University Hospitals

Fluzone HD vs SD cluster randomized trial in US NHs

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CASE WESTERN RESERVE UNIVERSITY SCHOOL OF MEDICINE

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insight therapeutics

Conflicts of Interest

- Grant, consultant and/or speaker for
  - Sanofi Pasteur, Seqirus (grant influenza vaccine, consultant, speaker)
  - Merck, Novartis, Janssen, GlaxoSmithKline (consultant shingles, flu, RSV, e coli, pneumococcal vaccines, antivirals)
  - Pfizer (speaker, vaccine contract)
  - Healthcentric Advisors (New England QIN), Catapult Consultants (for Informal Independent Dispute Resolution when CMS federal nursing home surveys are contested)
- Other support
  - NIAID (RO1, influenza, lymph nodes)
  - CDC (antibiotic stewardship in LTC)
  - Hartford, American Geriatrics Society (geriatrics co-management)
  - Gerontological Society of America (National Adult Vaccination Program)

Objectives

- A word about age, immune response, inflammation, complications from influenza
- Discuss results from a pragmatic large scale clinical effectiveness pilot and RCT

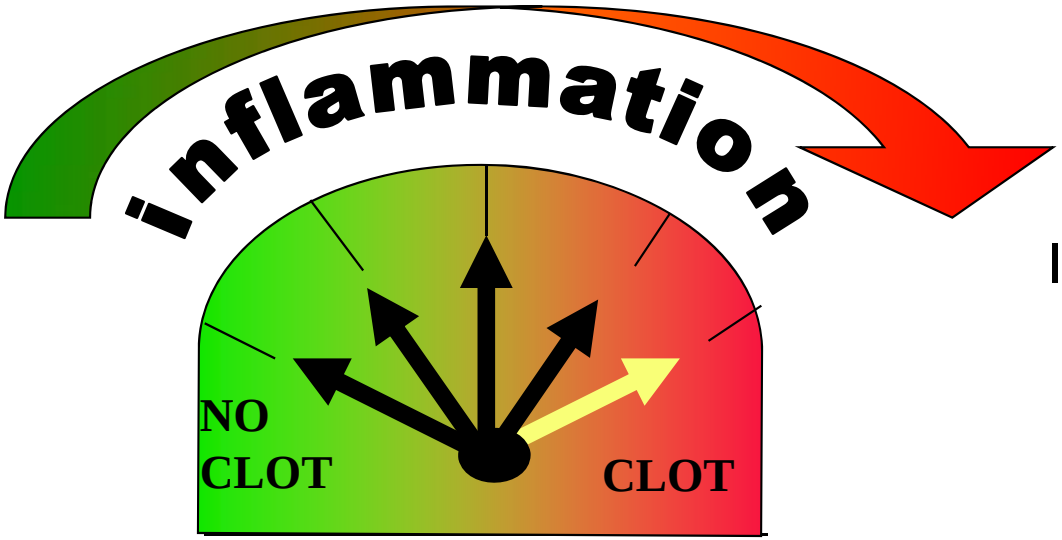
Age-Adjusted Incidence Ratios (IR) of 1st MI and CVA after Vaccination or Infection

Event (count) before First MI	Days 1-14 IR, n	Days 15-28 IR, n	Days 29-91 IR, n
Flu vaccine (20,486)	~0.72, 357	0.73, 417	~1, 2154
Td (7,966)	~1, 54	~1, 46	~1, 299
PPSV23 (5,925)	~1, 39	~1, 43	~1, 177
SRTI (20,921)	~3.8, 1020	1.95, 576	1.4, 1658
UTI (10,448)	~1.6, 233	1.32, 217	1.23, 820
Event (count) before First CVA	**Days 1-14**	**Days 15-28**	**Days 29-91**
Flu vaccine (19,063)	~ .77, 365	.88, 409	~1, 2051
Td (6,155)	~1, 41	~1, 40	~1, 209
PPSV23 (4,416)	~1, 38	~1, 29	~1, 160
SRTI (22,400)	~2.4, 849	1.68, 561	1.33, 1650
UTI (14,603)	~2.2, 555	1.71, 445	1.22, 1250

SRTI = systemic respiratory tract infection, UTI= urinary tract infection

Smeeth, L. et al. N Engl J Med 2004;351:2611-2618

“Thrombometer” – the propensity to clot



LOW	HIGH
CRP IL-1, 6 TNF-alpha	DVT Stroke MI Delirium Dementia

Increases with age

- Inflammatory markers of age
- IL-6, IL-8, C-reactive protein

Increases with disease

- Obesity
- Diabetes
- Arthritis, Vascular disease
- Dementia
- COPD

Increases with infection

- Influenza, pneumonia
- Bladder infection, pressure sores

Immune Senescence

- More permissive for infection including pneumonia
  - More permissive for severe infection that can result in hospitalization
- Lowers vaccine response
  - Need better vaccines to overcome declining response
- Slows recovery from infection
- Changes symptom presentation with age

1. Lambert Nathaniel D et al. Understanding the immune response to seasonal influenza vaccination in older adults: a systems biology approach. Expert Rev. Vaccines. 2012 August; 11(8): 985-994.
2. Taub D, Longo D. Insights into thymic aging and regeneration. *Immunol Rev*. 2005;205(1):72-93. (Abstract only)

High dose flu vaccine reduces clinical flu in outpatient elderly

Efficacy of High-Dose versus Standard-Dose Influenza Vaccine in Older Adults

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor,
N Engl J Med 2014; 371:635-645 | August 14, 2014 | DOI: 10.1056/NEJMoa1315727

- 31,989 volunteers, 2011-2013, 50:50 HD:SD
- Relative efficacy, ILI 24.2%; (95% CI 9.7 to 36.5)
  - Relative efficacy ILI hospitalization 30% (95% CI 9 to 46)

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

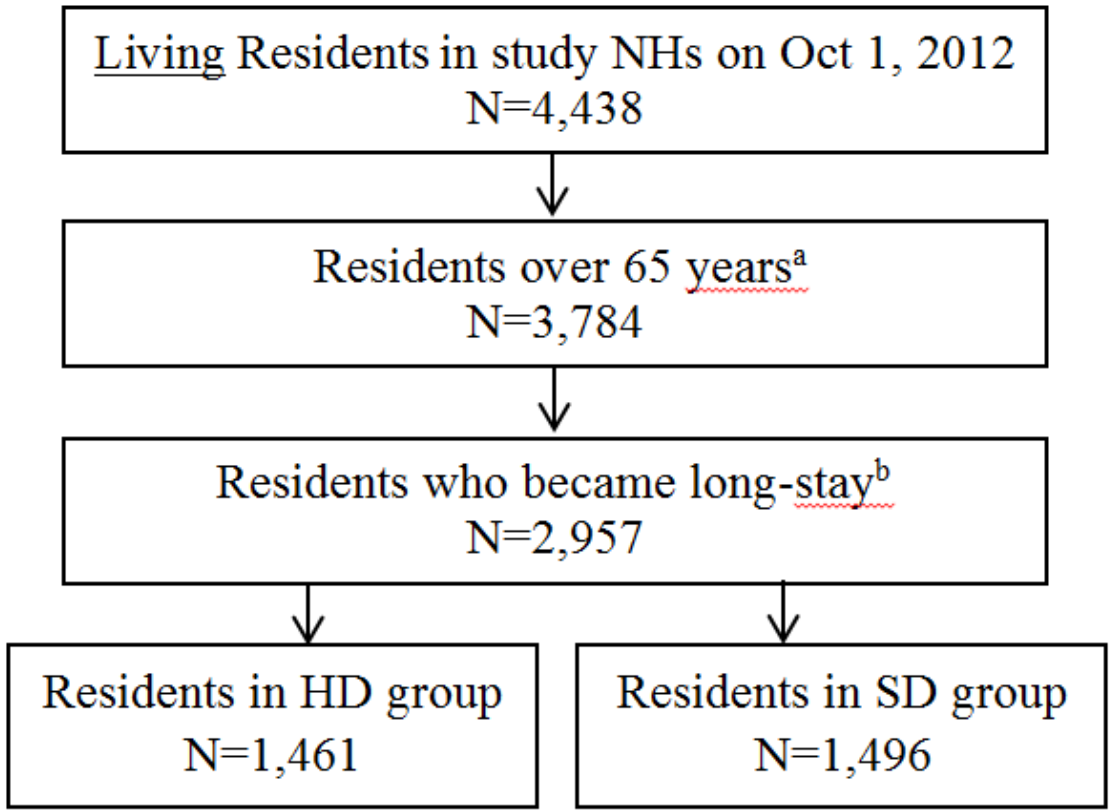
Hector S Izurieta, Nicole Thadani*, David K Shay, Yun Lu, Aaron Maurer, Ivo M Foppa, Riley Franks, Douglas Pratt, Richard A Forshee,*
Lancet Infect Dis 2015; 15:293-300. Online 9Feb2015; Mar 2015

- 900K HD vs 1600K SD, 2012-2013, retrospective cohort ≥65
- 22% fewer rapid test/oseltamivir in HD, and 22% fewer hospitalized

Pragmatic Large-Scale Cluster RCT on Comparative Effectiveness of HD vs SD Influenza Vaccine in Long-Term Care

- Review results from Pilot Study undertaken in 39 nursing facilities 2012-13 predominantly A/H3N2 influenza season
- Present findings from the Full cluster RCT of High Dose (HD) influenza vaccine vs. Standard Dose (SD) influenza vaccine in 823 nursing homes (NHs) 2013-2014 predominantly A/H1N1 influenza season

Pilot Study: Methods
Patient Eligibility and Selection



a Residents who were 65 years old on October 1, 2012.
b Long-stay residents are NH residents with quarterly and annual MDS assessments. Residents who were discharged from the nursing home to: 1) the community, 2) inpatient rehabilitation facility, 3) hospice, 4) other location, or 5) as dead in the baseline period are excluded from the analytical sample. Residents are included if they were discharged to another nursing home, acute hospital, psychiatric hospital, or MR/DD facility.

Pilot Results: Regression Models

Outcome	Unadjusted		Adjusted*	
	Hazard Ratio (LCL – UCL)	p-value		
Death in NH	1.059 (0.827-1.357)	0.650		
	Relative Risk (LCL – UCL)	p-value	Relative Risk	p-value
Total Hospitalizations	0.617 (0.461-0.827)	0.001	0.647 (0.512-0.818)	0.000
Ever Hospitalized	0.658 (0.496-0.873)	0.004	0.701 (0.543-0.905)	0.006

* Adjusted for prior year hospitalization rate, age of resident, mean age of residents in home, individual ADL score, mean ADL score in home, Cognitive Function Score (CFS), Mean CFS in home, history of CHF risk-group, prevalence of CHF risk-group in home

Pilot Results: Summary

- Large scale study feasible as pragmatic cluster RCT
- Can detect differential signal in hospitalization using MDS data
  - ~30% fewer people hospitalized in HD group in an A/H3N2 season predominant season, significant before and after adjustment
- Move forward to large trial

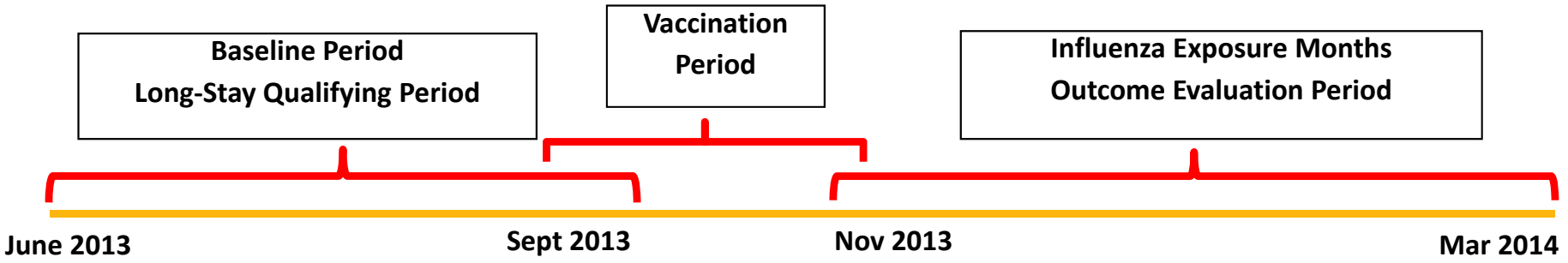
Pragmatic Cluster RCT of HD vs SD Flu Vaccine in Nursing Homes

- Recruit NH's in areas adjacent to 122 cities in CDC Influenza Surveillance System
- Use Federally Mandated Nursing Home Resident MDS Assessment to identify permanent NH residents with selected demographic and functional characteristics AND to measure outcomes
- Use Medicare hospital claims to measure outcome of hospitalization for Influenza (P&I) and Cardiovascular exacerbations of Influenza

Study Design

- Recruit facilities within 50 miles of CDC cities
  - Excluded those facilities already using HD, with fewer than 50 permanent residents, hospital-owned NHs, or >20% of residents UNDER 65
- Randomly assign facilities to 4 groups
  - High-Dose for NHs residents
    - Free Staff Vaccine
    - No Free Staff Vaccine
  - Standard Dose for NHs residents
    - Free Staff Vaccine
    - No Free Staff Vaccine
- Educate facility staff on influenza, study procedures
- Link to facility data (OSCAR), MDS, and Medicare Part A, MDS (discharge destination, function), vital status files
- Collect Vaccination Data Reports
- Patient eligibility:
  - >3 months' residence, over 65 years old on November 1, 2013, and Medicare Fee For Service (FFS)

Outcomes

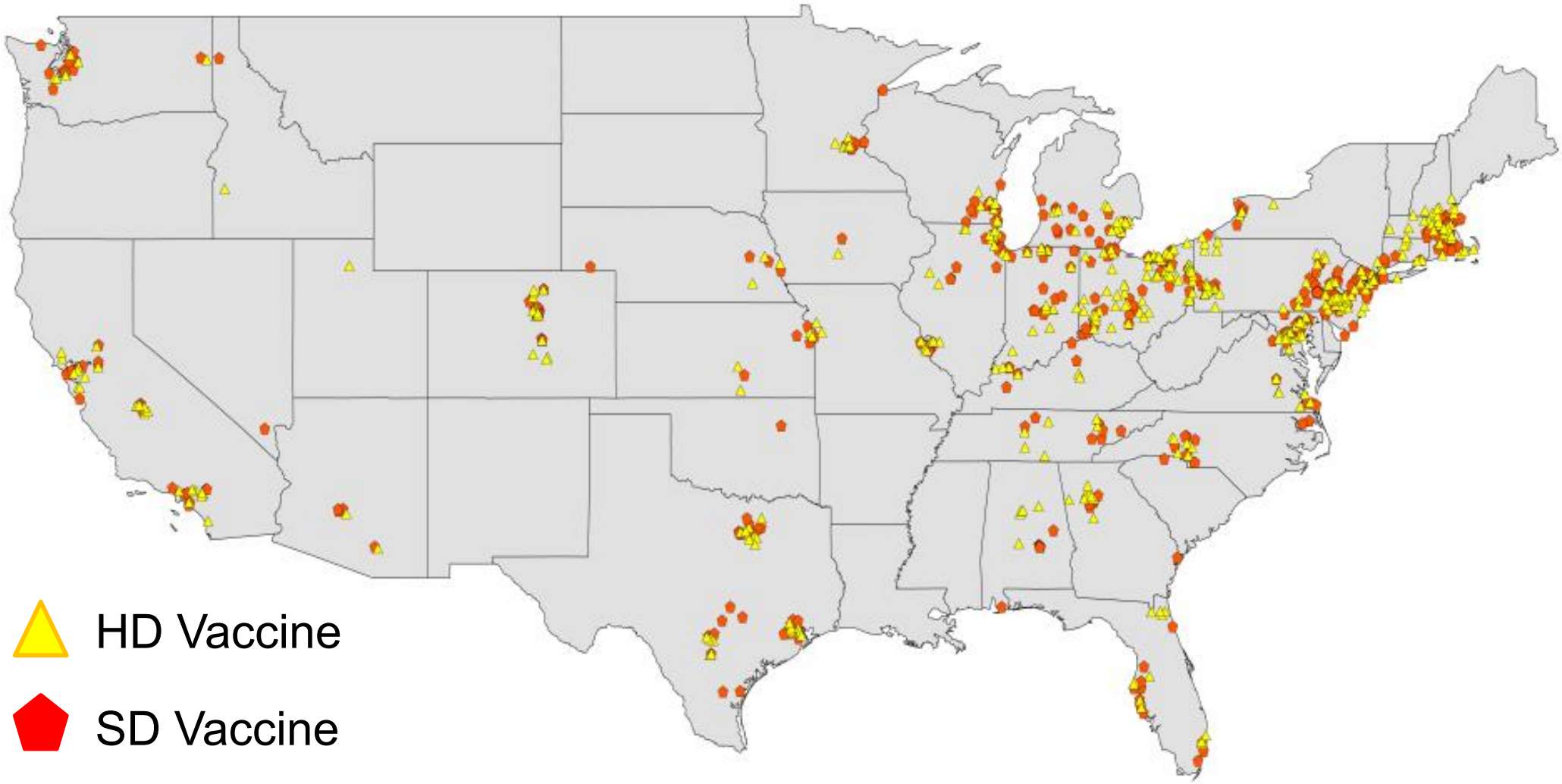


1. All-cause hospitalization per person-year
2. Mortality
3. Functional Decline (activities of daily living, ADLs)

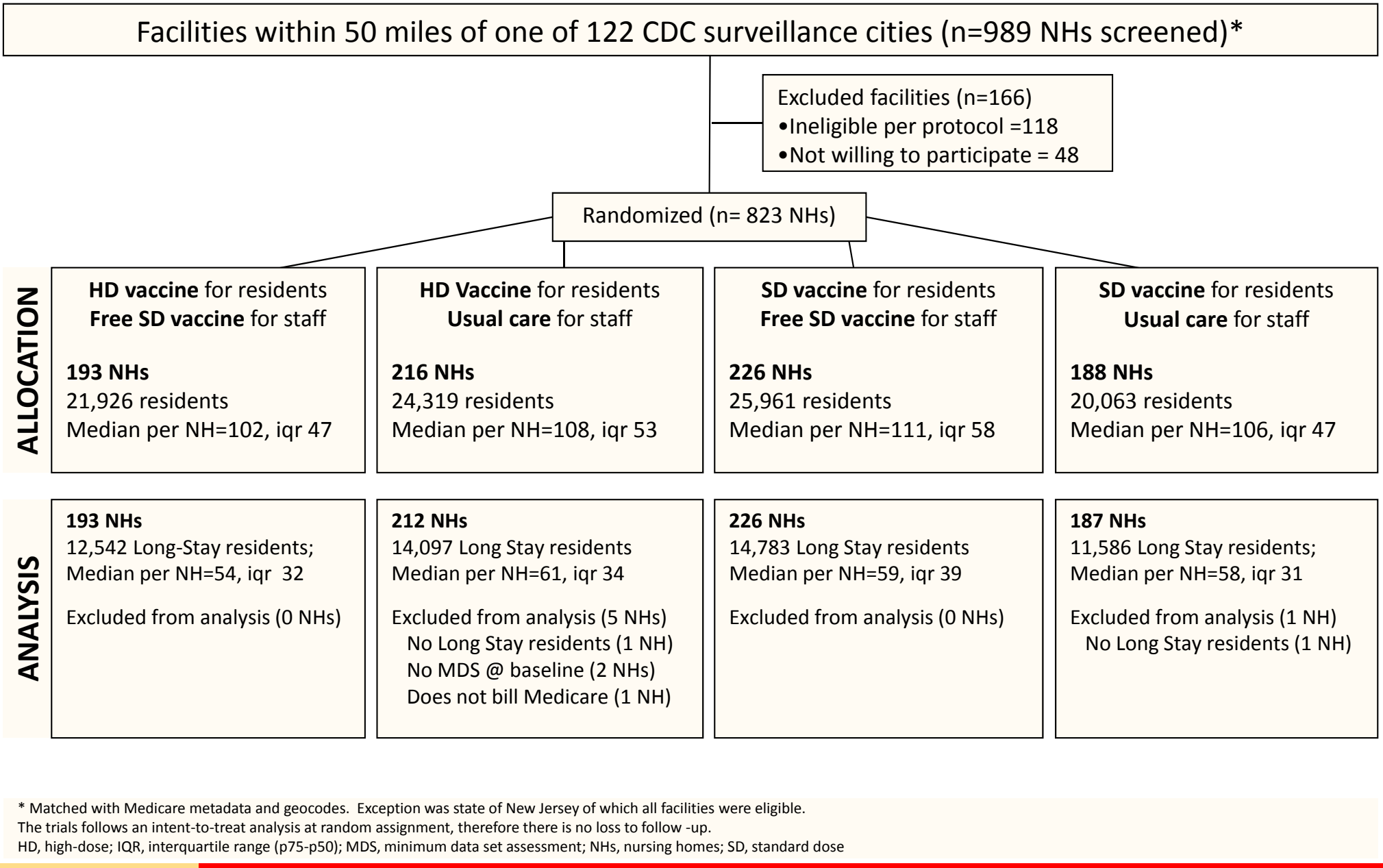
Outcome Determination

- PRIMARY. Medicare FFS permanent NH residents; risk of hospitalization due to Pulmonary and Influenza-related illness (P&I):
  - P&I hospitalization defined as: ICD9-CM codes 460–466, 480–488, 490–496, 500–518

Participating NHs by State (n=823)



Nursing Home Facilities Selection and Randomization



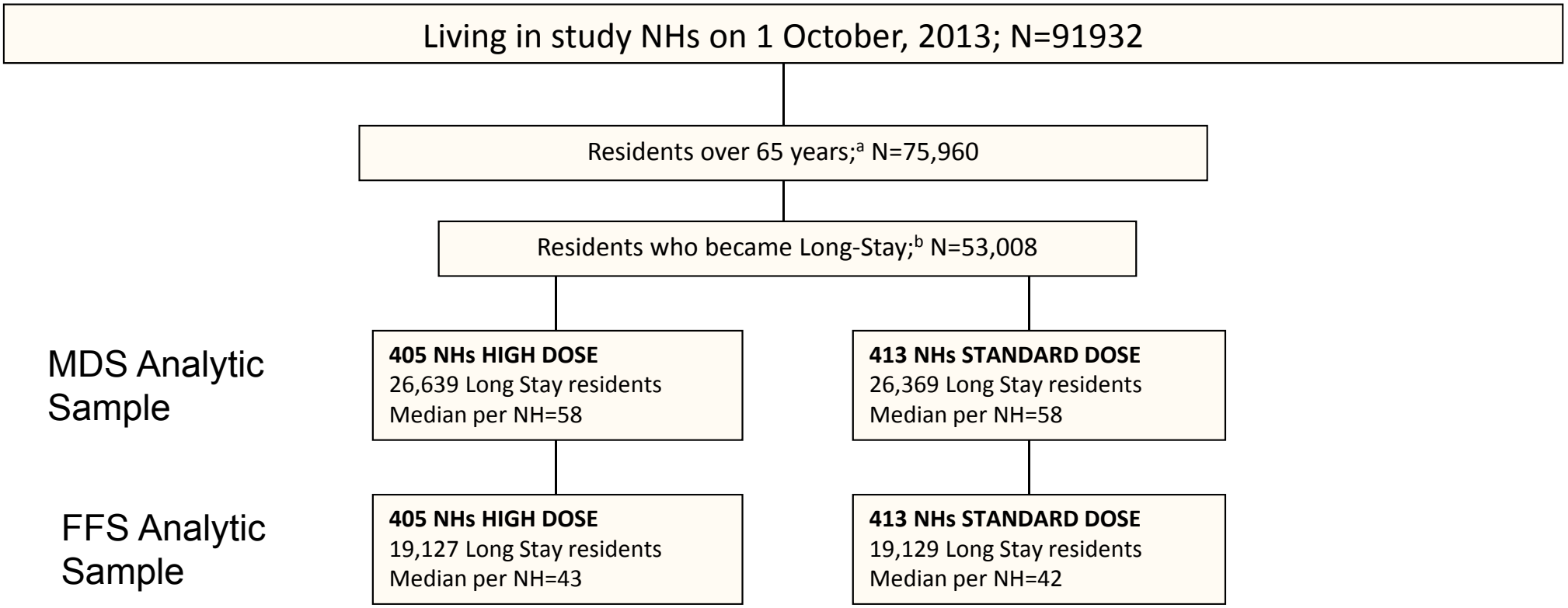
* Matched with Medicare metadata and geocodes. Exception was state of New Jersey of which all facilities were eligible.
The trials follows an intent-to-treat analysis at random assignment, therefore there is no loss to follow -up.
HD, high-dose; IQR, interquartile range (p75-p50); MDS, minimum data set assessment; NHs, nursing homes; SD, standard dose

NH groups are similar (N=823 NHs)

	HD Vaccine for Residents		SD Vaccine for Residents	
Characteristics	Staff Free (mean, SD)	Staff Usual Care (mean, SD)	Staff Free (mean, SD)	Staff Usual Care (mean, SD)
NHs randomized (N)	193	216	226	188
Facility-Reported Data[a]				
Residents per home (N)	118.0 (82.3)	118.7 (52.1)	118.3 (50.0)	112.2 (53.2)
% residents vaccinated	81.7 (14.4)	79.9 (16.6)	81.5 (16.3)	81.6 (15.4)
% LTC residents	77.4 (15.9)	78.2 (14.8)	78.2 (13.6)	79.8 (13.6)
% LTC residents vaccinated	86.0 (14.8)	86.5 (13.8)	84.4 (17.4)	85.2 (16.4)
% staff vaccinated	53.5 (26.2)	56.3 (26.9)	55.6 (26.6)	55.0 (26.4)
Medicare Claims/Facility Data[b]				
% Medicaid	59.9 (18.1)	64.2 (16.1)	63.3 (15.7)	61.7 (18.5)
Ratio of RN/RN+LPN	0.361 (0.15)	0.355 (0.16)	0.363 (0.15)	0.357 (0.15)
Average ADL score (0-28)	17.0 (1.77)	16.9 (2.10)	16.9 (2.13)	16.8 (2.24)

Cohort Selection, 2013-14

(ALL Long-stay NH residents over 65 years)



a Residents who were 65 years old on October 1, 2013.

b Long-stay residents are NH residents with quarterly and annual MDS assessments. Residents who were discharged from the nursing home to: 1) the community, 2) inpatient rehabilitation facility, 3) hospice, 4) other location, or 5) as dead in the baseline period are excluded from the analytical sample. Residents are included if they were discharged to another nursing home, acute hospital, psychiatric hospital, or MR/DD facility.

[Note: We could not obtain MDS records for 6 NH facilities (i.e., 1 veteran's home; 2 rehabilitation facilities that were randomized prior to their withdrawal; 1 facility stopped operation in Nov/Dec 2013)]

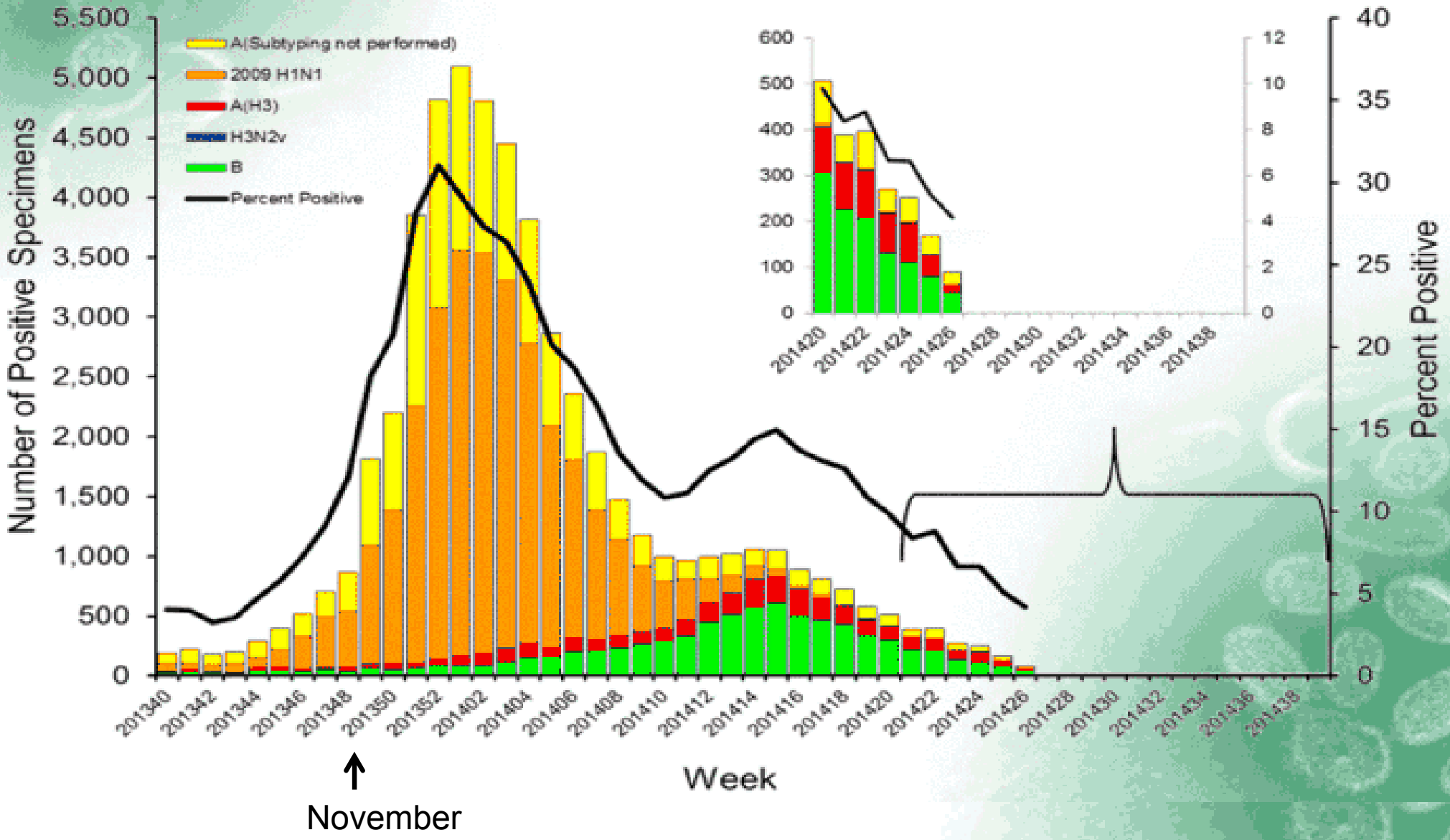
NH Resident Groups are similar (N=53,008)

	HD Vaccine for Residents		SD Vaccine for Residents	
Characteristics	Free Vaccine for Staff (N, %)	Usual Care for Staff (N, %)	Free Vaccine for Staff (N, %)	Usual Care for Staff (N, %)
LS residents >65 yo	12,542	14,097	14,783	11,586
Age (mean, sd)	83.7 (8.7)	83.5 (8.8)	83.6 (8.8)	83.6 (8.9)
Female	9,014 (71.9)	10,248 (72.7)	10,680 (72.3)	8,339 (72.0)
African American	1,800 (14.4)	2,088 (14.8)	2,195 (14.9)	1,783 (15.4)
White	9,469 (75.5)	10,690 (75.8)	11,143 (75.4)	8,694 (75.0)
Hispanic	715 (5.7)	681 (4.8)	782 (5.3)	509 (4.4)
Married	2,326 (18.6)	2,687 (19.1)	2,775 (18.8)	2,233 (19.3)
Heart Failure	2,547 (20.3)	2,868 (20.3)	3,119 (21.1)	2,338 (20.2)
Stroke/ CVA/ TIA	2,452 (19.6)	2,807 (19.9)	3,091 (20.9)	2,310 (19.9)
Hypertension	9,953 (79.4)	11,156 (79.1)	11,702 (79.2)	9,140 (78.9)
Diabetes Mellitus	4,229 (33.7)	4,826 (34.2)	5,155 (34.9)	4,035 (34.8)
Asthma/COPD/CLD	2,405 (19.2)	2,869 (20.4)	3,093 (20.9)	2,332 (20.1)

FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2013-14



Results: Censoring is Balanced

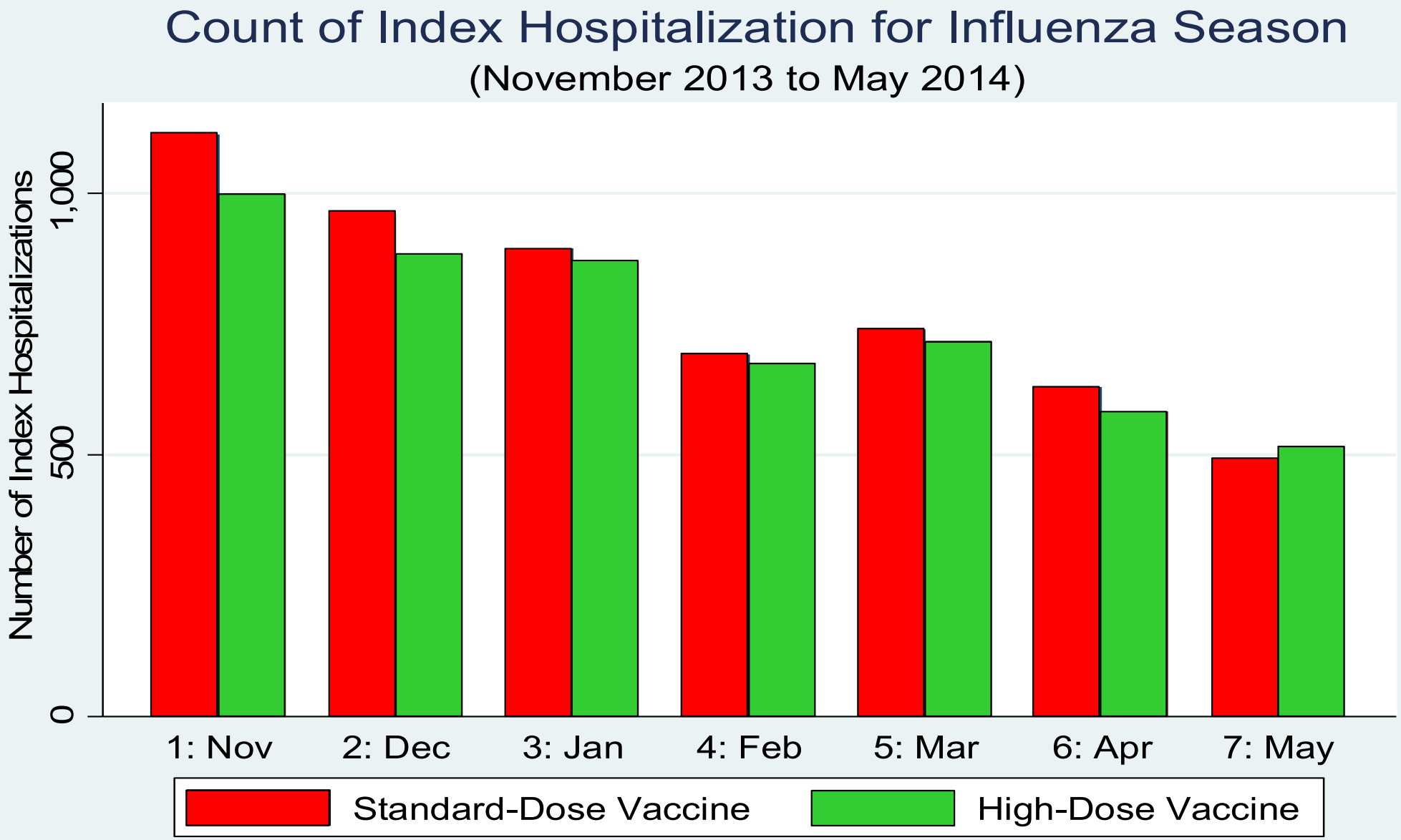
Outcome	HD vaccine (N, %)	SD vaccine (N, %)
Complete Follow Up	21,639 (80.2)	21,382 (80.1)
Death	4,542 (17.1)	4,531 (17.2)
Lost: Acute Impatient discharge, no return	173 (0.65)	158 (0.60)
Lost: Other institutional discharge, no return	31 (0.12)	35 (0.13)
Lost: Discharge to community or hospice	223 (0.84)	250 (0.95)
Lost: No discharge record	31 (0.12)	13 (0.05)
Total	26,639	26,369

Analytic Approach

- Unit of analysis: individual residents
  - Adjusted for clustering by NHs using robust variance estimates
- Multivariable logistic, Poisson, and Cox regression
  - Initial model assessed interaction between treatments
  - Adjusted for pre-specified NH- and resident-level covariates
- Analysis by Intention-To-Treat
  - Sensitivity analysis to assess effect of excluding deaths
- Number Needed to Treat (NNT)

Kahan BC (2013). Bias in randomised factorial trials. *Statistics in Medicine* vol. 32, (26) 4540-4549.

Seasonal Index Hospitalizations by Month



Number Needed to Treat (for Ever Hospitalized)

NNT = 1/ARR where ARR* = CER – EER

1/(0.2090-0.1967) = 81.3 (CI: 53, 182)

To prevent 1 person from being hospitalized, ~81 long-stay 65+ NH residents need to be treated with high-dose instead of standard dose influenza vaccine

Definitions

NNT= Number Needed to Treat

ARR = Absolute Risk Reduction

CER = Control Event Rate (i.e., Probability of Hospitalization for SD group)

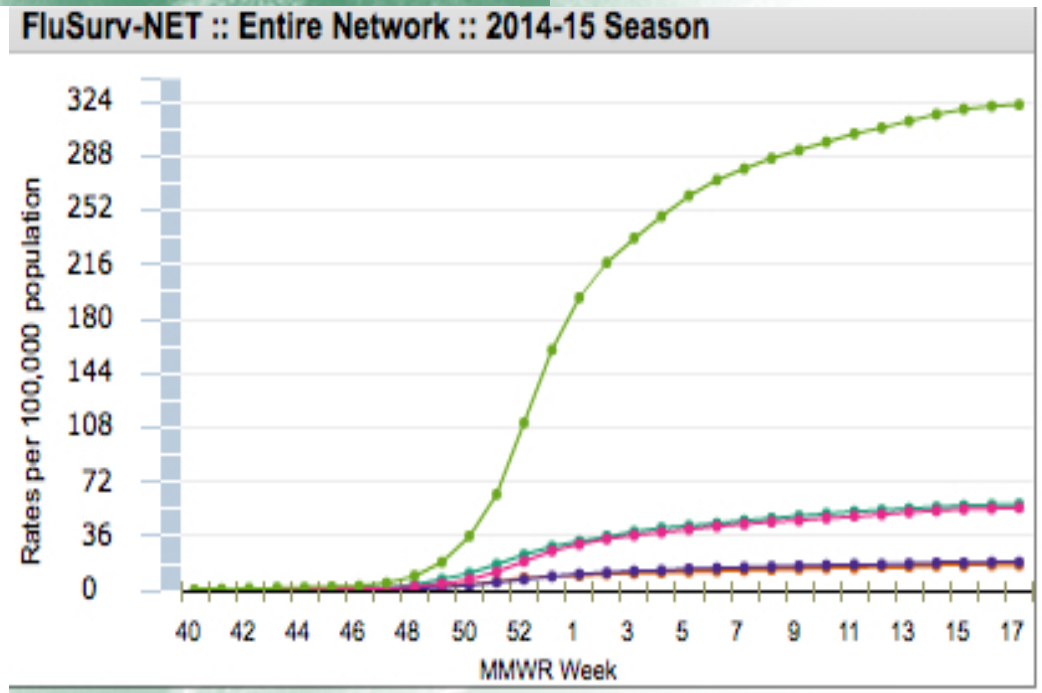
EER = Experimental Event Rate (i.e., Probability of Hospitalization for HD group)

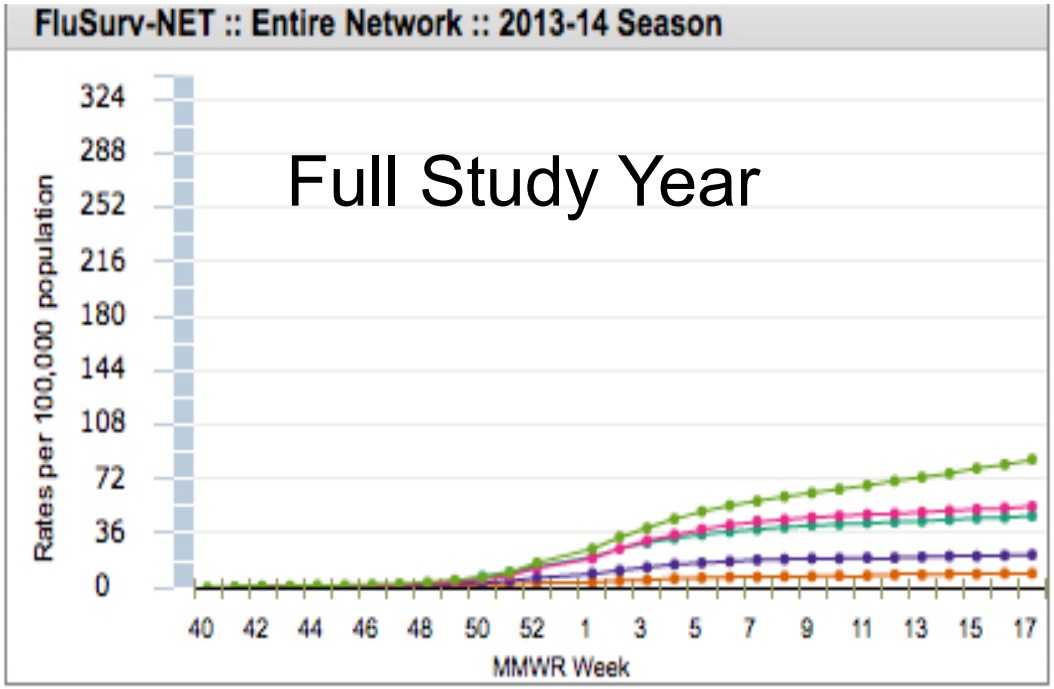
* Using unadjusted event rates.

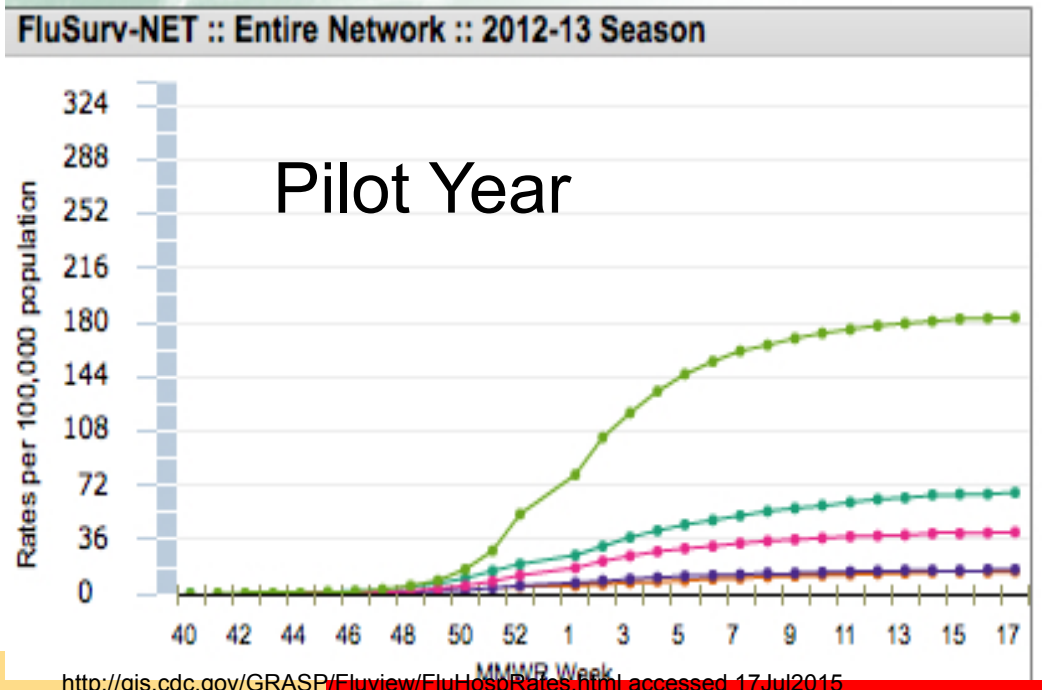
FluView

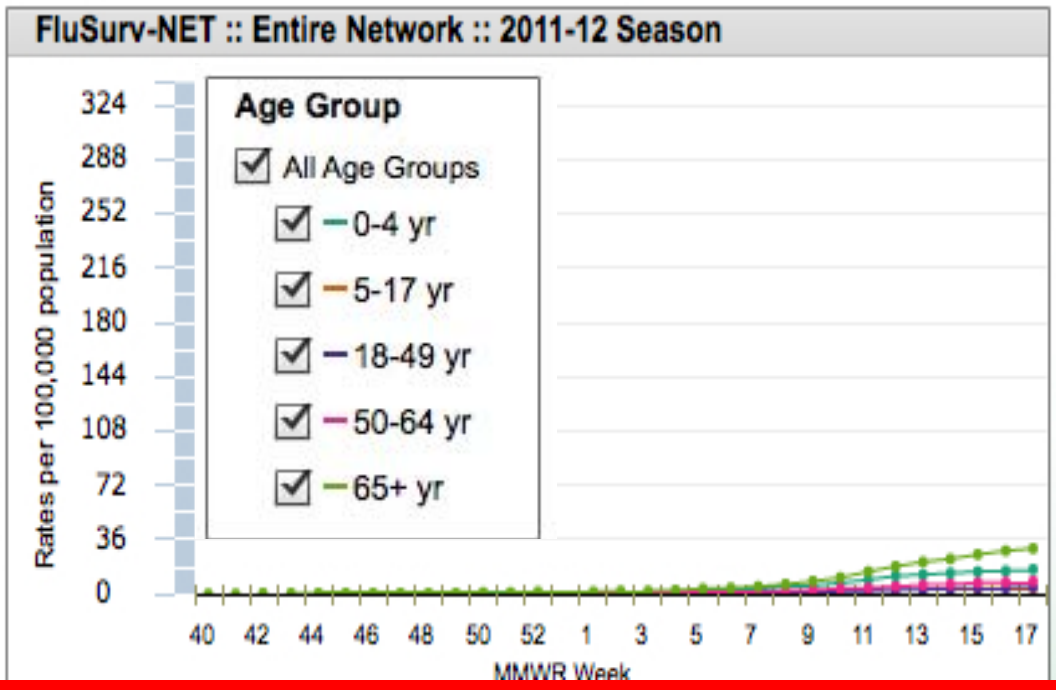
Laboratory-Confirmed Influenza Hospitalizations

Preliminary rates as of Jun 27, 2015









http://gis.cdc.gov/GRASP/Fluview/FluHospRates.html accessed 17Jul2015

Summary

- HD vaccine has been shown to reduce laboratory confirmed influenza among outpatient elderly
- NH residents have higher event rates (e.g., hospitalization) than others, enables health services impact study; cluster-randomized approach overcomes selection biases
- 2013-2014 season is of special interest because it offers a conservative estimate of relative benefit in this population
  - A(H1N1) predominated, and relative benefit of HD vaccine for this strain in a NH population has been unknown
  - A relatively low influenza attack rate to comparison seasons
- FFS claims differences consistent with biologic plausibility of effect on hospitalization based on diagnoses

Discussion

- Reasons our estimate may be conservative
  - Severity of influenza season
- ITT approach
  - Over 10% of residents not vaccinated
- Type of influenza virus circulating (A/H1N1)
- Reduced hospitalization likely underestimates net benefits to nursing home residents' health outcomes
- When ~20% of population is hospitalized, even a 1% absolute reduction in hospitalization can be cost effective (e.g., 81 vaccines at ~$30/vaccine = $2430, or less than the average cost of hospitalization)
- Limitations:
  - No laboratory data to confirm influenza
  - HD:SD relative benefit on A(H1N1) may underestimate difference when other strains dominate, especially A(H3N2)
  - Have not estimated relative benefit to no vaccine

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  - Stefan Gravenstein
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