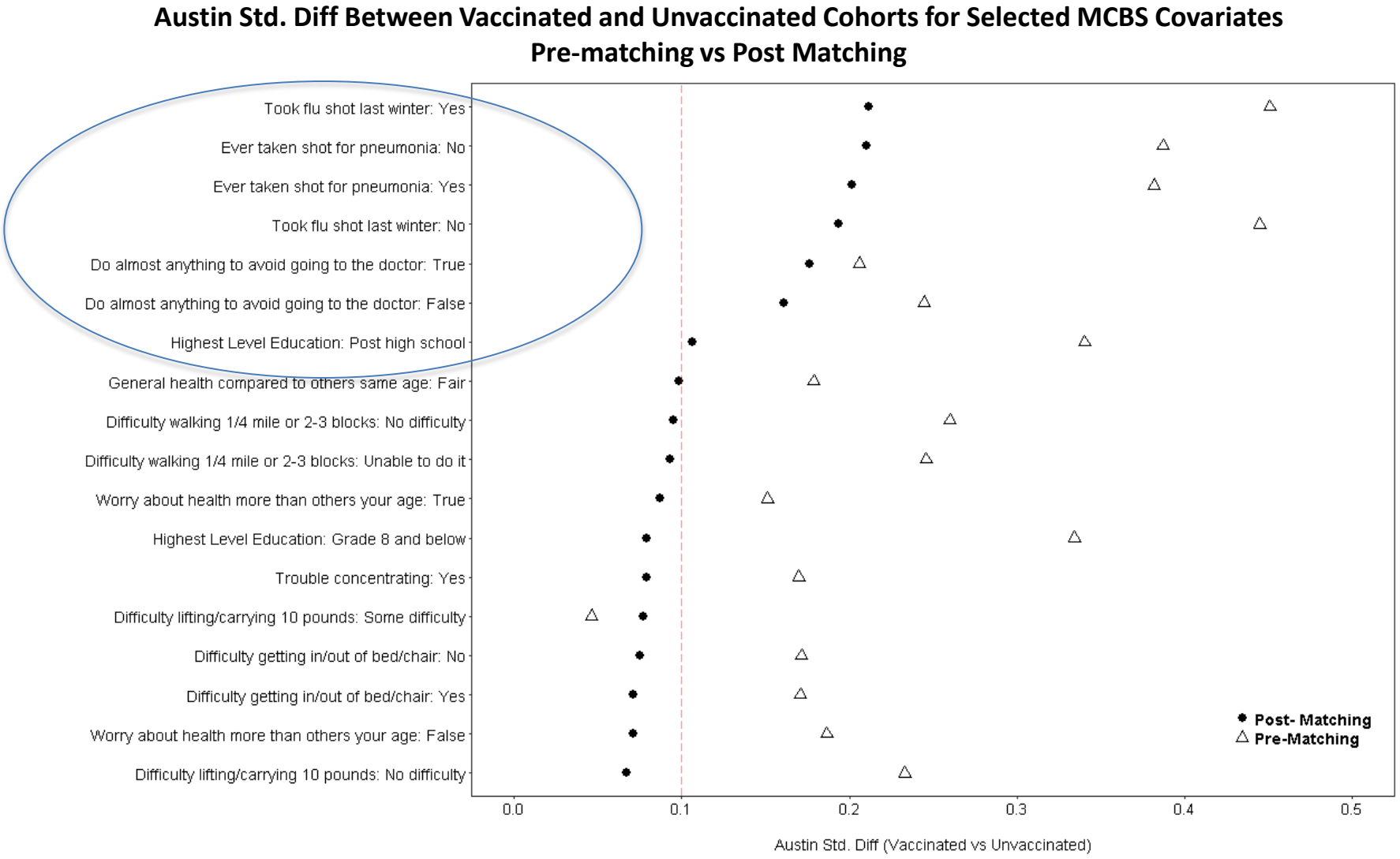
Has something been done since publication to detect/decrease bias….?

Can we assess cohort balance for covariates absent from the database?

Introducing the Medicare Current Beneficiary Survey (MCBS)

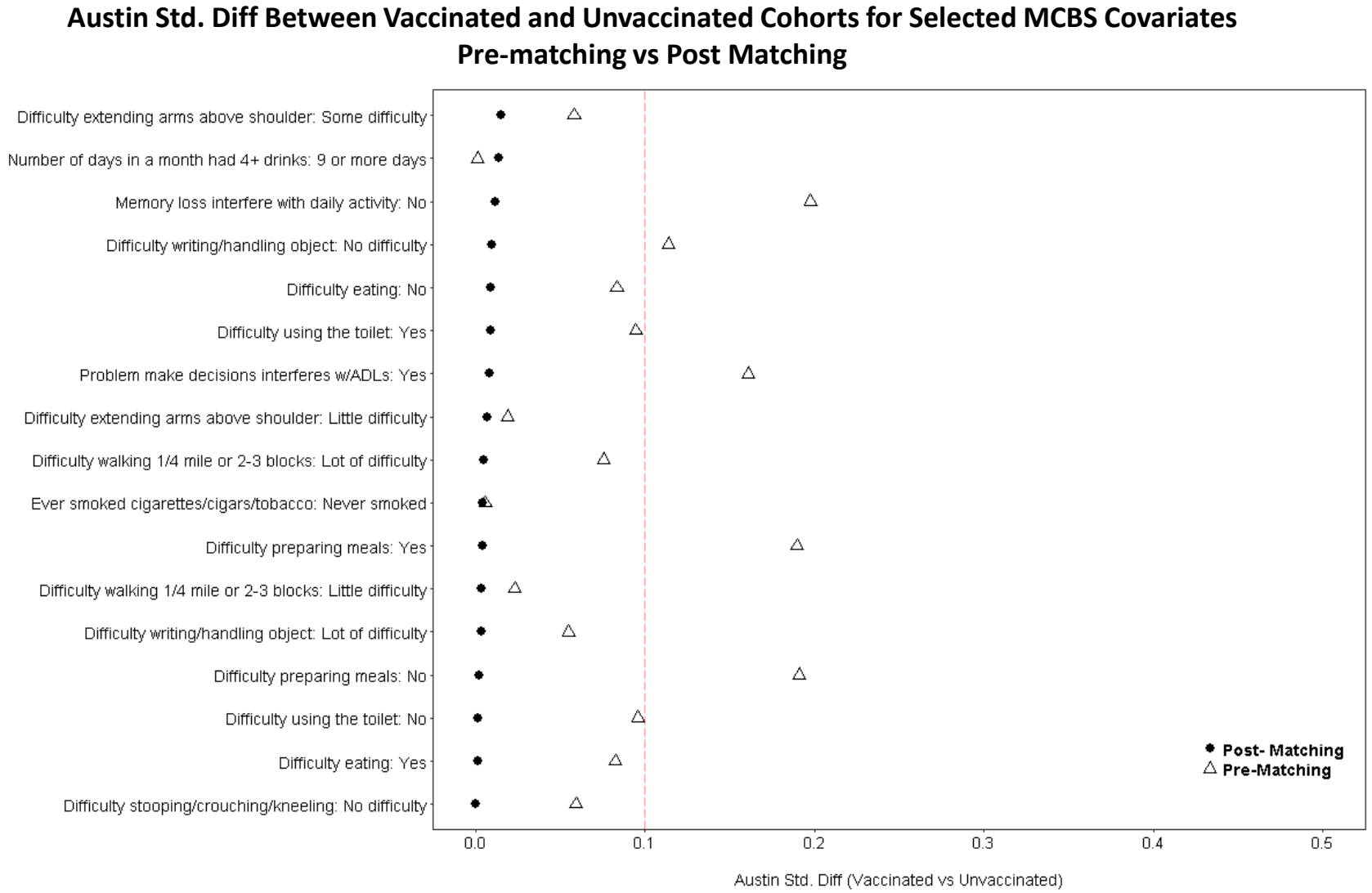
- MCBS is a representative survey of a small subset of the Medicare beneficiaries (oversampled the disabled and the very old)
- Includes data on many unmeasured confounders: health seeking behavior, frailty, education
- Can be linked to Medicare health claims

Cohort comparison, primary analysis population linked to MCBS Data: MCBS Covariate Match (1)



Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

Cohort comparison, primary analysis population linked to MCBS Data: MCBS Covariate Match (5)



Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

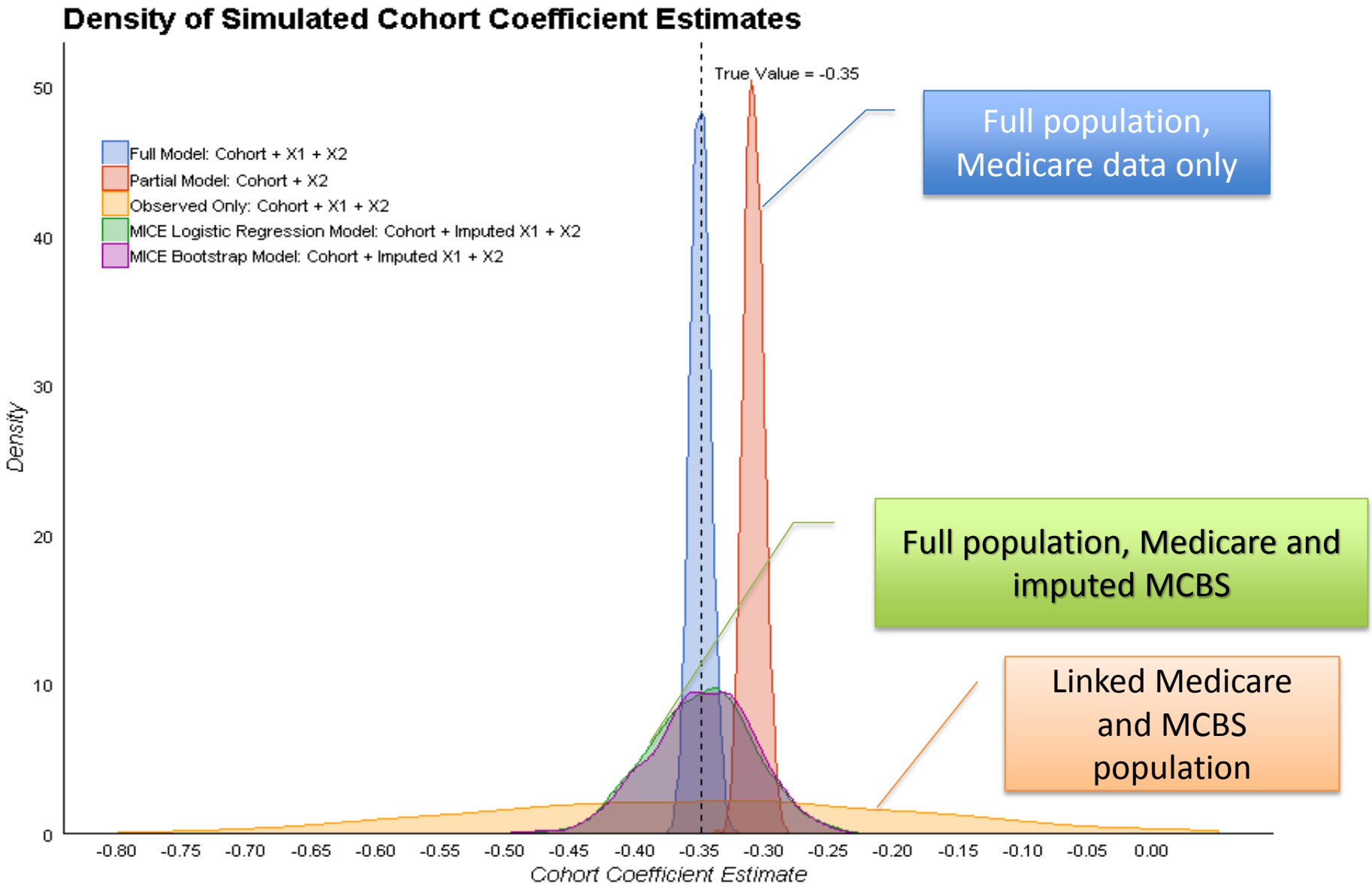
Could we use multiple imputation here???

- We piloted an approach to augment Medicare claims with data from the MCBS
- The missing variables in the non-MCBS subjects can be considered as missing at random (MAR)
- We explored whether multiple imputation could be used to reduce bias associated with variables in MCBS using simulation
- We reanalyzed the populations used in the published FDA analysis after linking them to MCBS

Linked MCBS responses to selected questions to HZ Population

Covariates from MCBS Data	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**1,608**	**1,511**	
Difficulty walking			
Yes	343 21%	352 23%	0.05
No	1,262 78%	1,154 76%	0.05
Data not available	3 0%	5 0%	0.03
Do almost anything to avoid going to the doctor			
True	315 20%	408 27%	0.18
False	1,236 77%	1,054 70%	0.16
Data not available	57 4%	49 3%	0.02
Highest Level Education			
High school or below	835 52%	865 57%	0.11
Post high school	765 48%	639 42%	0.11
Data not available	8 0%	7 0%	0.00

Step 1: Simulation Study



Full population, Medicare data only

Full population, Medicare and imputed MCBS

Linked Medicare and MCBS population

Step 2: Reanalyzed HZV Effectiveness Study after linking to MCBS

- Published HZV office visits effectiveness (primary):
  - 1-3 years of follow up, VE 34% (32% , 35%)
  - 4+ years of follow up, VE 19% (16% , 22%)
- Reanalyzed data after linking MCBS, plus multiple imputation:
  - 1-3 years of follow up, VE 31% (28% , 35%)
  - 4+ years of follow up, VE 16% (11% , 22%)

Note: In the published study (primary analysis), VE (years 1-3) for hospitalized zoster and PHN were, respectively, 74% and 57%. VE for office visits with antiviral prescription (secondary, supplementary), was 46% , obtained similar results with imputed data

Lessons Learned

- The Decision Aid appears useful for helping determine study validity and generalizability
- Unmeasured confounders (health seeking behavior, frailty, others, should be addressed, maybe with:
  - Negative endpoints and other strategies to detect bias
  - Linkages to surveys (e.g. MCBS) to identify/resolve unmeasured confounders
  - Others..
- Regarding MCBS
  - Linkages should not be expected to completely resolve bias
  - Answers can change over time (except for education level)
  - The noise in MCBS health-seeking behavior could be amplified when imputing missing values
  - Bias-variance trade off when linking MCBS w/CMS data

CBER(FDA)/CMS/ACUMEN team collaborators:

FDA: Izurieta Hector S, Forshee Richard, Lu Yun, Pratt Douglas

ACUMEN: Wu Zoe, Chillarige Yoganand, Wernecke Michael,

Lindaas Arnstein, Parulekar Shruti, Javaid Kiran, MaCurdy Thomas

CMS: Kelman Jeffrey

Acknowledgements: Harpaz Rafael (CDC), Wong Sarah, Sun

Qin, Wei Yuqin (ACUMEN)


THANKS

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BACKUP SLIDES

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Testing the use of the "Observational Studies Decision Aid":

Can we trust inference from this observational comparison?

Justification for the comparison

- Millions of seniors are at risk of HZ disease and its complications.
- Zostavax (HZV) reduces HZ risk, although questions regarding effectiveness and durability of protection in routine clinical practice remain
- FDA and CDC decided to perform a study among Medicare beneficiaries ages ≥65 years part D beneficiaries, eligible for HZ vaccination at no cost
- Medicare population representative of the U.S. elderly
- Disease believed to be sufficiently severe to seek care
- HZ vaccinees cohort compared to a one-to-one matched unvaccinated cohort

Was the protocol reviewed? How did the study facilitate replication?

- Study protocol was not made publicly available, although it was reviewed by FDA, CDC and CMS staff
  - *The possibility of registering protocols prior to study initiation is being examined by FDA*
- The study was published in CID*, and the full list of covariates used in the propensity score matching model protocol, as well as the definitions for all medical conditions and prescription drugs used by the study population were published as "Appendix"
- All sensitivity analyses were also published as "Supplementary materials"

* Izurieta et al, CID 2017

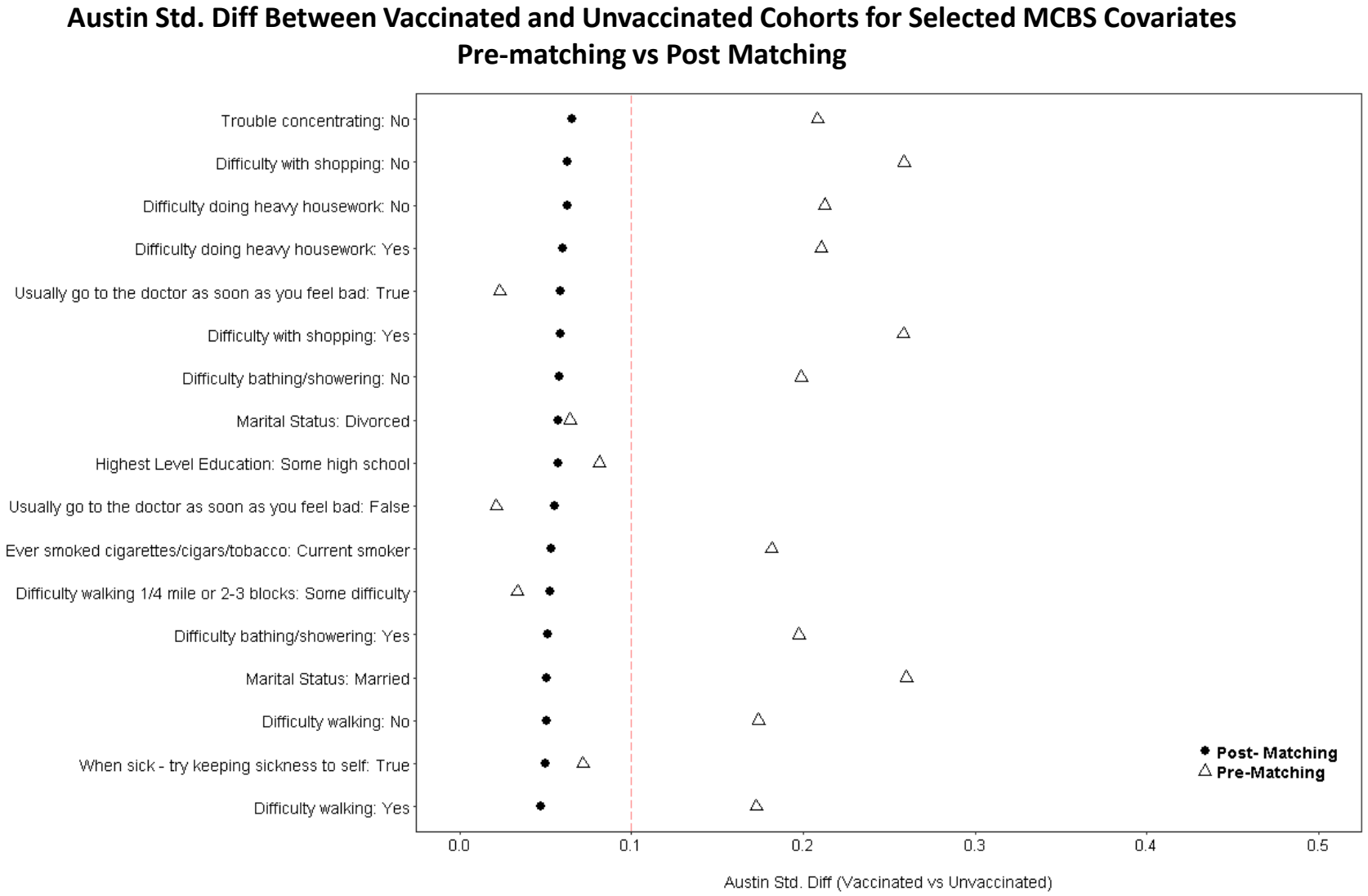
Testing for bias: Falsification outcomes

- As a test, in both the primary (comparison with unvaccinated) and secondary (comparison with pneumococcal vaccinated) study populations, we used falsification outcomes (negative endpoints) believed to be unrelated to HZ
- Calculated hazard ratios for 13 acute symptomatic office visit conditions in the vaccinated and matched cohorts (Tseng et al, JAMA 2011).
  - Hazard ratios expected to cluster around 1.0, on average
  - Deviations from 1.0 would alert us to potential biases

Performed linkages of three MCBS questions

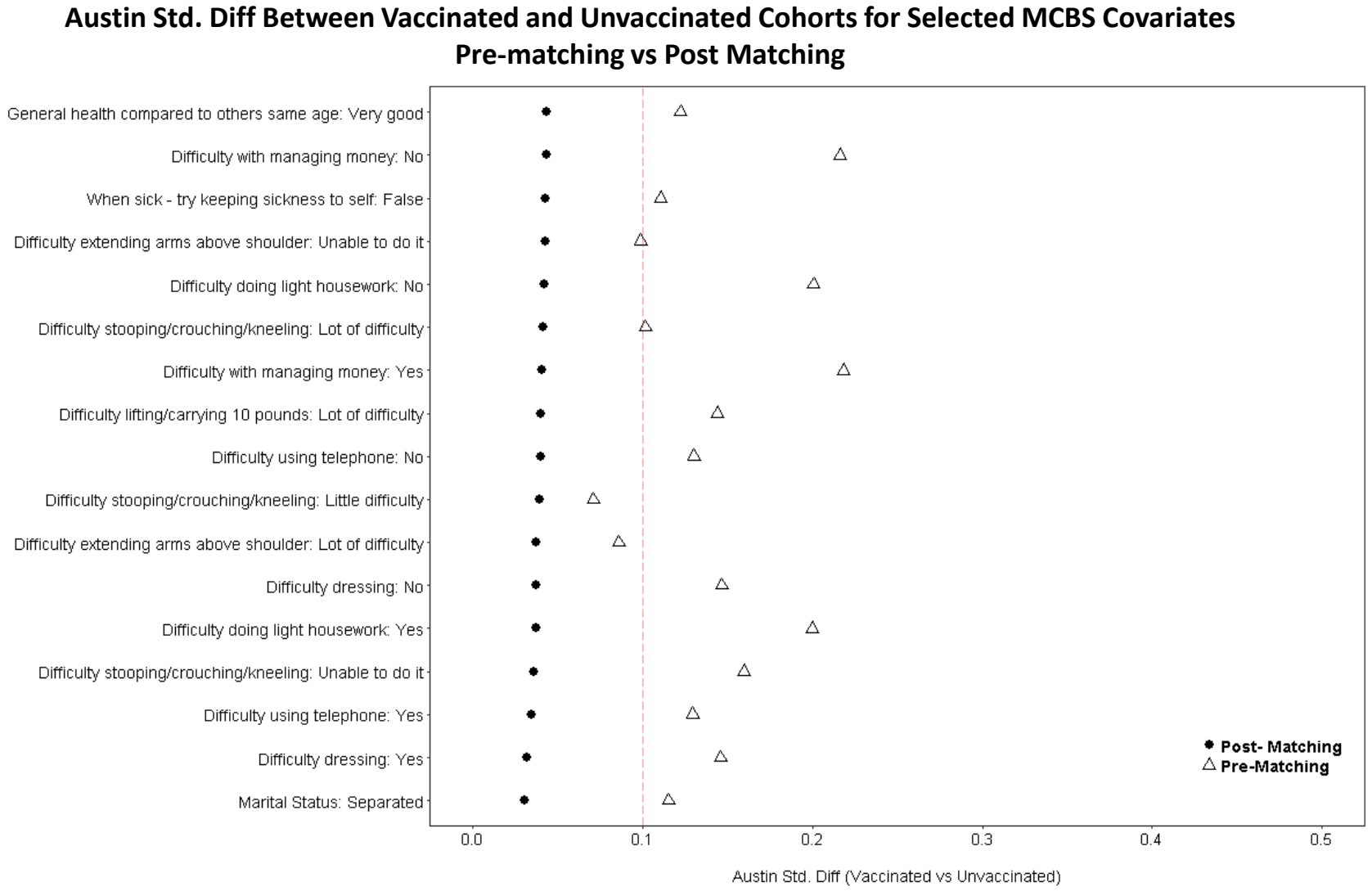
- We linked responses for three MCBS questions for vaccinated and unvaccinated study participants) that had also responded to the survey
- The survey questions chosen were “difficulty walking”, “avoid going to the doctor”, and “post-high school education”, surrogates for being ambulatory, health care seeking
- We conducted multiple imputation for those answers

Cohort comparison, primary analysis population linked to MCBS Data: MCBS Covariate Match (2)



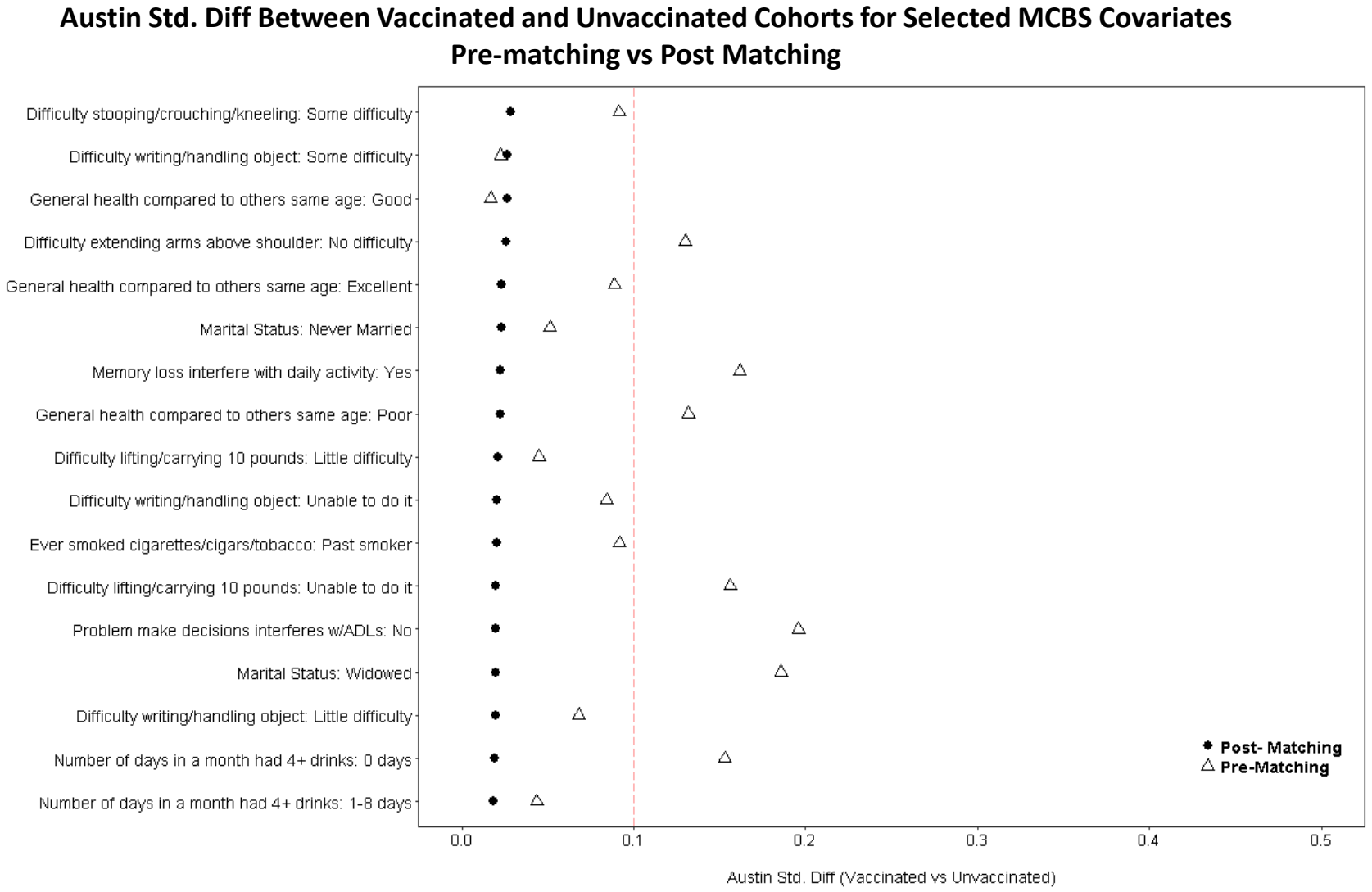
Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

Cohort comparison, primary analysis population linked to MCBS Data: MCBS Covariate Match (3)



Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

Cohort comparison, primary analysis population linked to MCBS Data: MCBS Covariate Match (4)



Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

Potential unmeasured confounders identified using MCBS

- Healthcare seeking behavior
  - Potential different healthcare seeking behavior for people receiving HZV versus unvaccinated people
- Education level
  - Effect on health seeking behaviors?

Beneficiaries use of services compared to their "Health seeking" survey responses

Type of Service	Number of Claims	Response to Health Seeking Behavior Questions in the MCBS Survey								
		Do almost anything to avoid going to the doctor					Go to the doctor as soon as you feel bad			
		False		True		SMD	False		True		SMD
		#Benes	%	#Benes	%		#Benes	%	#Benes	%	
Total Benes (N=12,214)		**8,582**	**100%**	**3,556**	**100%**		**7,443**	**100%**	**4,632**	**100%**	
Hospital Stays	0	7,000	82%	2,939	83%	0.03	6,174	83%	3,711	80%	0.07
	1	1,007	12%	389	11%	0.03	818	11%	573	12%	0.04
	2+	575	7%	228	6%	0.01	451	6%	348	8%	0.06
Outpatient ER Visits	0	6,480	76%	2,529	71%	0.10	5,642	76%	3,317	72%	0.10
	1	1,283	15%	602	17%	0.05	1,115	15%	759	16%	0.04
	2+	819	10%	425	12%	0.08	686	9%	556	12%	0.09
Outpatient Non-ER Visits	0	2,497	29%	1,214	34%	0.11	2,388	32%	1,303	28%	0.09
	1	1,260	15%	534	15%	0.01	1,107	15%	680	15%	0.01
	2+	4,825	56%	1,808	51%	0.11	3,948	53%	2,649	57%	0.08
Physician Visits	0	618	7%	456	13%	0.19	708	10%	363	8%	0.06
	1 -10	3,411	40%	1,638	46%	0.13	3,206	43%	1,823	39%	0.08
	11 - 20	2,256	26%	787	22%	0.10	1,855	25%	1,170	25%	0.01
	21+	2,297	27%	675	19%	0.19	1,674	22%	1,276	28%	0.12
Annual Wellness Visit	0	7,530	88%	3,265	92%	0.13	6,655	89%	4,092	88%	0.03
	1	981	11%	266	7%	0.14	728	10%	505	11%	0.04
	2+	71	1%	25	1%	0.01	60	1%	35	1%	0.01

Appendix

Response Pattern among Beneficiaries Having 4 consecutive Yes or No Responses

Survey Response Pattern				# Beneficiaries Answering the MCBS Question with the Corresponding Pattern									
				Difficulty walking		Do almost anything to avoid going to the doctor		Go to the doctor as soon as you feel bad		Try keeping sickness to self		Worry about health more than others of your age	
1st	2nd	3rd	4th	#	%	#	%	#	%	#	%	#	%
				57,980	**100%**	**42,531**	**100%**	**42,089**	**100%**	**42,091**	**100%**	**41,013**	**100%**
No	No	No	No	32,711	56%	19,760	46%	14,030	33%	13,721	33%	25,447	62%
Yes	Yes	Yes	Yes	6,398	11%	3,798	9%	4,519	11%	5,261	12%	2,724	7%
No	No	No	Yes	2,839	5%	2,081	5%	2,510	6%	2,355	6%	1,579	4%
Yes	No	No	No	2,564	4%	2,737	6%	2,879	7%	2,863	7%	2,244	5%
No	No	Yes	No	1,619	3%	1,878	4%	2,176	5%	2,125	5%	1,316	3%
No	Yes	No	No	1,530	3%	2,002	5%	2,180	5%	2,210	5%	1,398	3%
No	Yes	Yes	Yes	1,437	2%	1,267	3%	1,777	4%	1,606	4%	630	2%
No	No	Yes	Yes	1,397	2%	1,094	3%	1,483	4%	1,332	3%	646	2%
Yes	No	Yes	Yes	1,195	2%	994	2%	1,410	3%	1,461	3%	657	2%
Yes	Yes	Yes	No	1,092	2%	1,241	3%	1,624	4%	1,705	4%	798	2%
Yes	Yes	No	No	1,059	2%	1,295	3%	1,455	3%	1,524	4%	821	2%
Yes	Yes	No	Yes	1,055	2%	972	2%	1,375	3%	1,355	3%	653	2%
Yes	No	No	Yes	934	2%	865	2%	1,222	3%	1,184	3%	621	2%
Yes	No	Yes	No	768	1%	879	2%	1,118	3%	1,150	3%	560	1%
No	Yes	No	Yes	739	1%	751	2%	1,149	3%	1,063	3%	436	1%
No	Yes	Yes	No	643	1%	917	2%	1,182	3%	1,176	3%	483	1%

Cohort comparison, primary analysis population linked to MCBS Data: MCBS Covariate Match (1)

Covariates	Post-Matching			Pre-Matching		
	Vaccinated	Unvaccinated	Austin Std. Diff (Std. Diff > 0.1)	Vaccinated	Unvaccinated	Austin Std. Diff (Std. Diff > 0.1)
Base Population	**1,608**	**1,511**		**1,608**	**12,617**	
ADL						
Difficulty getting in/out of bed/chair						
Yes	153 10%	177 12%	0.07	153 10%	1,906 15%	0.17
No	1,452 90%	1,329 88%	0.08	1,452 90%	10,679 85%	0.17
Data not available	3 0%	5 0%	0.03	3 0%	32 0%	0.01
Difficulty bathing/showering						
Yes	120 7%	134 9%	0.05	120 7%	1,701 13%	0.20
No	1,485 92%	1,371 91%	0.06	1,485 92%	10,880 86%	0.20
Data not available	3 0%	6 0%	0.04	3 0%	36 0%	0.02
Difficulty dressing						
Yes	78 5%	84 6%	0.03	78 5%	1,070 8%	0.15
No	1,527 95%	1,422 94%	0.04	1,527 95%	11,514 91%	0.15
Data not available	3 0%	5 0%	0.03	3 0%	33 0%	0.02
Difficulty using the toilet						
Yes	72 4%	65 4%	0.01	72 4%	837 7%	0.09
No	1,533 95%	1,441 95%	0.00	1,533 95%	11,747 93%	0.10
Data not available	3 0%	5 0%	0.03	3 0%	33 0%	0.02
Difficulty eating						
Yes	29 2%	27 2%	0.00	29 2%	388 3%	0.08
No	1,576 98%	1,479 98%	0.01	1,576 98%	12,197 97%	0.08
Data not available	3 0%	5 0%	0.03	3 0%	32 0%	0.01
Difficulty walking						
Yes	343 21%	352 23%	0.05	343 21%	3,631 29%	0.17
No	1,262 78%	1,154 76%	0.05	1,262 78%	8,952 71%	0.17
Data not available	3 0%	5 0%	0.03	3 0%	34 0%	0.02

Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

MCBS Covariate Match (2)

Covariates	Post-Matching			Pre-Matching		
	Vaccinated	Unvaccinated	Austin Std. Diff (Std. Diff > 0.1)	Vaccinated	Unvaccinated	Austin Std. Diff (Std. Diff > 0.1)
Base Population	**1,608**	**1,511**		**1,608**	**12,617**	
IADL						
Difficulty doing heavy housework						
Yes	452 28%	466 31%	0.06	452 28%	4,790 38%	0.21
No	1,153 72%	1,040 69%	0.06	1,153 72%	7,789 62%	0.21
Data not available	3 0%	5 0%	0.03	3 0%	38 0%	0.02
Difficulty doing light housework						
Yes	135 8%	143 9%	0.04	135 8%	1,863 15%	0.20
No	1,470 91%	1,363 90%	0.04	1,470 91%	10,722 85%	0.20
Data not available	3 0%	5 0%	0.03	3 0%	32 0%	0.01
Difficulty preparing meals						
Yes	109 7%	101 7%	0.00	109 7%	1,556 12%	0.19
No	1,496 93%	1,405 93%	0.00	1,496 93%	11,026 87%	0.19
Data not available	3 0%	5 0%	0.03	3 0%	35 0%	0.02
Difficulty with managing money						
Yes	69 4%	78 5%	0.04	69 4%	1,243 10%	0.22
No	1,535 95%	1,428 95%	0.04	1,535 95%	11,336 90%	0.22
Data not available	4 0%	5 0%	0.02	4 0%	38 0%	0.01
Difficulty using telephone						
Yes	86 5%	93 6%	0.03	86 5%	1,091 9%	0.13
No	1,519 94%	1,413 94%	0.04	1,519 94%	11,494 91%	0.13
Data not available	3 0%	5 0%	0.03	3 0%	32 0%	0.01
Difficulty with shopping						
Yes	151 9%	169 11%	0.06	151 9%	2,300 18%	0.26
No	1,454 90%	1,337 88%	0.06	1,454 90%	10,284 82%	0.26
Data not available	3 0%	5 0%	0.03	3 0%	33 0%	0.02

Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

MCBS Covariate Match (3)

Covariates	Post-Matching			Pre-Matching		
	Vaccinated	Unvaccinated	Austin Std. Diff	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**1,608**	**1,511**	**(Std. Diff > 0.1)**	**1,608**	**12,617**	**(Std. Diff > 0.1)**
Functional Limitations						
Difficulty stooping/crouching/kneeling						
No difficulty	444 28%	417 28%	0.00	444 28%	3,155 25%	0.06
Little difficulty	407 25%	357 24%	0.04	407 25%	2,812 22%	0.07
Some difficulty	342 21%	304 20%	0.03	342 21%	2,228 18%	0.09
Lot of difficulty	257 16%	265 18%	0.04	257 16%	2,508 20%	0.10
Unable to do it	155 10%	162 11%	0.04	155 10%	1,875 15%	0.16
Data not available	3 0%	6 0%	0.04	3 0%	39 0%	0.02
Difficulty walking 1/4 mile or 2-3 blocks						
No difficulty	957 60%	828 55%	0.10	957 60%	5,885 47%	0.26
Little difficulty	186 12%	173 11%	0.00	186 12%	1,553 12%	0.02
Some difficulty	147 9%	162 11%	0.05	147 9%	1,279 10%	0.03
Lot of difficulty	132 8%	122 8%	0.00	132 8%	1,312 10%	0.08
Unable to do it	180 11%	216 14%	0.09	180 11%	2,530 20%	0.25
Data not available	6 0%	10 1%	0.04	6 0%	58 0%	0.01
Difficulty lifting/carrying 10 pounds						
No difficulty	1,075 67%	962 64%	0.07	1,075 67%	7,011 56%	0.23
Little difficulty	193 12%	171 11%	0.02	193 12%	1,704 14%	0.05
Some difficulty	133 8%	159 11%	0.08	133 8%	1,211 10%	0.05
Lot of difficulty	86 5%	95 6%	0.04	86 5%	1,144 9%	0.14
Unable to do it	117 7%	118 8%	0.02	117 7%	1,496 12%	0.16
Data not available	4 0%	6 0%	0.03	4 0%	51 0%	0.03
Difficulty extending arms above shoulder						
No difficulty	1,191 74%	1,102 73%	0.03	1,191 74%	8,602 68%	0.13
Little difficulty	180 11%	166 11%	0.01	180 11%	1,489 12%	0.02
Some difficulty	120 7%	107 7%	0.01	120 7%	1,143 9%	0.06
Lot of difficulty	77 5%	85 6%	0.04	77 5%	857 7%	0.09
Unable to do it	35 2%	43 3%	0.04	35 2%	488 4%	0.10
Data not available	5 0%	8 1%	0.03	5 0%	38 0%	0.00
Difficulty writing/handling object						
No difficulty	1,209 75%	1,130 75%	0.01	1,209 75%	8,848 70%	0.11
Little difficulty	197 12%	195 13%	0.02	197 12%	1,838 15%	0.07
Some difficulty	123 8%	105 7%	0.03	123 8%	1,043 8%	0.02
Lot of difficulty	66 4%	63 4%	0.00	66 4%	664 5%	0.05
Unable to do it	10 1%	12 1%	0.02	10 1%	187 1%	0.08
Data not available	3 0%	6 0%	0.04	3 0%	37 0%	0.02

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MCBS Covariate Match (4)

Covariates	Post-Matching			Pre-Matching		
	Vaccinated	Unvaccinated	Austin Std. Diff	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**1,608**	**1,511**	**(Std. Diff > 0.1)**	**1,608**	**12,617**	**(Std. Diff > 0.1)**
Subjective health						
General health compared to others same age						
Excellent	277 17%	247 16%	0.02	277 17%	1,767 14%	0.09
Very good	520 32%	458 30%	0.04	520 32%	3,378 27%	0.12
Good	531 33%	480 32%	0.03	531 33%	4,066 32%	0.02
Fair	205 13%	245 16%	0.10	205 13%	2,432 19%	0.18
Poor	67 4%	70 5%	0.02	67 4%	910 7%	0.13
Data not available	8 0%	11 1%	0.03	8 0%	64 1%	0.00
Cognitive Status						
Trouble concentrating						
Yes	156 10%	184 12%	0.08	156 10%	1,930 15%	0.17
No	1,396 87%	1,277 85%	0.07	1,396 87%	9,969 79%	0.21
Data not available	56 3%	50 3%	0.01	56 3%	718 6%	0.11
Memory loss interfere with daily activity						
Yes	120 7%	122 8%	0.02	120 7%	1,549 12%	0.16
No	1,432 89%	1,340 89%	0.01	1,432 89%	10,366 82%	0.20
Data not available	56 3%	49 3%	0.01	56 3%	702 6%	0.10
Problem make decisions interferes w/ADLs						
Yes	74 5%	67 4%	0.01	74 5%	1,083 9%	0.16
No	1,478 92%	1,397 92%	0.02	1,478 92%	10,823 86%	0.20
Data not available	56 3%	47 3%	0.02	56 3%	711 6%	0.10
Smoking Status						
Ever smoked cigarettes/cigars/tobacco						
Never smoked	759 47%	710 47%	0.00	759 47%	5,919 47%	0.01
Past smoker	757 47%	696 46%	0.02	757 47%	5,364 43%	0.09
Current smoker	90 6%	104 7%	0.05	90 6%	1,328 11%	0.18
Data not available	2 0%	1 0%	0.02	2 0%	6 0%	0.03
Alcohol Consumption						
Number of days in a month had 4+ drinks						
0 days	1,177 73%	1,093 72%	0.02	1,177 73%	8,351 66%	0.15
1-8 days	34 2%	28 2%	0.02	34 2%	193 2%	0.04
9 or more days	7 0%	8 1%	0.01	7 0%	56 0%	0.00
Data not available	390 24%	382 25%	0.02	390 24%	4,017 32%	0.17

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MCBS Covariate Match (5)

Covariates	Post-Matching			Pre-Matching		
	Vaccinated	Unvaccinated	Austin Std. Diff	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**1,608**	**1,511**	**(Std. Diff > 0.1)**	**1,608**	**12,617**	**(Std. Diff > 0.1)**
Influenza Vaccine Status						
Took flu shot last winter						
Yes	1,389 86%	1,184 78%	0.21	1,389 86%	8,569 68%	0.45
No	211 13%	307 20%	0.19	211 13%	3,929 31%	0.44
Data not available	8 0%	20 1%	0.09	8 0%	119 1%	0.05
Reasons not taking flu shot (Not Mutually Exclusive)						
No flu shot b/c didn't know it was needed	26 12%	41 13%	0.03	26 12%	655 17%	0.12
No flu shot b/c it could cause flu	24 11%	50 16%	0.14	24 11%	605 15%	0.12
No flu shot b/c could have side effects	36 17%	53 17%	0.01	36 17%	662 17%	0.01
No flu shot b/c didn't think it prevent flu	20 9%	35 11%	0.06	20 9%	450 11%	0.06
No flu shot b/c not at risk of catching flu	7 3%	25 8%	0.21	7 3%	287 7%	0.18
No flu shot b/c of other reasons	90 43%	117 38%	0.09	90 43%	1,409 36%	0.14
No flu shot but no information on the reason	18 9%	18 6%	0.10	18 9%	356 9%	0.02
Pneumococcal Vaccine Status						
Ever taken shot for pneumonia						
Yes	1,293 80%	1,086 72%	0.20	1,293 80%	8,020 64%	0.38
No	286 18%	400 26%	0.21	286 18%	4,351 34%	0.39
Data not available	29 2%	25 2%	0.01	29 2%	246 2%	0.01
Reasons not taking vaccine (Not Mutually Exclusive)						
No vaccination b/c didn't know it was needed	142 50%	210 53%	0.06	142 50%	2,284 52%	0.06
No vaccination b/c it could cause pneumonia	3 1%	11 3%	0.12	3 1%	170 4%	0.18
No vaccination b/c could have side effects	12 4%	14 4%	0.04	12 4%	198 5%	0.02
No vaccination b/c didn't think it prevent pneumonia	17 6%	18 5%	0.06	17 6%	223 5%	0.04
No vaccination b/c not at risk of catching pneumonia	9 3%	16 4%	0.05	9 3%	174 4%	0.05
No vaccination b/c of other reasons	97 34%	129 32%	0.04	97 34%	1,260 29%	0.11
No vaccination but no information on the reason	44 15%	45 11%	0.12	44 15%	575 13%	0.06

Preliminary data, ongoing FDA(CBER)/CMS/ACUMEN Study

MCBS Covariate Match (6)

Covariates	Post-Matching			Pre-Matching		
	Vaccinated	Unvaccinated	Austin Std. Diff	Vaccinated	Unvaccinated	Austin Std. Diff
Base Population	**1,608**	**1,511**	**(Std. Diff > 0.1)**	**1,608**	**12,617**	**(Std. Diff > 0.1)**
Attitudes About Seeking Health Care						
Worry about health more than others your age						
True	185 12%	218 14%	0.09	185 12%	2,115 17%	0.15
False	1,346 84%	1,224 81%	0.07	1,346 84%	9,624 76%	0.19
Data not available	77 5%	69 5%	0.01	77 5%	878 7%	0.09
Do almost anything to avoid going to the doctor						
True	315 20%	408 27%	0.18	315 20%	3,576 28%	0.21
False	1,236 77%	1,054 70%	0.16	1,236 77%	8,312 66%	0.24
Data not available	57 4%	49 3%	0.02	57 4%	729 6%	0.11
When sick - try keeping sickness to self						
True	525 33%	529 35%	0.05	525 33%	4,550 36%	0.07
False	1,019 63%	926 61%	0.04	1,019 63%	7,314 58%	0.11
Data not available	64 4%	56 4%	0.01	64 4%	753 6%	0.09
Usually go to the doctor as soon as you feel bad						
True	574 36%	497 33%	0.06	574 36%	4,364 35%	0.02
False	970 60%	952 63%	0.06	970 60%	7,479 59%	0.02
Data not available	64 4%	62 4%	0.01	64 4%	774 6%	0.10
Socio-Economic Status						
Marital Status						
Married	908 56%	815 54%	0.05	908 56%	5,498 44%	0.26
Widowed	496 31%	480 32%	0.02	496 31%	5,006 40%	0.19
Divorced	136 8%	153 10%	0.06	136 8%	1,304 10%	0.06
Separated	7 0%	10 1%	0.03	7 0%	200 2%	0.12
Never Married	60 4%	50 3%	0.02	60 4%	601 5%	0.05
Data not available	1 0%	3 0%	0.04	1 0%	8 0%	0.00
Highest Level Education						
Grade 8 and below	155 10%	183 12%	0.08	155 10%	2,726 22%	0.33
Some high school	680 42%	682 45%	0.06	680 42%	5,847 46%	0.08
Post high school	765 48%	639 42%	0.11	765 48%	3,936 31%	0.34
Data not available	8 0%	7 0%	0.00	8 0%	108 1%	0.04

Multiple Imputation

- What is multiple imputation
  - Multiple imputation is a group of simulation based imputation methods that attempts to incorporate the uncertainty surrounding missing data when imputing values
  - The objective of multiple imputation is not to predict missing values as close as possible to the true ones, but to handle missing data in a way resulting in valid statistical inference

Multiple Imputation

- Multiple imputation:
  1. **Imputation step** - Imputed values are drawn from the distribution of missing data conditional on variables with complete data. Multiple sets of values are drawn to create *m* datasets, where *m*>1. Each dataset has the same values for the observed data, but possibly different values for the previously missing data depending on the certainty of the imputations.
  2. **Analysis step** - Statistical analysis is performed on each dataset. This yields *m* sets of parameter estimates.
  3. **Pooling step** - The *m* parameter estimates are combined into a single set of estimates. This is known as the *pooling* stage, and is completed using Rubin's rules.

Main steps used in multiple imputation.