Influenza in Seniors

Helping to Protect a Vulnerable Population – the BC Perspective

Hold Ctrl & Click on picture to start WHO video
(https://www.youtube.com/watch?v=LL-TJjCJPaI)

Add “Life to Years”

“For the first time in human history, the world will soon have more older people than children. The human race is ageing and we are unprepared. Unless we change the way we think and act about ageing, we will miss the opportunity to age in good health and to build a society where older people are respected and valued members of society.”

WHO March 28, 2018 - Add "life to years" through healthy ageing

A Senior’s Perspective

Pharmacist Perspective

- Ajit Johal BSc (Pharm) RPh BCPP CDE CTH
- Community Pharmacist
- Clinical Instructor and Course Coordinator at UBC Faculty of Pharmaceutical Sciences
- Area’s of interest - Infectious Disease, Immunology, Vaccines

Disclosure

I have the following relationships with commercial interests:

- Advisory Board/Speakers Bureau – AA Pharma, Sanofi Pasteur
- Speaker/Consulting Fees: BCPHA, Eli Lily, Novartis, Boeringher Ingelhiem, Mckesson Canada, Ensemble IQ, Valeneva INC
- Other:

Current Employee of UBC Faculty of Pharmaceutical Sciences

Welcome to…..

u·to·pi·a
yo͞oˈtōpēə/
noun

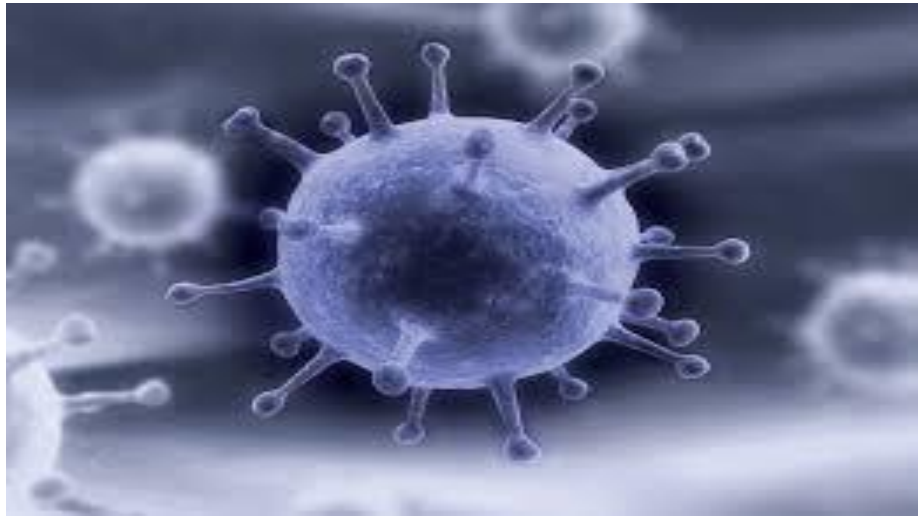
imagined place or state of things in which everything is perfect.

Utopia in LTC

Shift Happens…

BC Care Providers ASSOCIATION

Influenza



in·flu·en·za
ˌinflə'wenzə/
noun
a highly contagious viral infection of the respiratory passages causing fever, severe aching, and catarrh, and often occurring in epidemics.

Influenza hits LTC residences hard

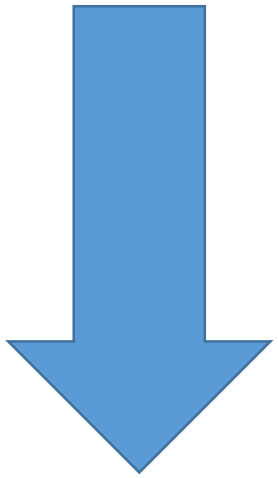
- BC Flu watch - To date this season, 1,508 influenza/ILI outbreaks have been reported, of which 917 (61%) occurred in LTC facilities[1].

*Does this sound **FAMILIAR TO YOU?***

- This leads to strict infection control measures to deal with a number of influenza outbreaks.

Quality of Life

- Meals delivered to client rooms
- Family visitations limited
- Emotional Impact
- Decreased staffing
- Decreased services
- Bed closures
- Decreased Admissions



What is the most effective method of preventing flu??

Are all Influenza Vaccines Equal?

What is the Current Program in BC?

In B.C., influenza vaccines are provided free to people who are at **high risk** of serious illness from influenza

- Young children
- Pregnant women
- The elderly
- People with certain medical conditions
- Those able to transmit or spread influenza to those at high risk
- People who provide essential community services.

Funded Vaccines for 65+

2016-2017 Influenza Season

- TIIV (standard dose) trivalent inactive influenza vaccine, or
- ATIIV (adjuvanted standard dose) trivalent inactive influenza vaccine

2017-2018 Influenza Season

- TIIV (standard dose) trivalent inactive influenza vaccine.

  (ATIIV program discontinued by public health)

Available Vaccines for 65+

2016-2017 Influenza Season

- TIIV (standard dose) trivalent inactive influenza vaccine
- ATIIV (adjuvanted standard dose)
- *HD TIIV (High dose)*

2017-2018 Influenza Season

- TIIV (standard dose) trivalent inactive influenza vaccine
- ATIIV discontinued for seniors by public health due to limited data on effectiveness
- *HD TIIV (High Dose)*

Now seniors are faced with a choice….

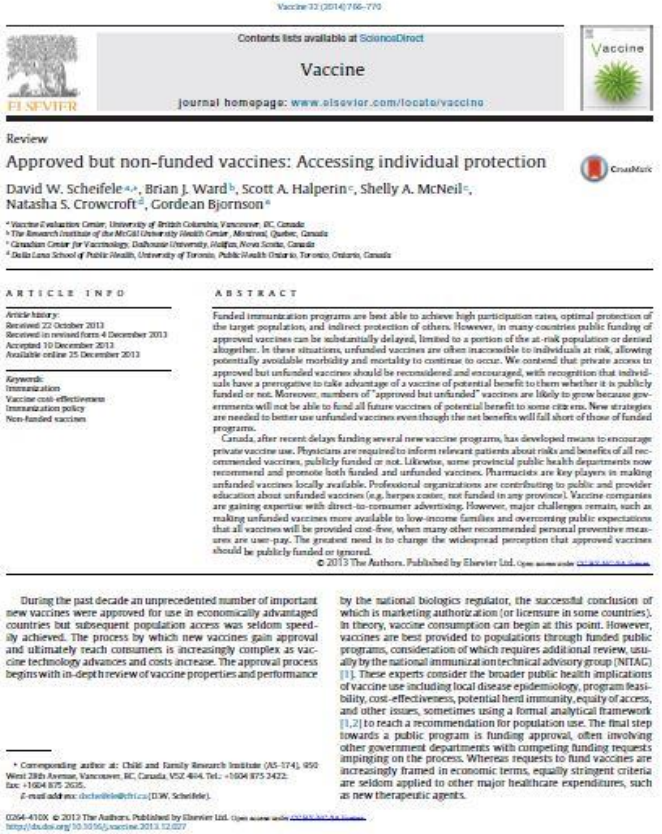
Publicly funded Standard Dose TIIV

OR

Private pay High Dose TIIV

Approved But Non Funded Vaccines

" The greatest need is to change the widespread perception that vaccines should be ***publicly funded or ignored.*** *The long-standing and total dominance of* ***population over individual considerations*** *for vaccines needs to end or the potential benefits of some vaccines will not be realized, to the detriment of those at risk. It is a form of* ***discrimination against vaccines*** *compared with (preventive) drugs that urgently needs to be corrected"*[2]



Vaccine 32 (2014) 766–770

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Review

Approved but non-funded vaccines: Accessing individual protection

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ABSTRACT

Funded immunization programs are best able to achieve high participation rates, optimal protection of the target population, and indirect protection of others. However, in many countries public funding of approved vaccines can be substantially delayed, limited to a portion of the at-risk population or denied altogether. In these situations, unfunded vaccines are often inaccessible to individuals at risk, allowing potentially avoidable morbidity and mortality to continue to occur. We contend that private access to approved but unfunded vaccines should be reconsidered and encouraged, with recognition that individuals have a prerogative to take advantage of a vaccine of potential benefit to them whether it is publicly funded or not. Moreover, members of "approved but unfunded" vaccines are likely to grow because governments will not be able to fund all future vaccines of potential benefit to some citizens. New strategies are needed to better use unfunded vaccines even though the net benefits will fall short of those of funded programs.

Canada, after recent delays funding several new vaccine programs, has developed means to encourage private vaccine use. Physicians are required to inform relevant patients about risks and benefits of all recommended vaccines, publicly funded or not. Likewise, some provincial public health departments now recommend and promote both funded and unfunded vaccines. Pharmacists are key players in making unfunded vaccines locally available. Professional organizations are contributing to public and provider education about unfunded vaccines (e.g. herpes zoster, not funded in any province). Vaccine companies are gaining expertise with direct-to-consumer advertising. However, major challenges remain, such as making unfunded vaccines more available to low-income families and overcoming public expectations that all vaccines will be provided cost-free, when many other recommended personal preventive measures are user-pay. The greatest need is to change the widespread perception that approved vaccines should be publicly funded or ignored.

During the past decade an unprecedented number of important new vaccines were approved for use in economically advantaged countries but subsequent population access was seldom speedily achieved. The process by which new vaccines gain approval and ultimately reach consumers is increasingly complex as vaccine technology advances and costs increase. The approval process begins with in-depth review of vaccine properties and performance by the national biologics regulator, the successful conclusion of which is marketing authorization (or licensure in some countries). In theory, vaccine consumption can begin at this point. However, vaccines are best provided to populations through funded public programs, consideration of which requires additional review, usually by the national immunization technical advisory group (NITAG) [1]. These experts consider the broader public health implications of vaccine use including local disease epidemiology, program feasibility, cost-effectiveness, potential herd immunity, equity of access, and other issues, sometimes using a formal analytical framework [1,2] to reach a recommendation for population use. The final step towards a public program is funding approval, often involving other government departments with competing funding requests impinging on the process. Whereas requests to fund vaccines are increasingly framed in economic terms, equally stringent criteria are seldom applied to other major healthcare expenditures, such as new therapeutic agents.

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http://dx.doi.org/10.1016/j.vaccine.2013.12.027

Issues….

- No special consideration for seniors
- Lack of education about the burden of influenza and vaccine options
- Lack of awareness amongst the public, and health care providers
- Lack of education from the public sector on non-publicly funded vaccines…

BC Pharmacist Perspective

Expanding immunization scope of practice, leading to;

- Increase in accessibility to **government funded** influenza program
- Continuing education on newly marketed vaccines
- Reimbursement discrepancy in public and private sector

Missed opportunity

If this season the government is NOT going to offer high dose flu vaccine through the public program, it is up to front-line immunization providers to inform their patients about the **OPTION**

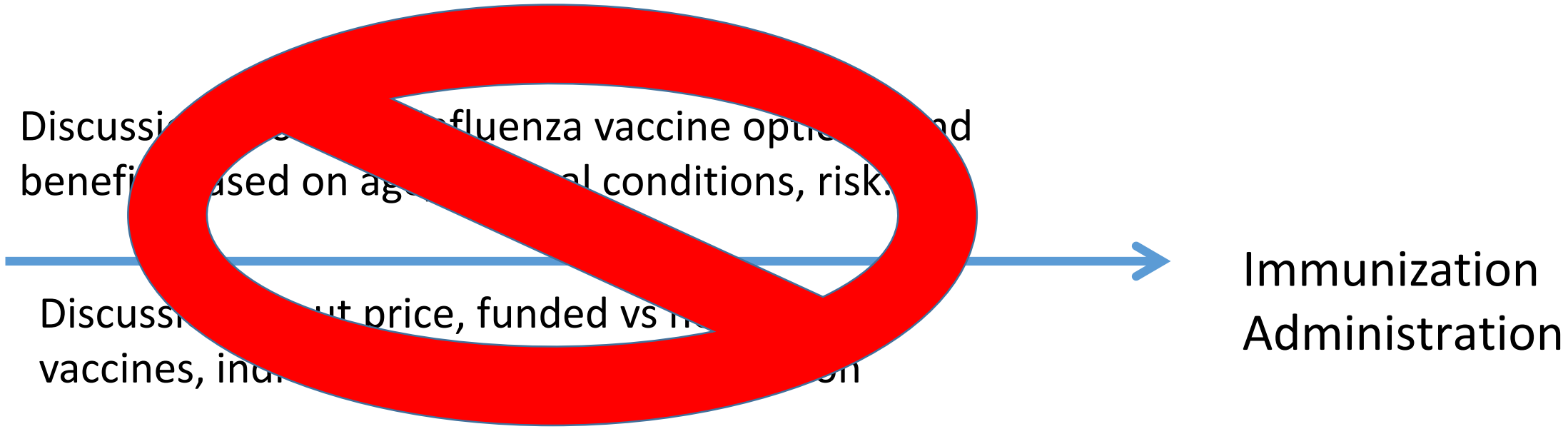
Discussion about the influenza vaccine options, and benefits based on age, medical conditions, risk.

Discussion about price, funded vs non-funded vaccines, individual vs population protection

Immunization Administration

Missed opportunity

If the government is NOT going to offer high dose flu vaccine through the public program, it is up to front-line immunization providers to inform their patients about the **OPTION**



Unfortunately information given to HCP is “confusing”

BCCDC Q & A Statement August 2017:

“Given the lack of an explicit recommendation for preferential use of high dose TIIV by NACI and/or endorsement of superiority by provincial advisory committees, **providers are under no greater obligation to inform patients of the high dose TIIV option than any other TIIV product approved for seniors in Canada.**

Just because there is a publicly funded alternative, does that mean our patients should not be informed that they have a choice?

Missed opportunity

If this season the government is NOT going to offer high dose flu vaccine through the public program, it is up to front-line immunization providers to inform their patients about the **OPTION**

Discussion about the influenza vaccine options, and benefits based on age, medical conditions, risk.

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Immunization Administration

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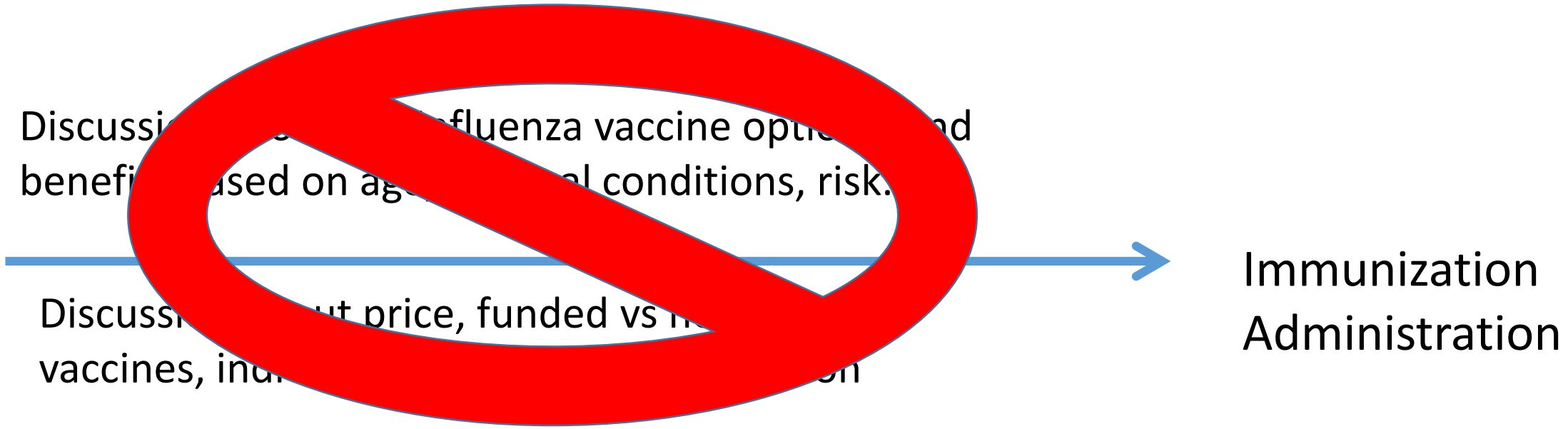

Lack of Public Awareness of approved but non-funded vaccines[2]

- Need to change widespread perception that approved vaccines should be publically funded or ignored
- Recognition that individuals have a prerogative to take advantage of a vaccine of potential benefit
- Provincial Health Programs should recommend and promote both funded and private vaccines
- Pharmacists are key players in making unfunded vaccines locally available

NACI's 2018/2019 Seasonal Influenza Vaccine Recommendations

Recipient by Age Group	Vaccine Types Available for Use†	Comments
NACI's 2018/2019 Seasonal Influenza Vaccine Recommendations for Adults 65+		
Adults 65+ years of age	TIVQIV ATIV High dose TIV	At the **programmatic level**, NACI recommends that any of the four influenza vaccines available for use in adults 65 years of age and older should be used: standard-dose TIV, high-dose TIV, MF59-adjuvanted TIV, and QIV. High-dose TIV is expected to provide superior protection compared to standard-dose TIV; however, with cost-effectiveness assessments having been outside the scope of the evidence review and without data on the relative efficacy/effectiveness between high-dose TIV, MF59-adjuvanted TIV, and QIV, there is insufficient evidence to make a comparative recommendation on the use of these vaccines at the programmatic level (Grade I). At the **individual level**, NACI recommends that high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older. NACI concludes that, given the burden of disease associated with influenza A(H3N2) and the good evidence of better efficacy compared to standard-dose TIV in this age group, high-dose TIV should be offered over standard-dose TIV to persons 65 years of age and older (Grade A). There is insufficient evidence to make comparative recommendations on the use of MF59-adjuvanted TIV and QIV over standard-dose TIV.

There is **good evidence that Fluzone® High-Dose provides superior protection** (e.g., decrease in ILI, influenza-related death and all-cause hospitalization) compared with standard-dose TIV in the elderly **(Grade A Evidence)**

A Vaccine to Prevent Heart Attack? What We Can Learn From Old People

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Gerontology Center
Brown University

Disclosures

- Grant and contract support from Centers for Disease Control, Centers for Medicare and Medicaid, National Institutes of Health, Pfizer, Sanofi Pasteur, Seqirus
- Consulting with American Geriatrics Society, Gerontological Society of America, Longeveron, Merck, Novartis, Novavax, Pfizer, Janssen
- Speaker for Gerontologic Society for America, GlaxoSmithKline, Merck, Pfizer, Sanofi Pasteur, Seqirus

I do not intend to discuss any non-FDA approved or investigational uses of any therapies.

Objectives

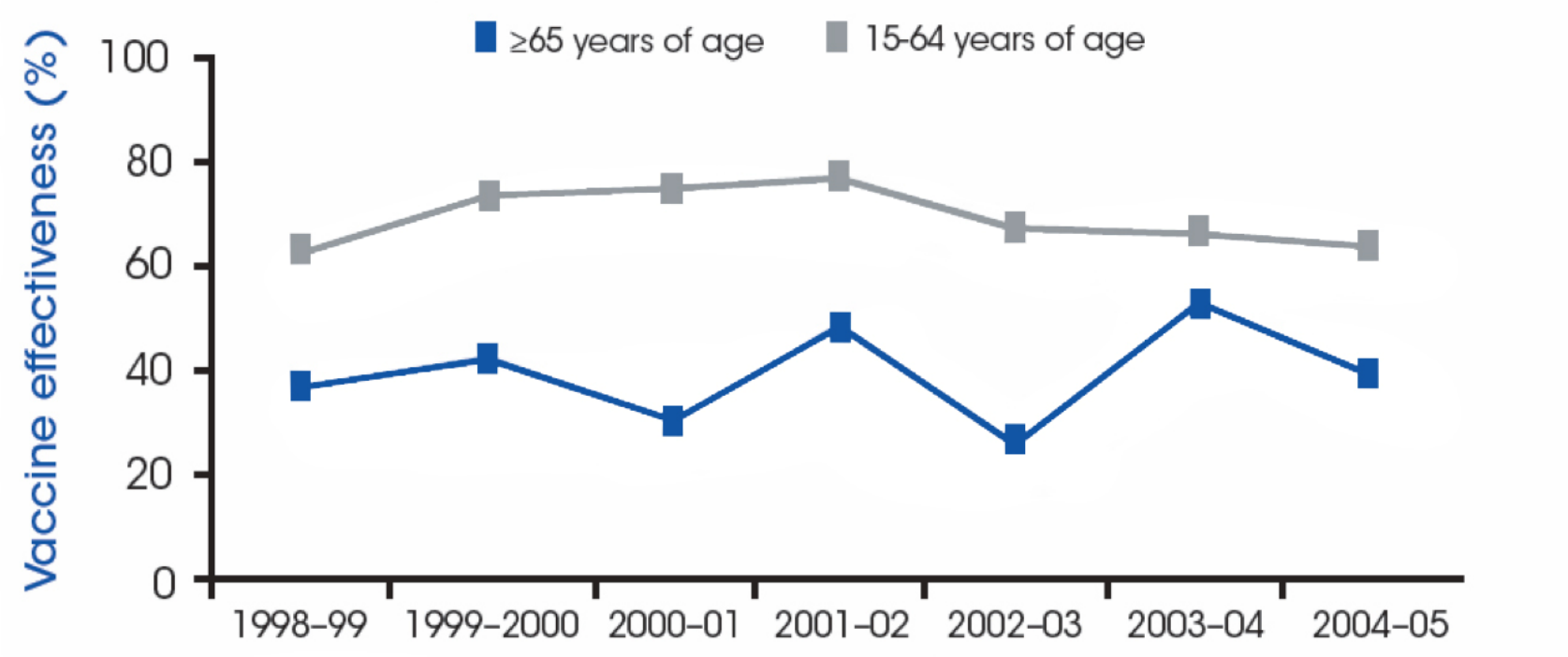
- Use knowledge on vaccine effectiveness to improve vaccine uptake in your patient population
- Recognize direct and indirect effects of disease and vaccines
- Demonstrate knowledge of the relationship between infectious disease and heart attacks

POLLING QUESTION

Are the following persons at increased risk of complications from influenza? (YES or NO)

1. A 70-year-old man whose type 2 diabetes is currently controlled with medication
2. A 66-year-old woman without medical complaints
3. A 90-year-old man without medical complaints who competes in the Senior Olympics

Effectiveness by Age of Influenza Vaccines Against Influenza-like Illness (ILI)[1,2]



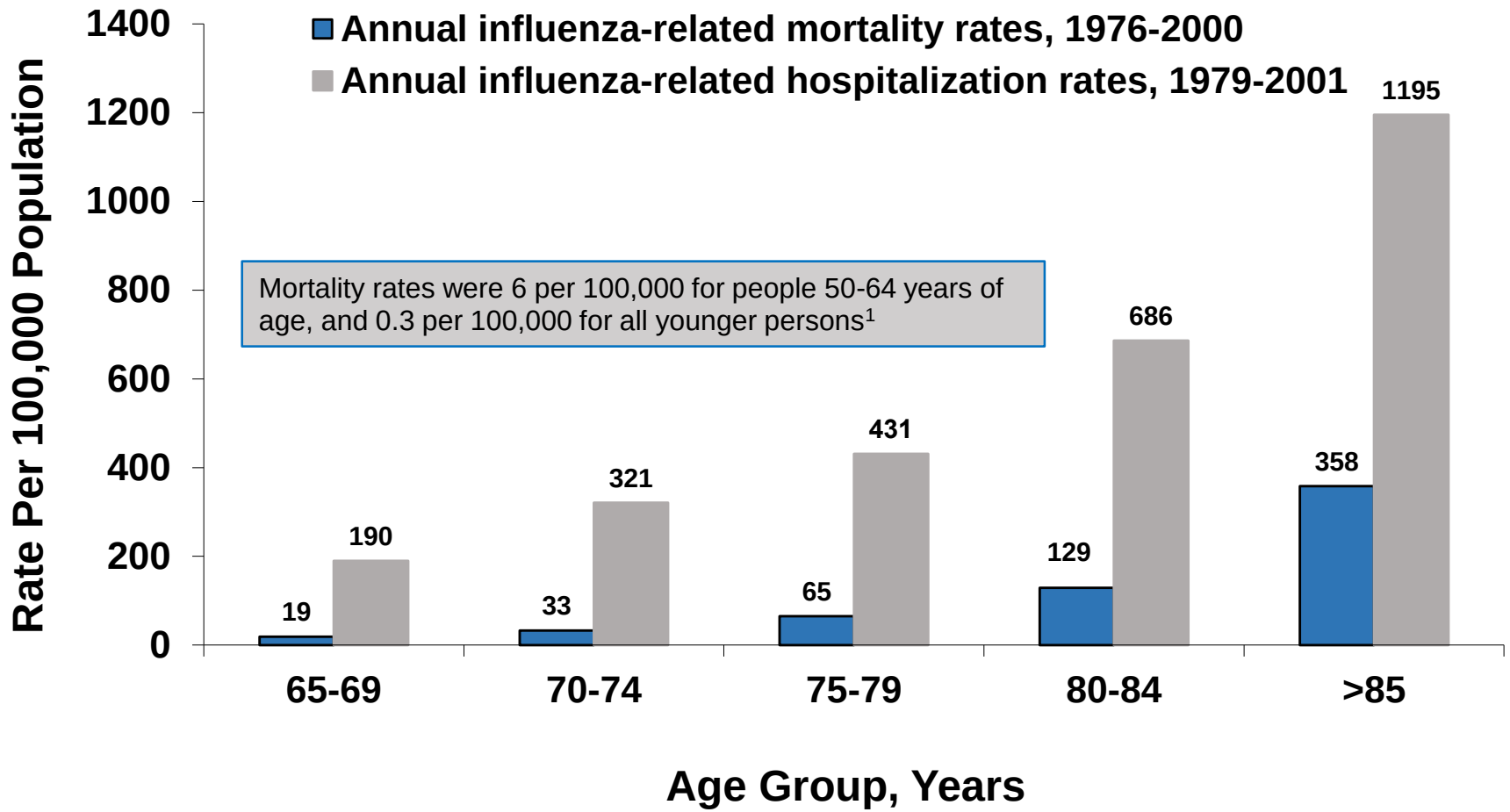
Adapted from Monto AS, et al.[1]

During the 7 influenza seasons shown, the range of vaccine effectiveness was 26%-52% in persons ≥65 years of age and 62%-76% in those 15-64 years of age

References:

1. Monto AS, et al. *Vaccine.* 2009;27(37):5043-5053.
2. Legrand J, et al. *Vaccine.* 2006;24(44-46):6605-6611.

Influenza-Associated Hospitalizations and Death Rates Increase With **Age**[1]



Reference:

1. Thompson WW, et al. *J Infect Dis*. 2006;194(suppl 2):S82-S91.

POLLING QUESTION 2

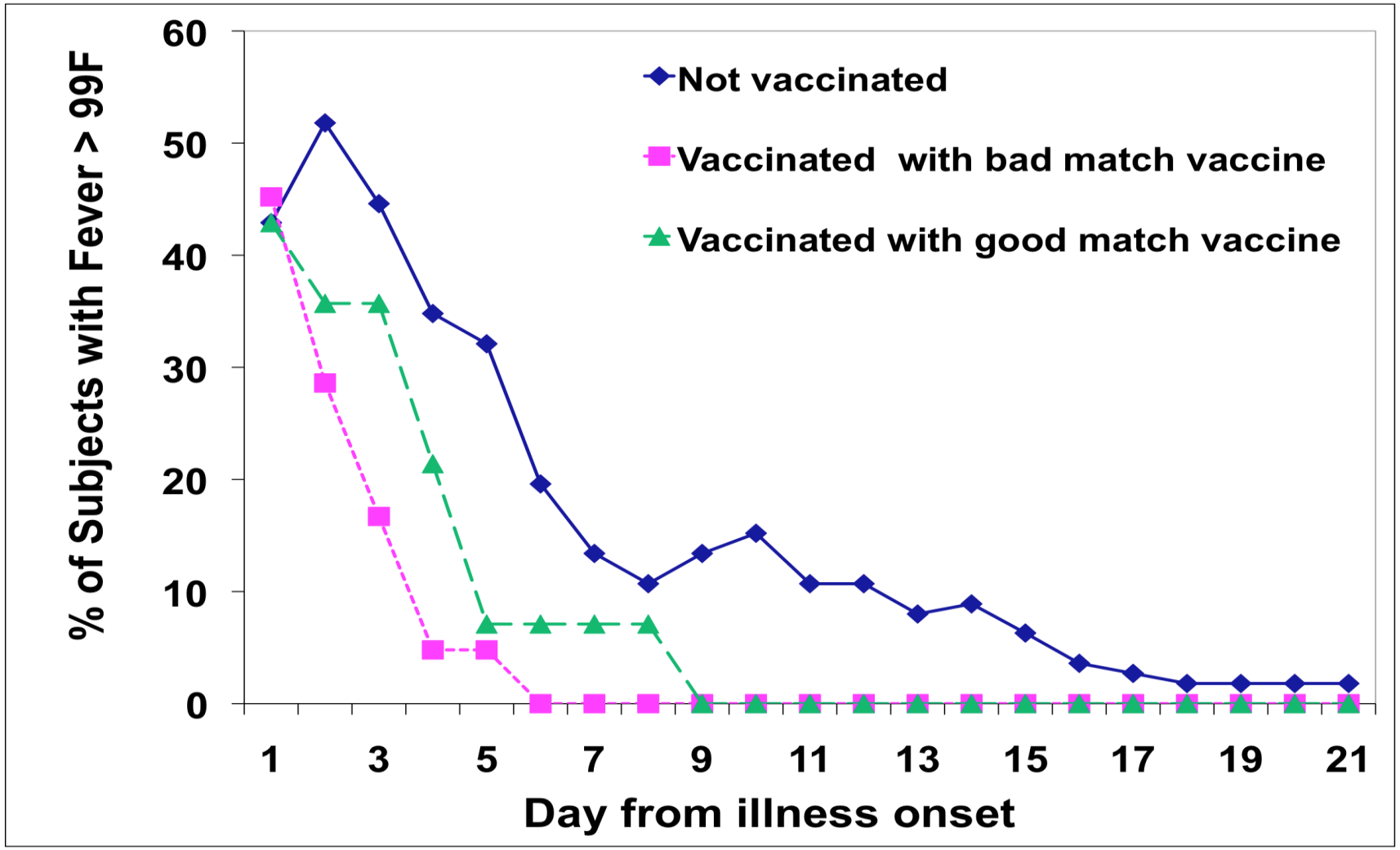
True or False?

Influenza is less symptomatic in the oldest patients.

A. True

B. False

In LTC, Residents' Fever From Flu Is Less, and Fever Is Attenuated More If Vaccinated[1]



Reference:

1. Gravenstein S, et al. *Med Health R I.* 2010;93(12):382-384.
2. Ambrozaitis A, et al. *J Am Med Dir Assoc* 2005;6:367-374.

Influenza, Age and Chronic Medical Conditions:

How These Add to Risk for Influenza-Related Complications in the Older Adult

Chronic Conditions in Adults Hospitalized with Laboratory-Confirmed Influenza[1]

Condition	Age group, percentage of patients			
	18–49 years	50–64 years	65–74 years	≥75 years
Asthma	27.4	19.4	14.5	8.0
Cardiovascular disease	12.2	37.6	53.5	60.8
Chronic metabolic disease	19.7	39.7	45.1	35.3
Chronic lung disease	9.0	27.5	37.9	27.6
Immunosuppressive condition	17.6	14.2	11.4	5.1
Renal disease	9.8	13.5	17.2	17.3
Cognitive dysfunction	4.9	4.0	5.7	13.7
Pregnancy	11.6	0.0	0.0	0.0

Data are from the 2005-2006, 2006-2007, and 2007-2008 influenza seasons in the US.
Over 80% of adults (all ages) who were hospitalized for lab-confirmed influenza had 1 or more comorbid conditions.
More than 50% had 2 or more comorbid conditions.

Reference:

1. Dao CN, et al. *J Infect Dis*. 2010;202(6):881-888.

Infection and Inflammation:

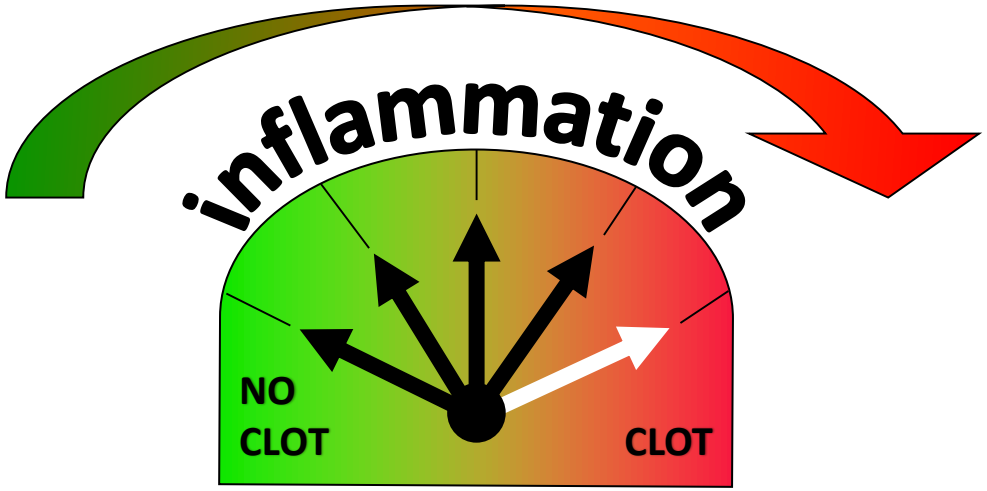
How These Conflate Risk for Vascular Complications in the Older Adult

Age-Adjusted Incidence Ratios of First MI and First 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	0.87, 417	~ 1, 2154
Td (7966)	~ 1, 54	~ 1, 46	~ 1, 253
PPSV23 (5925)	~ 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)	~ 0.77, 365	0.88, 409	~ 1, 2051
Td (6155)	~ 1, 41	~ 1, 40	~ 1, 209
PPSV23 (4416)	~ 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

Reference:
1. 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 following infection

- Influenza
- Community acquired neumonia
- Shingles
- Bladder infection
- Pressure sores

AMI after Influenza

- Of 277k respiratory virus tests, 19k influenza
- 499 of these hospitalized for AMI
- Of these, 332 unique patients and had flu in week before AMI
  - Risk AMI (incidence ratio) 6-fold higher in week after flu
- Risk also increased for AMI following RSV and other viruses by about 3-fold

Kwong JC, et al, N Engl J Med 2018; 378:345-353

Table 2. Incidence Ratios for Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection.*

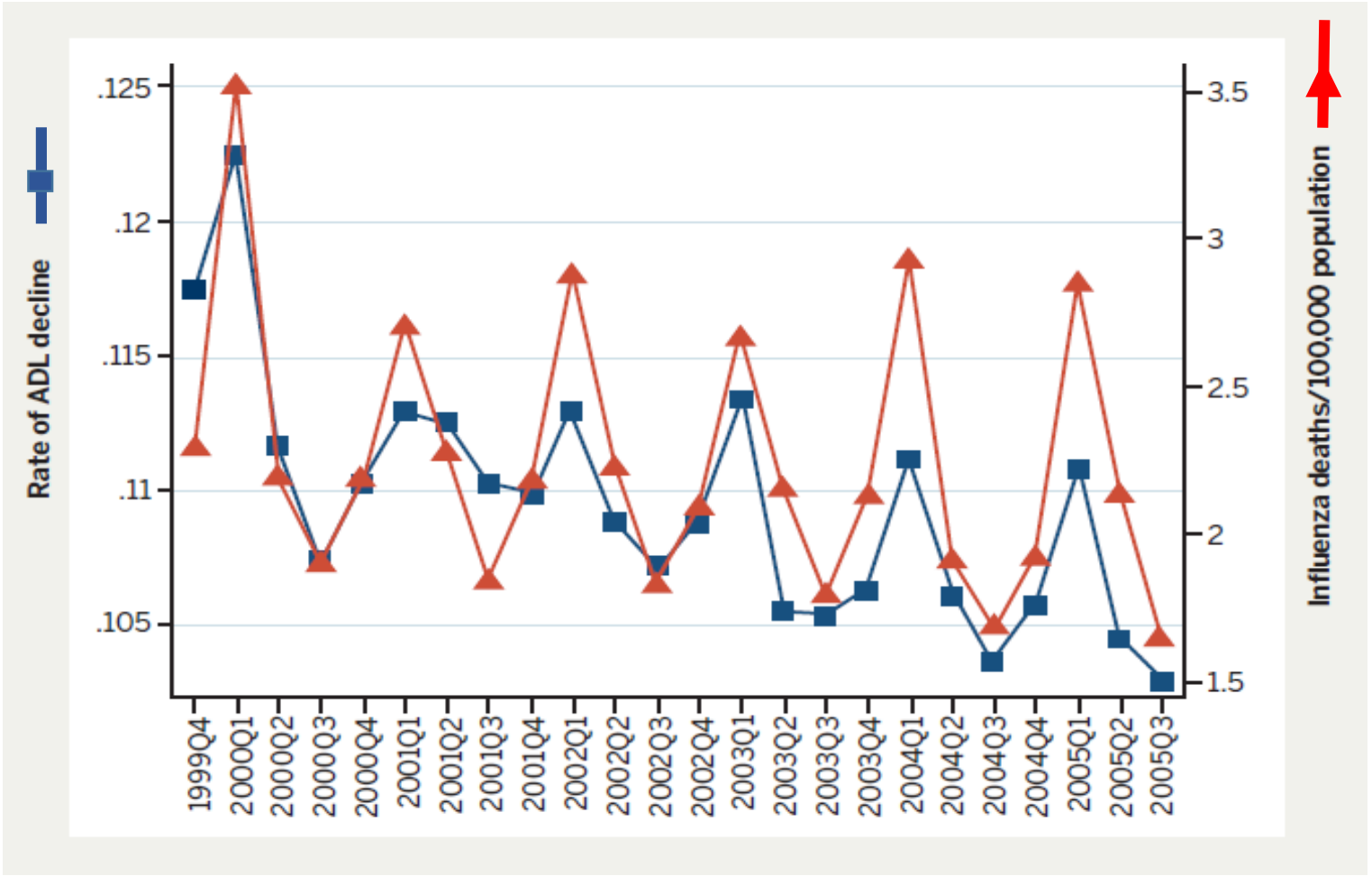
Variable	Incidence Ratio (95% CI)
Primary analysis: risk interval, days 1–7	6.05 (3.86–9.50)
Days 1–3	6.30 (3.25–12.22)
Days 4–7	5.78 (3.17–10.53)
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)
Sensitivity analyses	
Controlled for calendar month	6.19 (3.88–9.88)
Control interval limited to postexposure observation time	8.08 (5.04–12.95)
Control interval limited to preexposure observation time	4.84 (3.06–7.65)
Control interval limited to 2 months before and after influenza detection	5.01 (3.04–8.27)
Includes AMI cases with specimen obtained during admission	4.45 (2.85–6.97)
Induction interval†	
2 days before exposure	5.72 (3.65–8.98)
4 days before exposure	5.92 (3.77–9.29)
7 days before exposure	6.02 (3.83–9.45)
Alternative exposure	
RSV	3.51 (1.11–11.12)
Respiratory virus other than influenza or RSV	2.77 (1.23–6.24)
Illness with no respiratory virus identified‡	3.30 (1.90–5.73)
Hospitalization for diabetes and associated complications§	1.35 (0.50–3.62)

Influenza Negatively Affects Functional Status in Nursing Home Residents

WORSE

Function
Dressing
Bathing
Eating
Toileting
Transferring
Bed mobility
Locomotion

BETTER



Influenza Mortality

Quarterly pattern of the rate of decline of activities of daily living [ADL (■)] vs influenza city-level mortality (▲) for long-stay (>90 days) nursing home residents in 122 CDC-monitored cities in the US, 1999-2005.

Reference:

1. Gozalo PL, et al. *J Am Geriatr Soc*. 2012;60(7):1260-1267.

Focus on LTC Facilities and Influenza Does Vaccine Match Matter?

POLLING QUESTION 3

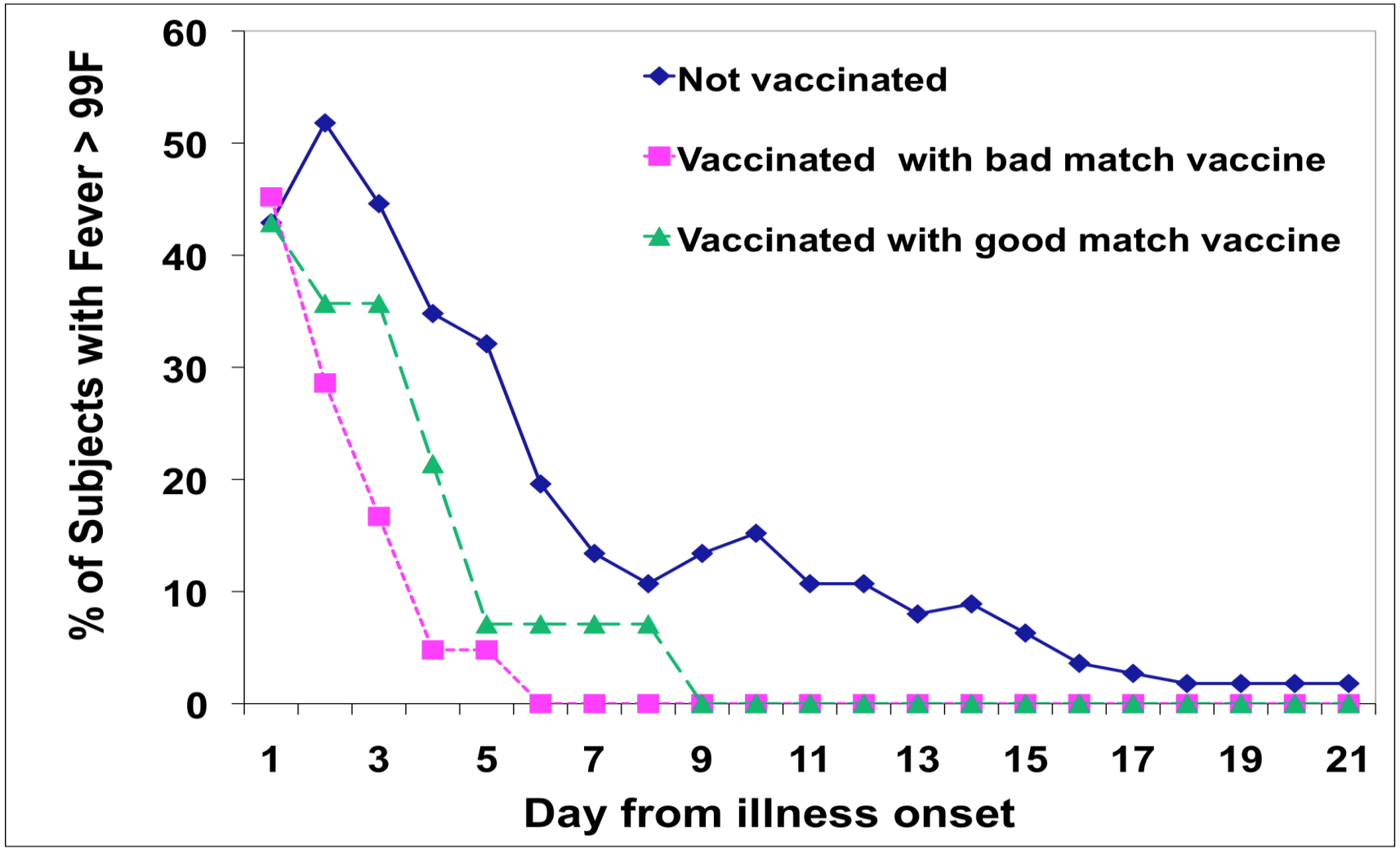
True or False?

Bad match vaccines also reduce influenza severity.

A. True

B. False

In LTC, Residents' Fever From Flu Is Less, and Fever Is Attenuated More If Vaccinated[1]



Reference:

1. Gravenstein S, et al. *Med Health R I.* 2010;93(12):382-384.
2. Ambrozaitis A, et al. J Am Med Dir Assoc 2005;6:367-374.

Match matters

- Attenuated symptoms even with bad match influenza vaccine, so vaccine confers value even if not perfect
- Bad match vaccine is not as effective in preventing hospitalization as good match vaccine

Influenza Vaccination and Cardiovascular Impact

Influenza Vaccine and Cardiovascular Events[1]

- Meta-analysis of 5 clinical trials of >6000 patients with varying degrees of cardiovascular (CV) risk looked at the link between influenza vaccine and CV outcomes
- Influenza vaccine was associated with 36% lower incidence of major CV events within 1 year of vaccination
  - 1.7 major CV events prevented for every 100 persons with CV disease who were vaccinated
- In patients with recent acute coronary syndrome (ACS), influenza vaccine was associated with a 55% lower risk of major adverse cardiovascular events (MACE)

Reference:
1. Udell JA, et al. *JAMA*. 2013;310(16):1711-1720.

The Range of Efficacy of Coronary Interventions Compared With Influenza Vaccination

Table 1 Efficacy of accepted coronary interventions and influenza vaccine in the prevention of myocardial infarction

Coronary intervention	Prevention	Intervention efficacy/effectiveness against acute myocardial infarction (%)
Smoking cessation[4 23–25]	Secondary	32–43
Statins[38]	Secondary	19–30
Antihypertensive drugs[26–29 32]	Secondary	17–25
Influenza vaccine[5 9 18]	Secondary	15–45

MacIntyre CR et al. *Heart*. 2016;102:1953-1956.

Older Adults Have Decreased Immunologic Responses to Vaccines

Summary

- Immune senescence conflates with underlying inflammation and multimorbidity in nursing homes to drive clinical and cost outcomes
  - Reduced vaccine response
  - Increased consequences for vascular outcomes
  - poorly conceived vaccine and influenza prevention and control programs
- Although current vaccines show substantial efficacy, a better vaccine can overcome some of these considerations in the populations at greatest risk

Can More Immunogenic Vaccines Offer Better Clinical Protection?

Vaccines and aging

- If influenza causes such diverse morbidity and mortality, and vaccine response declines with age, can influenza vaccine work in elderly,
  - and if so, also in the frailest old?
- Can it provide benefit for “all” strains?

Effectiveness of High Dose Influenza Vaccine

- Traditional vaccine produces less antibody in elderly; may need more immunogenic vaccine
- In a RCT with over 32000 outpatient elderly, those who got high dose influenza vaccine had 24.2% less laboratory-proven influenza than those who got standard dose[1]
- Similar results (~22% more effective) retrospective cohort metadata-type studies, over millions of people[2,3]

[1]DiazGranados CA, et al. N Engl J Med 2014; 371:635-645.
[2]Izurieta Hset al. Lancet Infect Dis. 2015
[3] Shay DK, et al. (2017). J Infect Dis, 215(4), 510-517.

Cluster-Randomized Trials are Pragmatic for Clinical Research: A Influenza Vaccine Case Study

Influenza Vaccine Reduces Hospitalization and Cardiovascular Events in Nursing Home Residents

Stefan Gravenstein, MD, MPH

Vincent Mor, PhD

Pedro Gozalo, PhD

Monica Taljaard, PhD

Roshani Dahal, MPH

H. Edward Davidson, PharmD, MPH

Lisa F. Han, MPH

Jessica Ogarek, MS

Background

- Diaz Granados, et al: outpatient RCT with 24% reduction in influenza
- Nursing home RCT: more antibody to HD from all 3 vaccine strains to 180 days over two seasons except ~ for 2012-3 for A/H1N1 at 30 days

Randomized, Controlled Trial of High-Dose Influenza Vaccine Among Frail Residents of Long-Term Care Facilities

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[1]Division of Geriatric Medicine, [2]Department of Family Medicine, University of Pittsburgh, Pennsylvania; and [3]Vaccine and Gene Therapy Institute of Florida, Port Saint Lucie

But, does HD also provide better clinical protection for nursing home residents?

Diaz Granados, et al, NEJM 2014:371.
Nace, et al, JID 2015:211 (15 June)

Objectives

- Review results from pilot study undertaken in 39 nursing facilities during the 2012-13 influenza season
- Present findings from the full cluster randomized controlled trial (RCT) of high-dose (HD) influenza vaccine vs. standard-dose (SD) influenza vaccine in 823 nursing homes (NHs) during the 2013-2014 influenza season
- Additional analyses

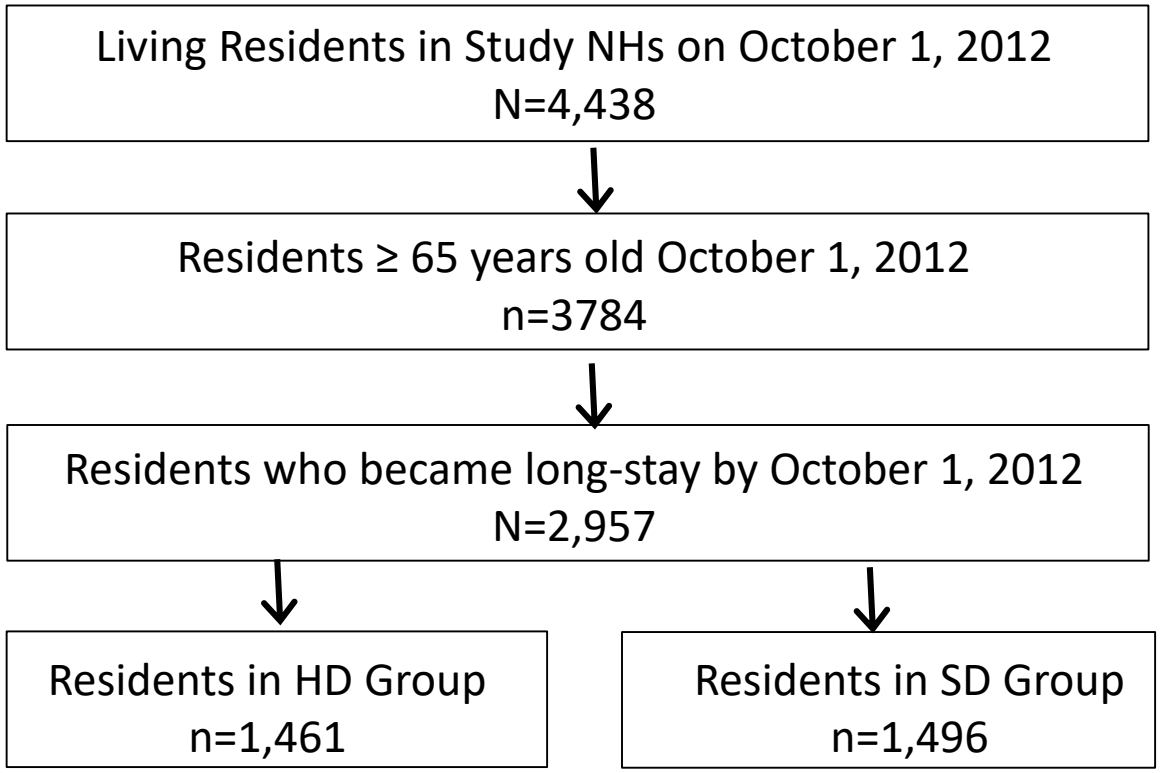
Pilot Study: Methods

	2012				2013		
	Sept	Oct	Nov	Dec	Jan	Feb	Mar
Facility recruitment	→	→					
Random assignment	→	→					
Vaccine distribution		→	→				
Staff education	→	→	→	→			
Outcome			→	→	→	→	→

- **39 total NHs**, with the majority from 2 states (14 NHs in New Jersey, 17 in Colorado)
  - ✓ All NHs administered SD as standard of care the prior season
- NHs randomly assigned to either HD or SD
- 19 NHs assigned to SD; 20 NHs assigned to HD

Gravenstein S et al, *Hum Vaccin Immunother* 2017 Nov

Feasibility Study: Methods
Patient Eligibility and Selection

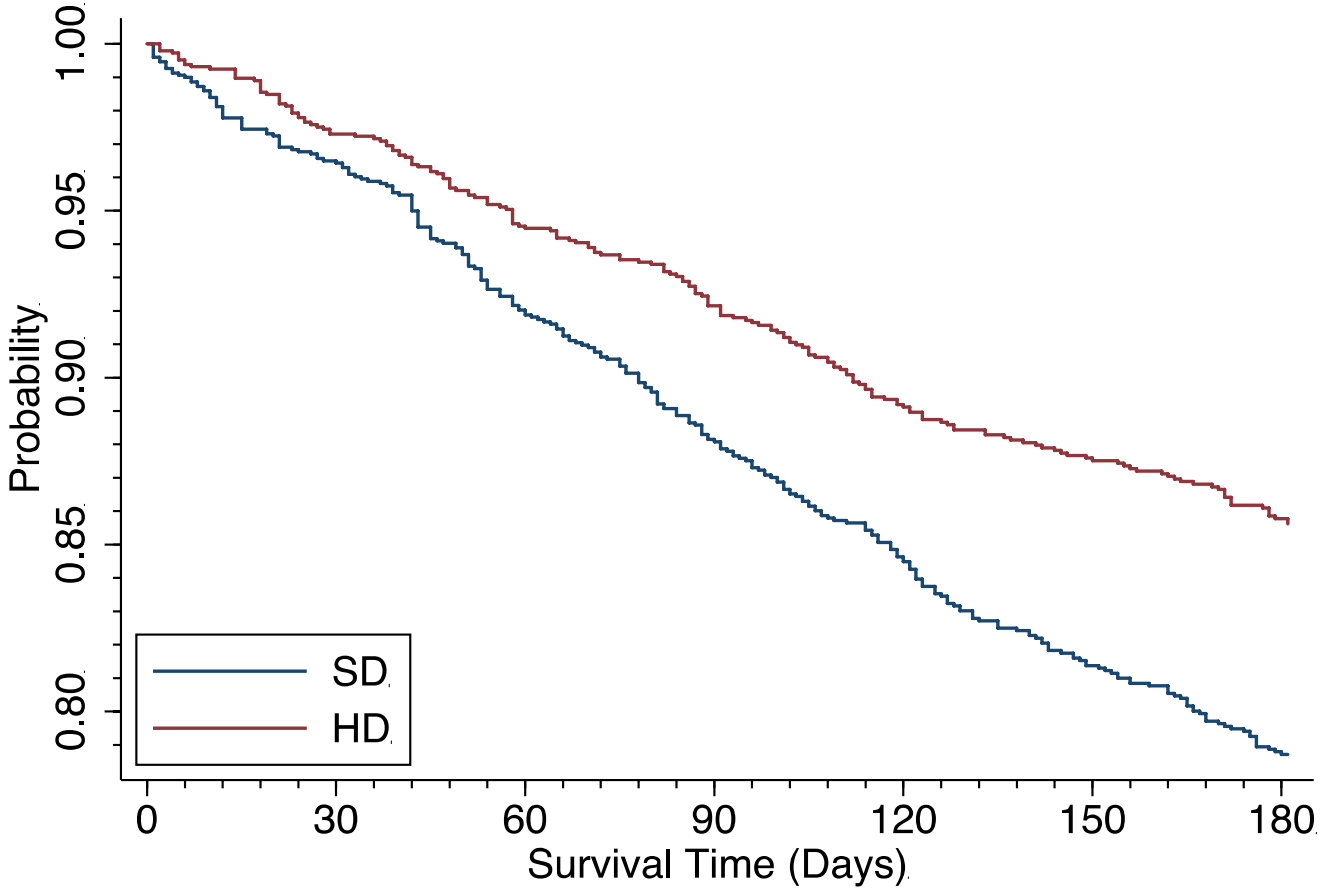


[a] Residents who were 65 years old on October 1, 2012.

[b] Long-stay residents = NH residents with quarterly and annual Minimum Data Set (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 mental retardation/developmental disabilities (MR/DD) facility.

Gravenstein S et al, *Hum Vaccin Immunother 2*017

Feasibility: Ever Hospitalized

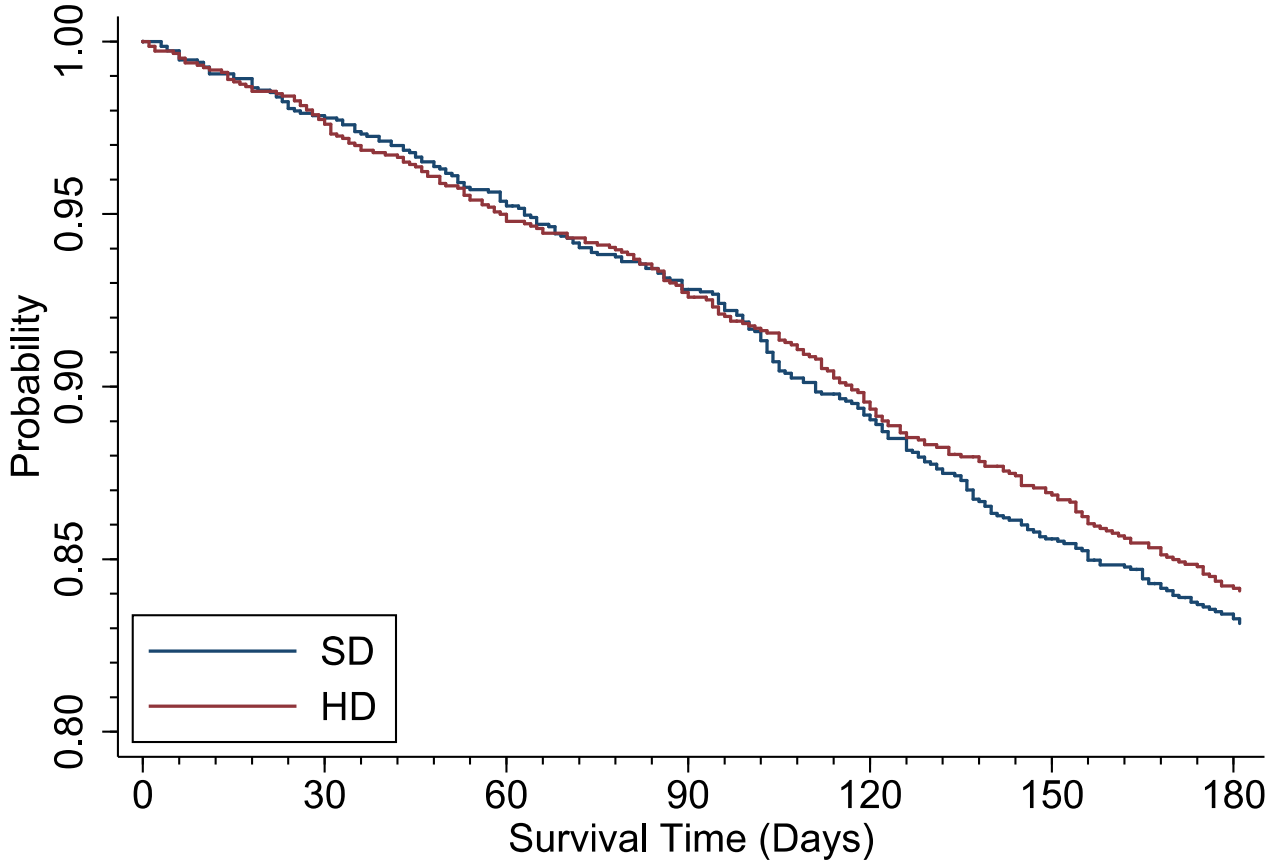


Number at risk

SD	1494	1418	1322	1241	1159	1082	1028
HD	1460	1395	1323	1264	1184	1129	1080

Gravenstein S et al, *Hum Vaccin Immunother* 2017

Feasibility Study: Mortality



Number at risk

SD	1494	1460	1419	1378	1319	1262	1220
HD	1460	1425	1383	1349	1298	1253	1211

Gravenstein S et al, *Hum Vaccin Immunother* 2017

Pilot Results: Poisson Regression Models

Outcome	HD	SD	Unadjusted		Adjusted[a]	
	n (%)	n (%)	Relative Risk (LCL – UCL)[b]	*P*-value	Relative Risk (LCL – UCL)	*P*-value
Ever hospitalized	197 (13.5%)	301 (20.1%)	0.669 (0.512-0.873)	0.003	0.680 (0.537-0.862)	0.001
Death in NH	192 (13.1%)	207 (13.8%)	0.945 (0.738-1.210)	0.651	0.822 (0.655-1.030)	0.089

[a] Adjusted for prior year hospitalization rate, age of resident, mean age of residents in home, individual activities of daily living (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

[b] LCL = lower control limit; UCL = upper control limit

Gravenstein S et al, *Hum Vaccin Immunother* 2017

Pilot Results: Summary

- Large-scale study feasible as pragmatic **cluster** RCT
- Can detect differential signal in hospitalization using **administrative data**
  - Administrative data: data collected by the government such as
    - Data on care quality (in US nursing homes: “Minimum Dataset” or **MDS**)
    - Insurance claims (fees charged to and/or collected from the insurance company that also contain a diagnosis and service for why the claim was made; in the US, this is the **Medicare Fee for Service** claims)

Gravenstein S et al, *Hum Vaccin Immunother 2*017

INFLUENZA SEASON 2013-2014

LARGE TRIAL (823 NHs)

BROWN
School of Public Health

CASE WESTERN RESERVE UNIVERSITY
SCHOOL OF MEDICINE

insight therapeutics

Comparative effectiveness of high-dose versus standard-dose influenza vaccination on numbers of US nursing home residents admitted to hospital: a cluster-randomised trial

Stefan Gravenstein, H Edward Davidson, Monica Taljaard, Jessica Ogarek, Pedro Gozalo, Lisa Han, Vincent Mor

Summary

Background Immune responses to influenza vaccines decline with age, reducing clinical effectiveness. We compared the effect of the more immunogenic high-dose trivalent influenza vaccine with a standard-dose vaccine to identify the effect on reducing hospital admissions of nursing home residents in the USA.

Methods We did a single-blind, pragmatic, comparative effectiveness, cluster-randomised trial with a 2×2 factorial design. Medicare-certified nursing homes in the USA located within 50 miles of a Centers for Disease Control and Prevention influenza reporting city were recruited, so long as the facilities were not located in a hospital, had more

Lancet Respir Med 2017

Published Online
July 20, 2017
http://dx.doi.org/10.1016/S2213-2600(17)30235-7

See Online/Comment
http://dx.doi.org/10.1016/S2213-2600(17)30290-4

Pragmatic Cluster RCT of HD in Nursing Homes (NHs)

- Recruit NHs in areas adjacent to 122 cities in CDC Influenza Surveillance System
- Use government-required nursing home **MDS** assessment to:
  - Identify permanent NH residents, and their
  - Associated demographic and functional characteristics
  - Measure outcomes over time
- Use **Medicare** hospital claims to measure outcome of hospitalization for influenza (pneumonia and influenza [**P&I**]) and **cardiovascular** exacerbations of influenza

Gravenstein et al, *Lancet Respir Med* 2017

Study Design

Design

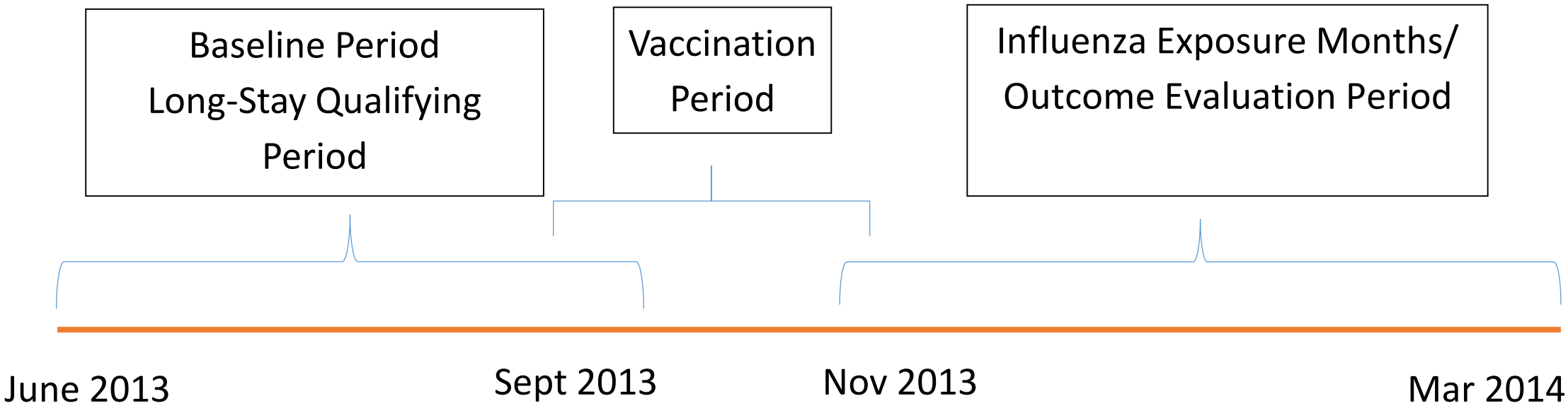
- Recruit facilities within 81 km of CDC cities
- Randomly assigned facilities to High Dose vs Standard Dose influenza vaccine
- Educate facility staff on influenza, study procedures
- Link to facility data, MDS, and Medicare files
- Collect vaccination data reports

Data from Federal Databases

- Nursing home characteristics ("OSCAR")
- Nursing home resident characteristics (Minimum Dataset or "MDS")
- Hospitalization
- Diagnoses listed in the hospitalization record (Medicare Fee for Service claim or "FFS")
- Death (Vital Status file)

MDS is part of the federally mandated process for clinical assessment of all residents in CMS-certified NHs. It provides a comprehensive assessment of each resident's functional capabilities and helps nursing home staff identify health problems.

Gravenstein et al, *Lancet Respir Med* 2017



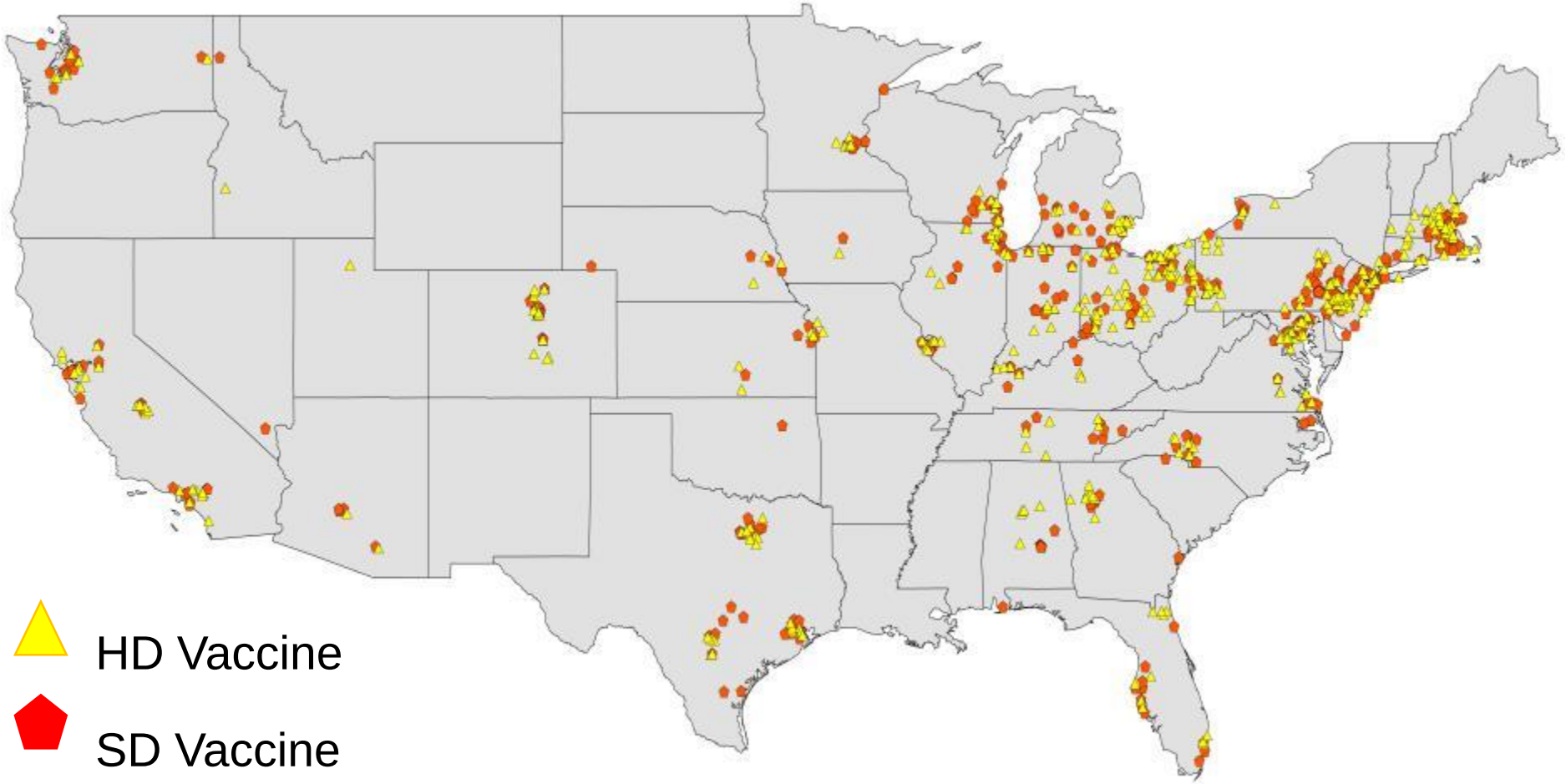
Gravenstein et al, *Lancet Respir Med* 2017

Outcome Determination

- PRIMARY: **Medicare FFS** permanent NH residents; number of hospitalizations due to P&I per patient day:[1]
  - ✓ P&I hospitalization defined as:
    - ✓ ICD9-CM codes 460–466, 480–488, 490–496, 500–518
- ALL permanent NH residents (90+ days), mortality
- ALL permanent NH residents, total hospitalizations per patient-day based upon MDS discharge records
- SECONDARY: Cardiovascular outcomes[2]
  - ICD-9 AMI: 410.xx, 411.xx; HF: 428.x, 429.0, 429.1, 419.7;
  - ICD-9 Atrial fibrillation: 427.3x;
  - ICD-9 Cerebrovascular: 433.xx-438.xx

Reference:
1. Gravenstein et al, *Lancet Respir Med* 2017
2. Gravenstein et al, *IAGG*, San Francisco July 2017

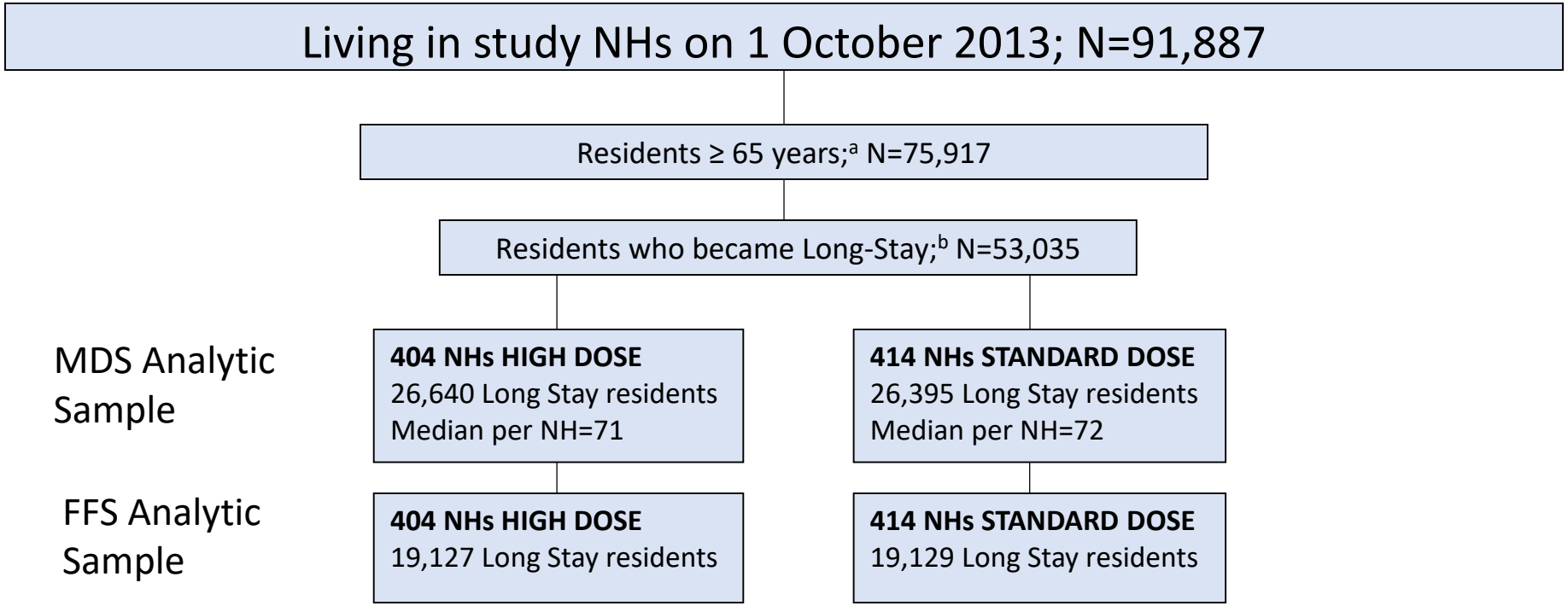
Participating NHs by State (n=823)



Gravenstein et al, *Lancet Respir Med* 2017

Cohort Selection, 2013-2014

(ALL Long-stay NH residents ≥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 (ie, 1 veterans home; 2 rehabilitation facilities that were randomized prior to their withdrawal; 1 facility stopped operation in Nov/Dec 2013; still exploring the remaining 2 facilities that did not match]

Gravenstein et al, *Lancet Respir Med* 2017

Analytic Approach

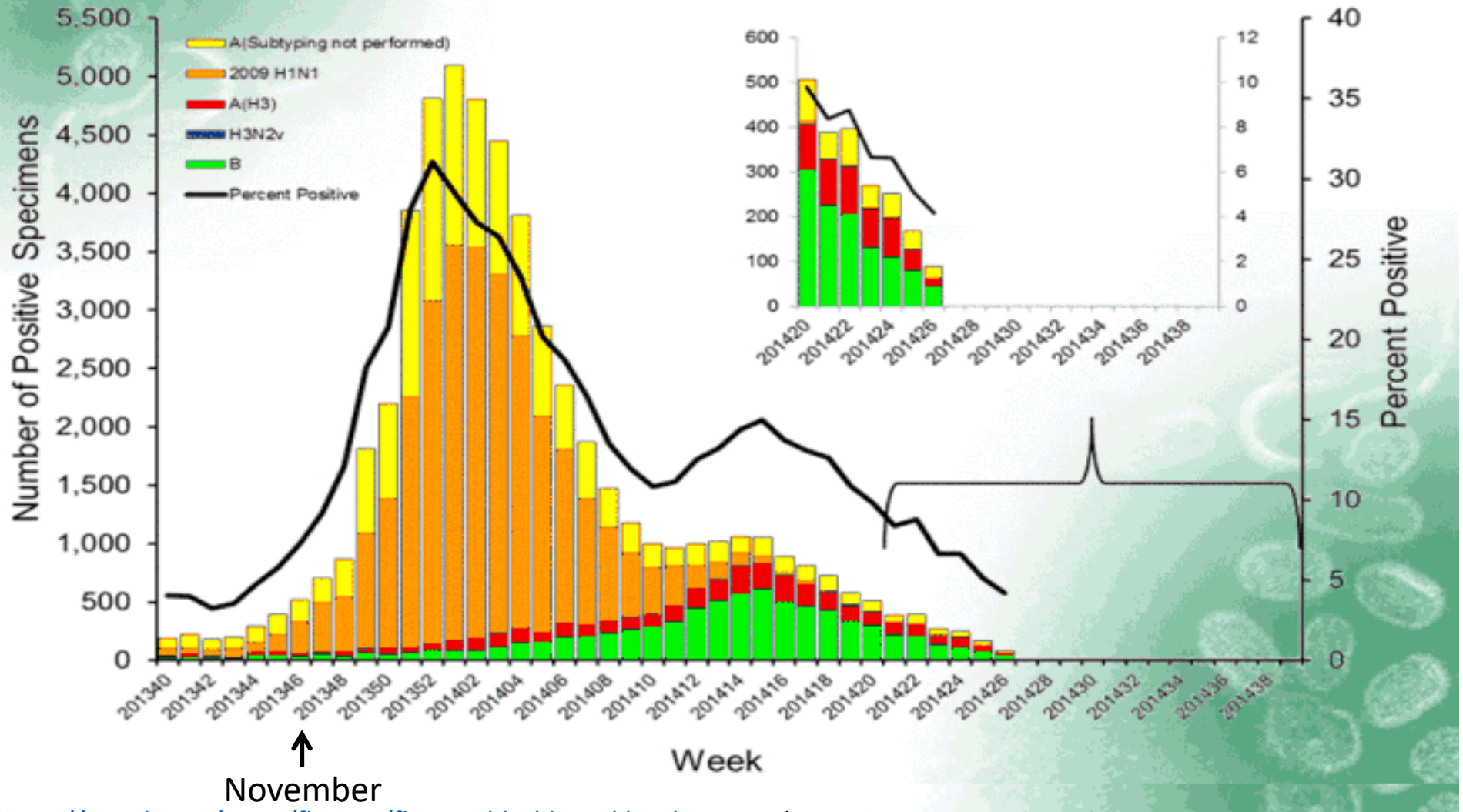
- Unit of analysis: individual residents
  - Adjusted for clustering by NHs using robust variance estimates
- Multivariable logistic, Poisson, and Cox regression
  - Initial model assessed interaction between treatments
  - Adjusted for pre-specified NH- and resident-level covariates
- Analysis by Intention-to-Treat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

Reference: 1. Kahan BC. Bias in randomised factorial trials. *Stat Med*. 2013;32(26):4540-4549.

FLUVIEW

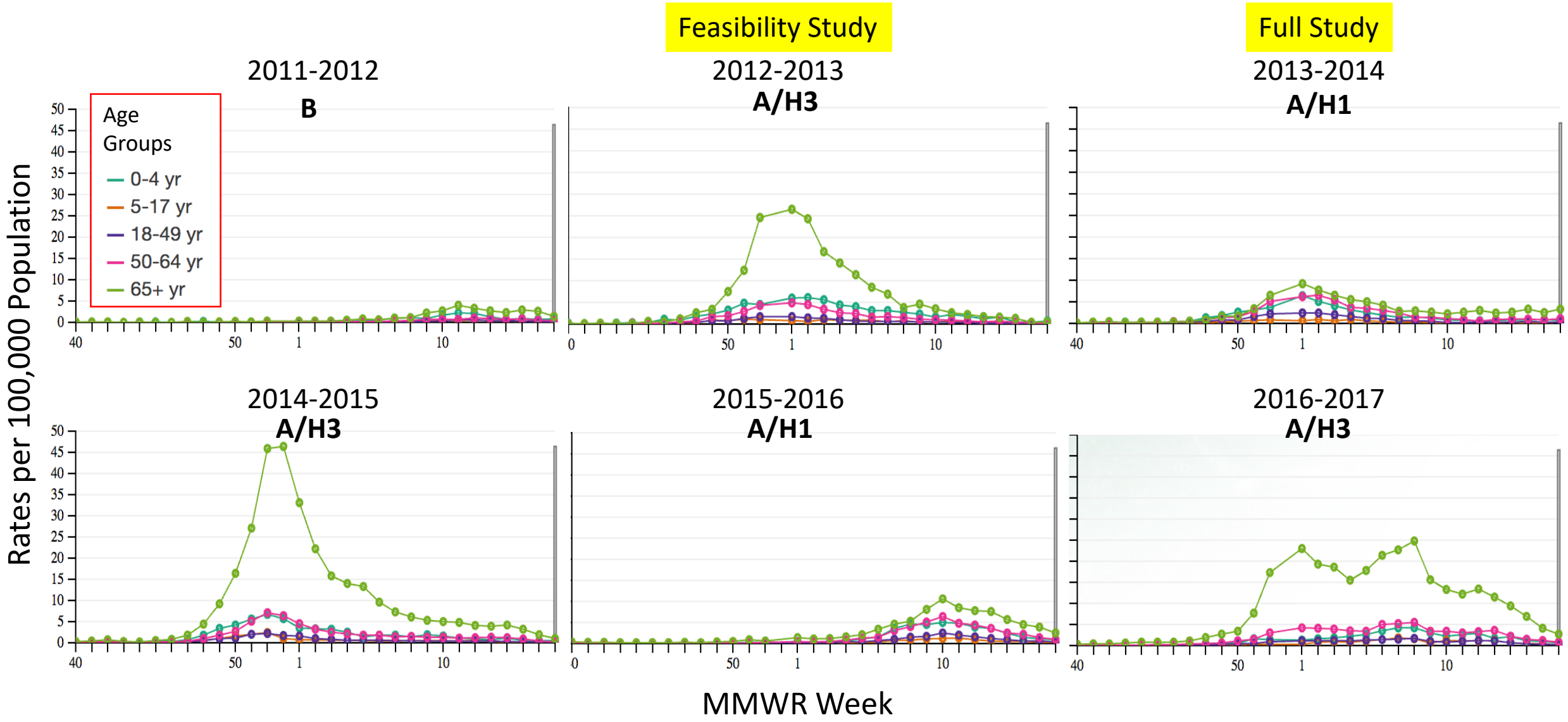
A Weekly Influenza Surveillance Report Prepared by the Influenza Division

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

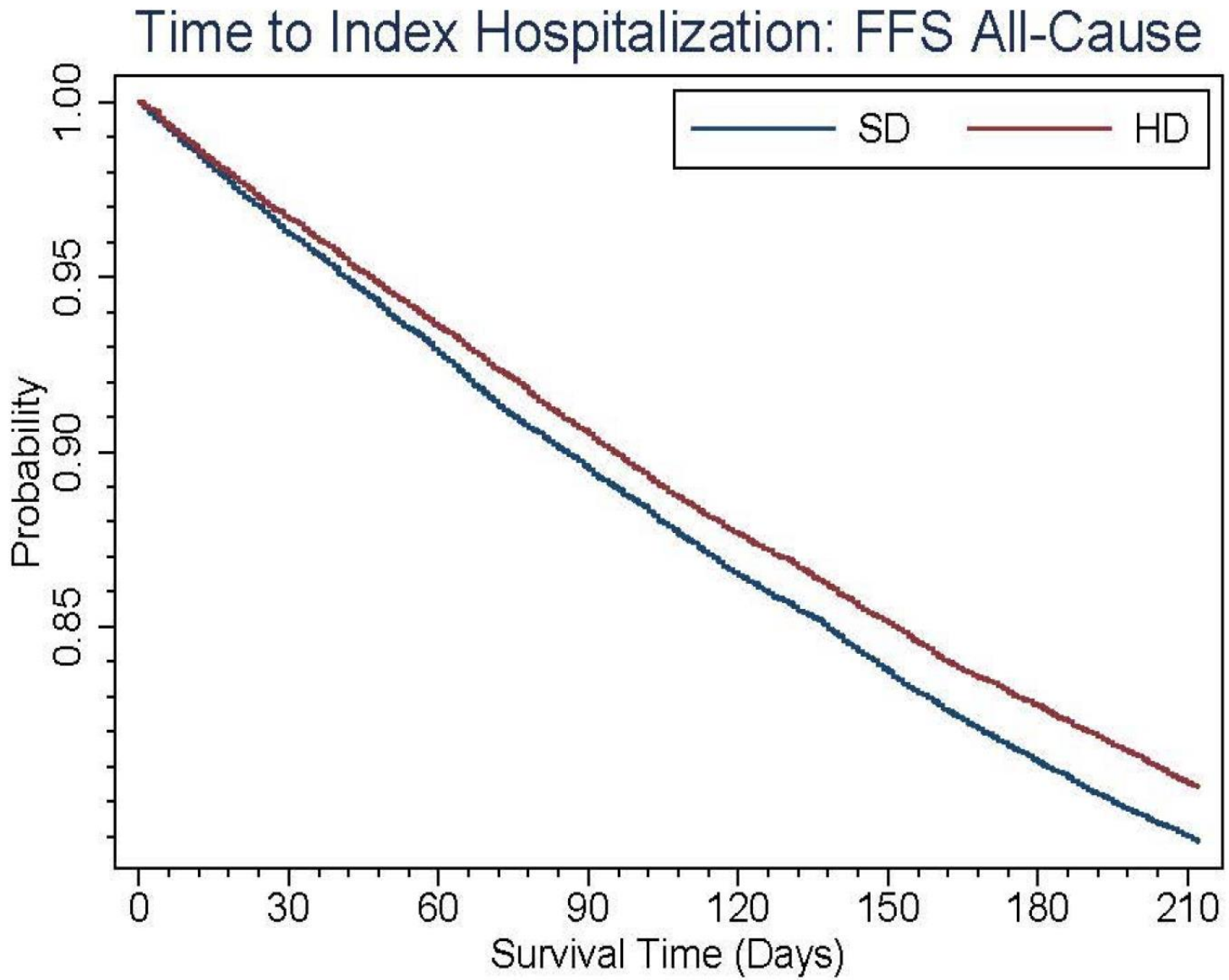


https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html accessed May, 2017

Weekly CDC Surv-NET Lab-Confirmed Flu Hospitalizations by Age and Season 2011-2017



https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html; Downloaded 20 JUN 2017

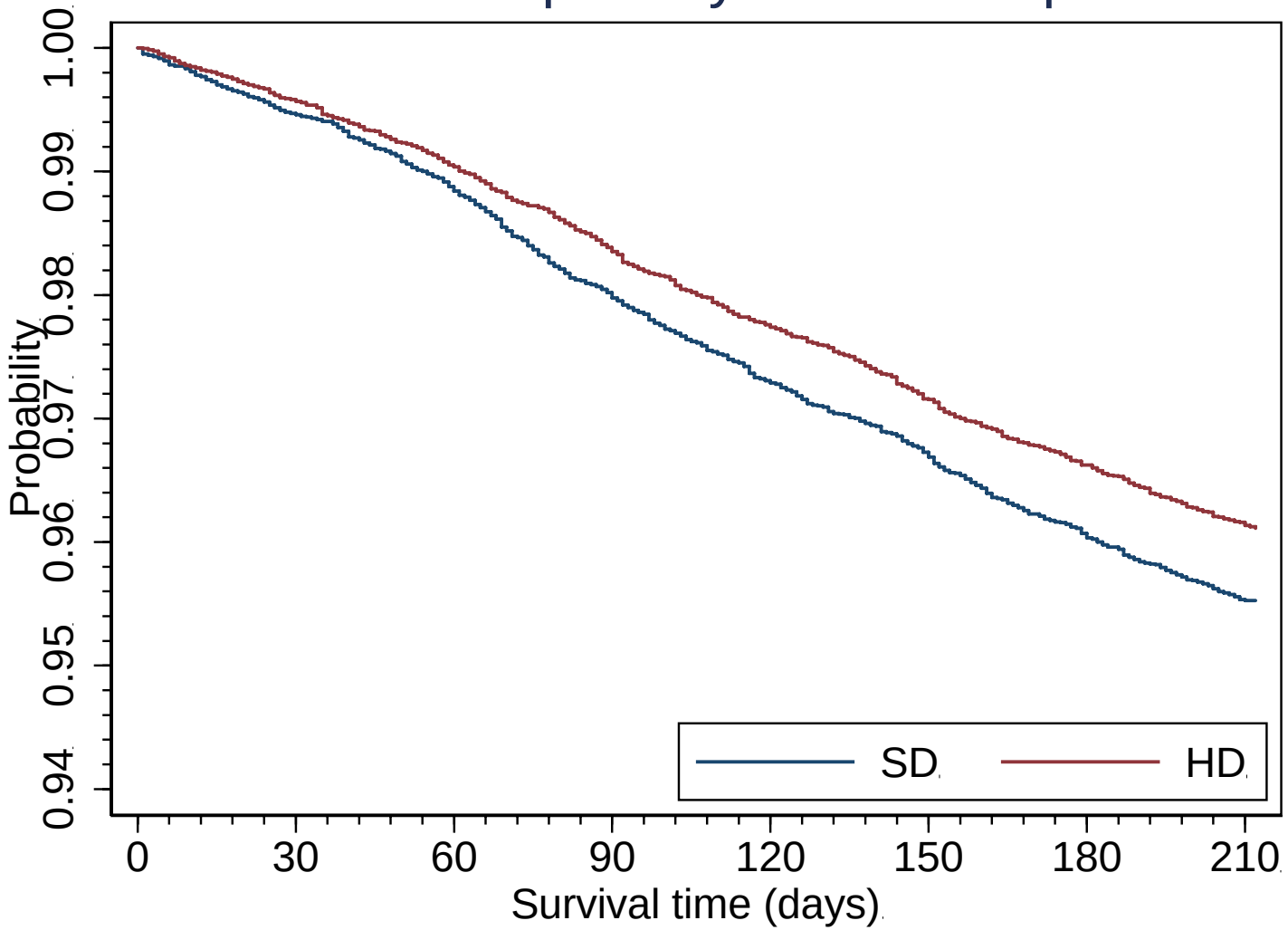


Number at risk

Group: SD Vaccine	19129	18226	17410	16471	15600	14834	14125	13535
Group: HD Vaccine	19127	18301	17511	16612	15790	15053	14368	13768

Gravenstein et al, *Lancet Respir Med* 2017

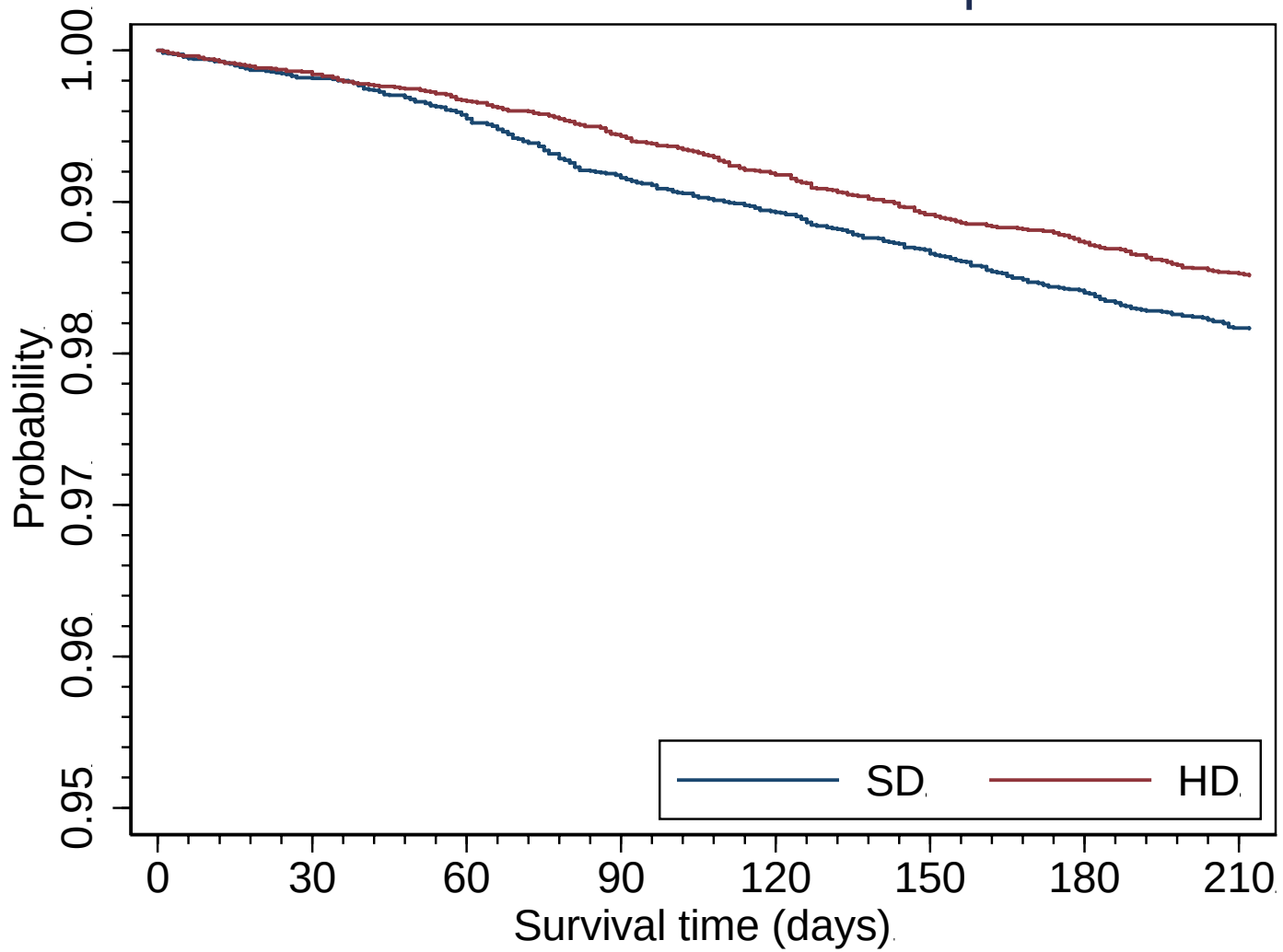
Time to Index Respiratory Illness Hospitalization



Number at risk								
Group: SD Vaccine	19129	18812	18477	17898	17375	16904	16443	16053
Group: HD Vaccine	19127	18827	18482	17959	17467	17001	16562	16166

Gravenstein et al, *Lancet Respir Med* 2017

Time to Index Pneumonia Hospitalization



Number at risk

Group: SD Vaccine	19129	18878	18601	18087	17626	17199	16787	16431
Group: HD Vaccine	19127	18878	18594	18144	17709	17285	16887	16516

Gravenstein et al, *Lancet Respir Med* 2017

Number Needed to Vaccinate (for All Causes, Ever Hospitalized)

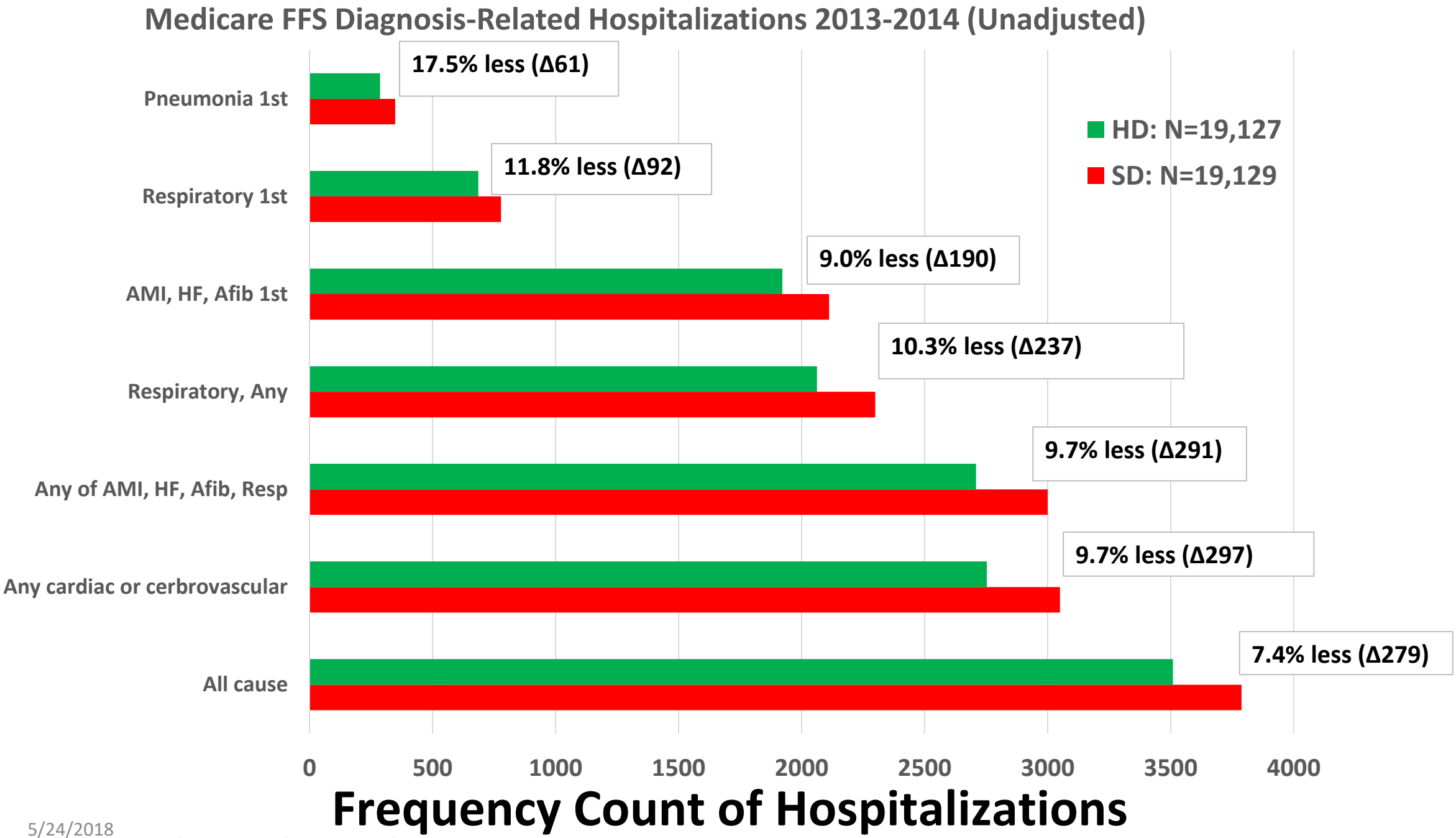
NNT = 1/ARR where ARR = CER – EER[a]

69, FFS sample

To prevent 1 hospitalization, 69 long-stay NH residents 65+ years of age need to be vaccinated with high-dose influenza vaccine compared to standard dose vaccine.

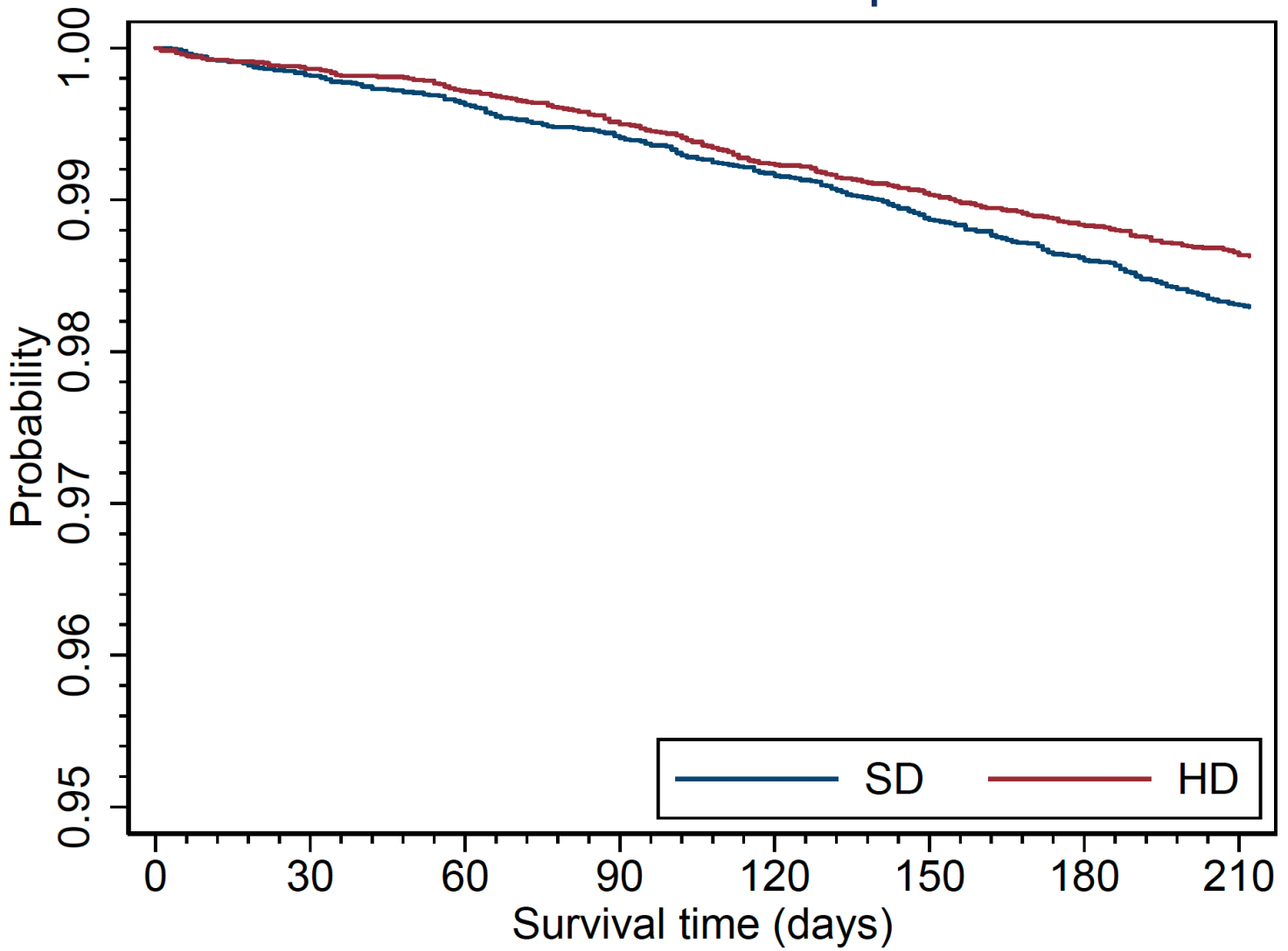
[a] NNT (or NNV) = number needed to treat; ARR = absolute risk reduction; CER = control event rate (i.e., probability of hospitalization for the SD group); EER = experimental event rate (i.e., probability of hospitalization for the HD group)

Gravenstein et al, *Lancet Respir Med* 2017



Gravenstein et al. Presented at IAGG July 2018

Time to Index AMI Hospitalization *

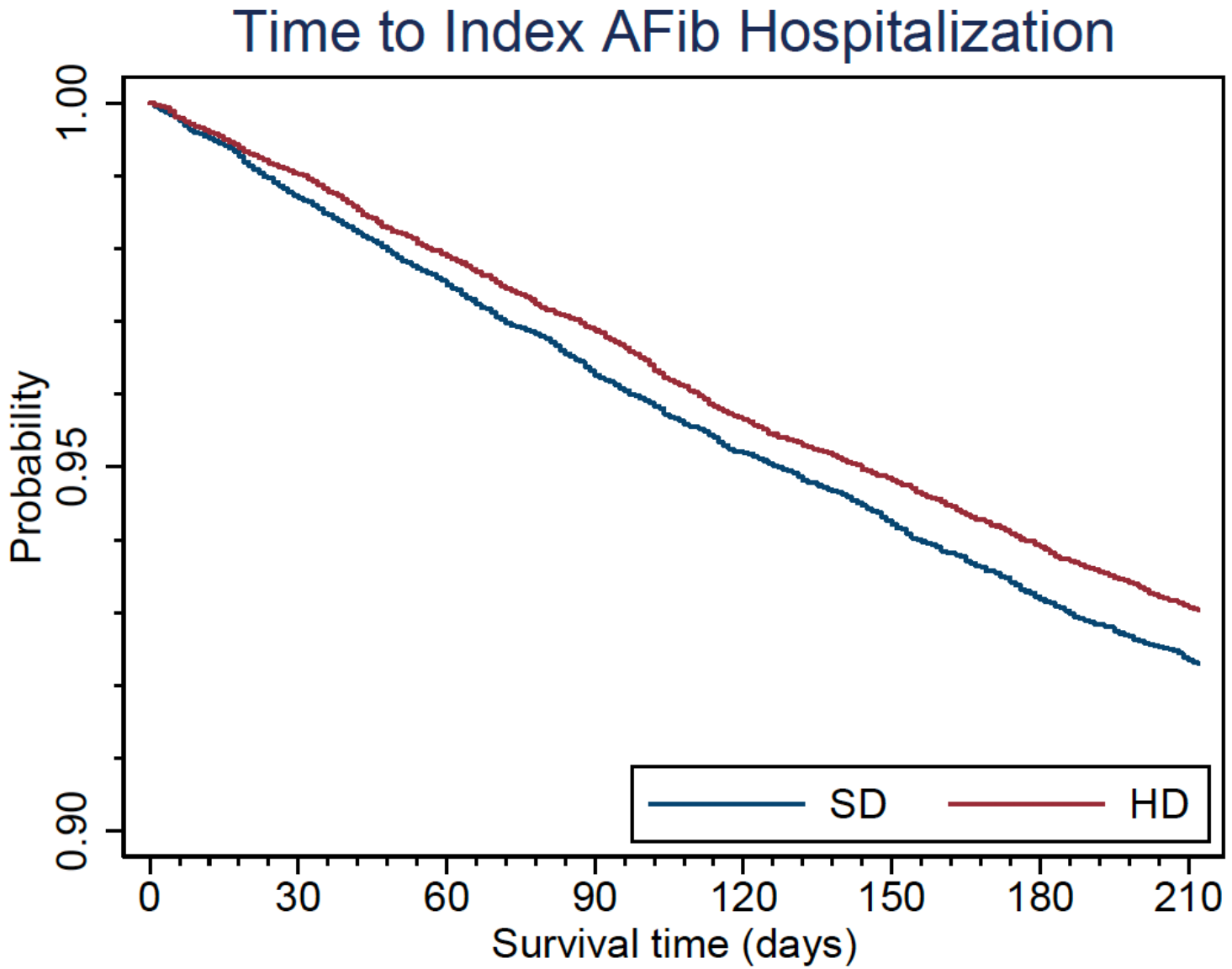


Number at risk								
Group: SD Vaccine	19129	18876	18611	18133	17674	17237	16835	16477
Group: HD Vaccine	19127	18879	18605	18160	17716	17306	16902	16536

*p=0.017

Gravenstein, et al, IAGG, San Francisco, 2017

Gravenstein et al. Presented at IAGG July 2018

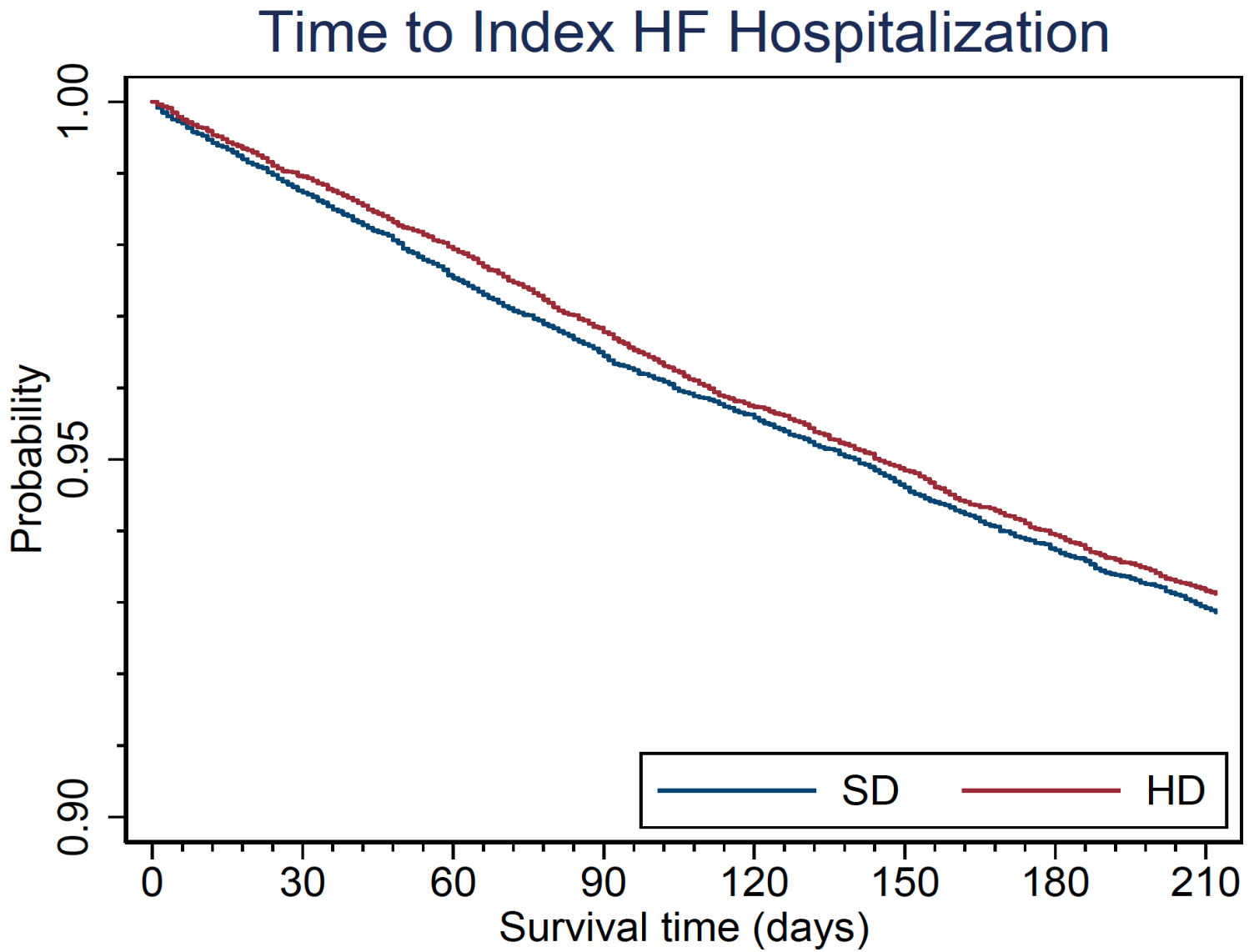


Number at risk

Group: SD Vaccine	19129	18676	18249	17619	17032	16523	16018	15598
Group: HD Vaccine	19127	18726	18285	17711	17132	16639	16145	15703

Gravenstein, et al, IAGG, San Francisco, 2017

Gravenstein et al. Presented at IAGG July 2018



Number at risk								
Group: SD Vaccine	19129	18680	18247	17637	17093	16569	16085	15667
Group: HD Vaccine	19127	18710	18285	17690	17135	16632	16141	15716

Gravenstein et al. Presented at IAGG July 2018

Gravenstein, et al, IAGG, San Francisco, 2017

Unadjusted and adjusted marginal Poisson regression analysis outcomes accounting for clustering by NHs

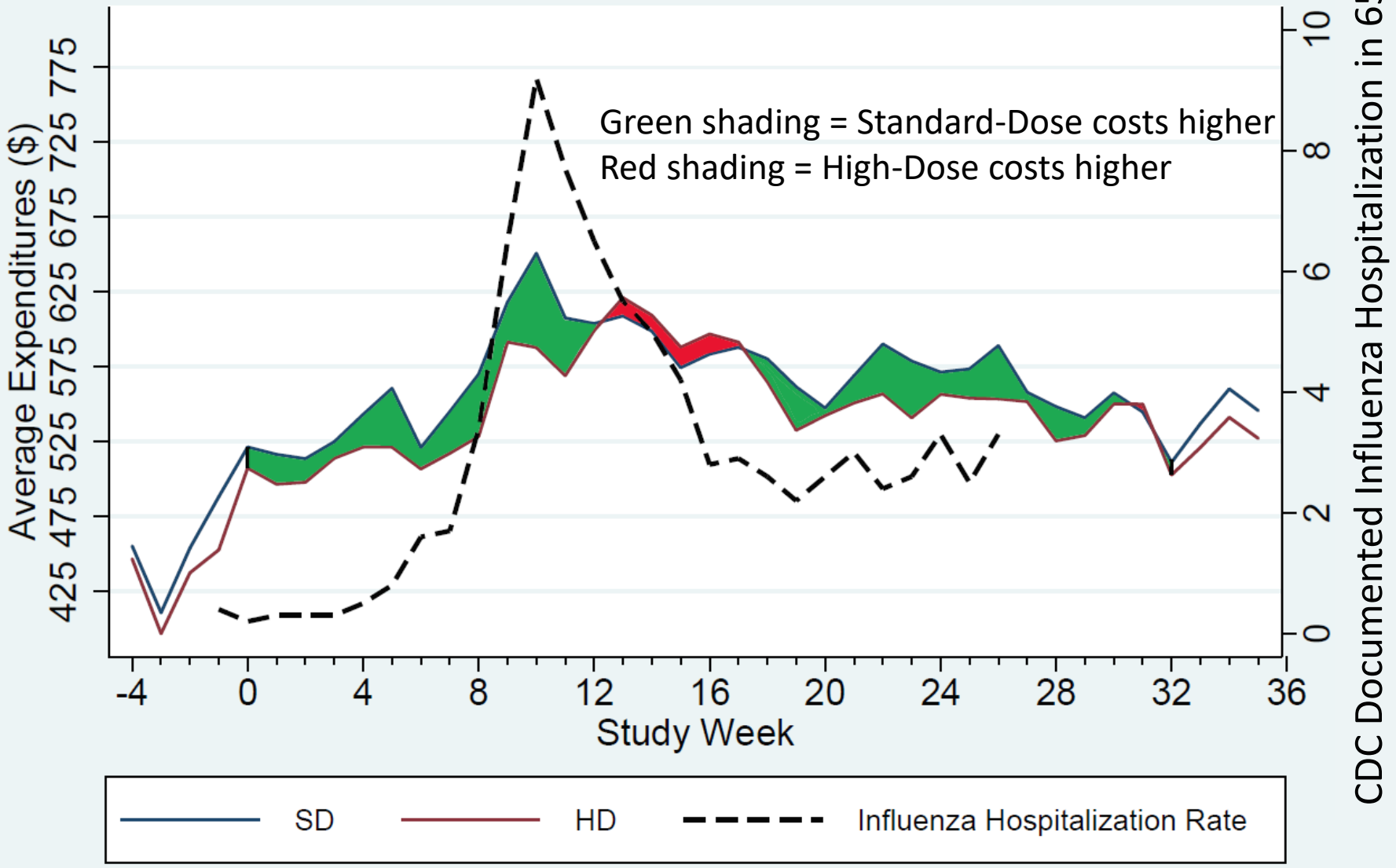
	UNADJUSTED				ADJUSTED			
	# homes # residents	RR	95% CI	p-value	# homes # residents	**RR**	95% CI	p-value
Hospitalization for respiratory Illness (FFS)	818 38,256	0.888	0.785 - 1.005	0.0608	817 38,225	**0.873**	0.776 - 0.982	0.0234
All-cause hospitalization (FFS)	818 38,256	0.920	0.859 - 0.985	0.0167	817 38,225	**0.915**	0.863 - 0.970	0.0028
Hospitalization for Pneumonia (FFS)	818 38,256	0.845	[illegible]	0.0799	817 38,225	0.825	[illegible]	0.0438

Abbreviations: CI = confidence interval, FFS = fee-for-service, MDS = minimum data set, RR=relative risk (HD vs. SD homes)

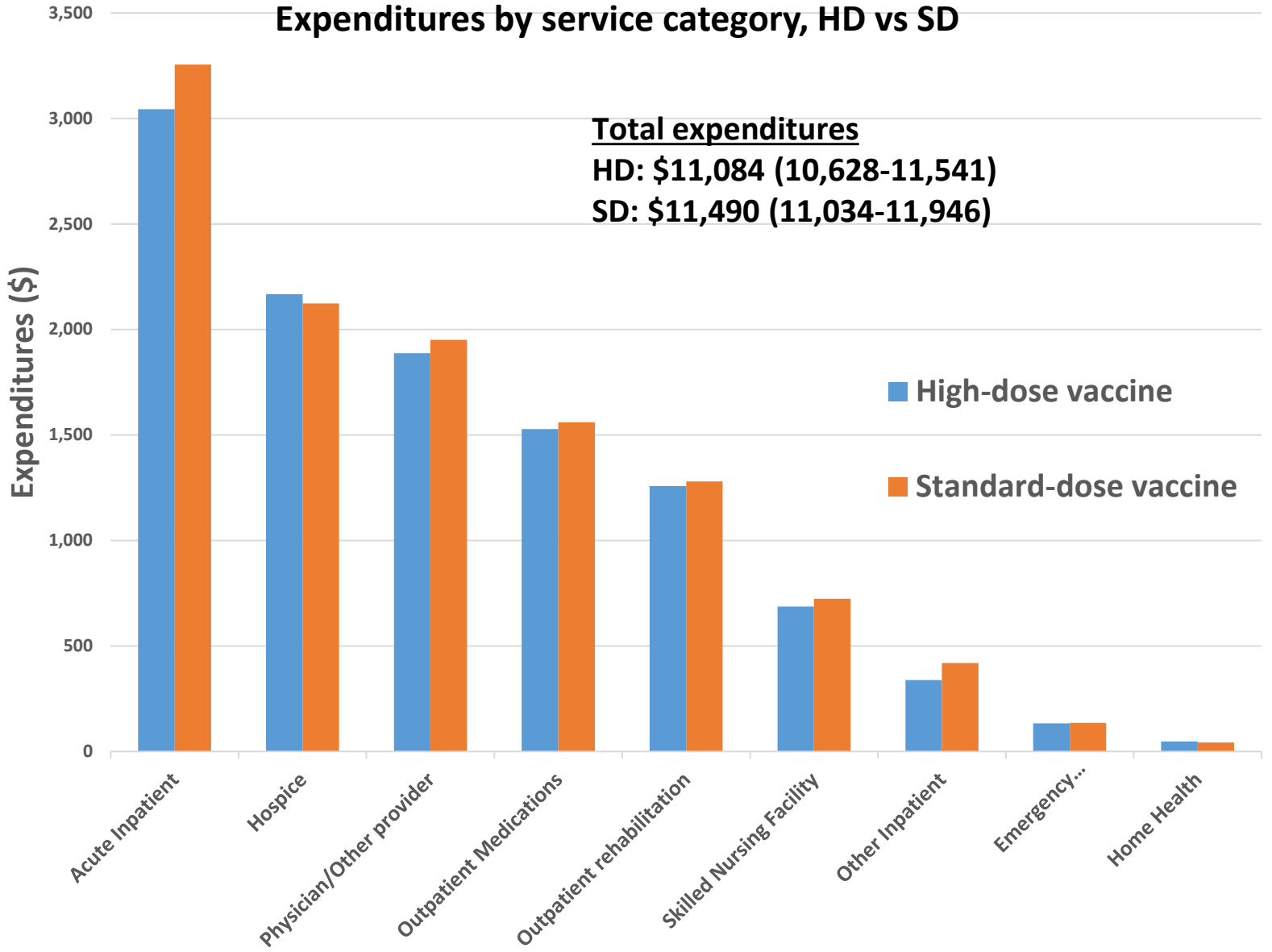
[1] Adjusted for age and average age of facility residents, ADL and average ADL of facility residents, cognitive function, facility hospitalization in prior year and patient chronic heart failure as reported in the MDS. One facility had missing facility covariates, so was excluded from all adjusted analyses.

Gravenstein S, et al. *Lancet Respir Med* 2017.

Average Weekly Expenditures [1]



[1]Shireman T, et al. AGS Orlando May 2018



[1]Shireman T, et al. AGS Orlando May 2018

Differences in costs ($)	Standard-Dose minus High-Dose
Service category	Mean (95% CI)
Acute Inpatient	262 (-0.06, 524)
Other Inpatient	85 (2, 168)
Emergency Room/Observation	6 (-7, 18)
Skilled Nursing Facility	52 (-24, 129)
Outpatient rehabilitation	43 (-3, 89)
Physician/Other provider	106 (44, 160)
Hospice	-33 (-158, 91)
Home Health	4 (-14, 7)
Outpatient Medications	30 (-16, 76)
Total	546 (153, 939)

[1]Shireman T, et al. AGS Orlando May 2018

Study Results

FLUZONE® High-Dose is associated with net cost savings vs. SD TIV in adults 65+

Resource	High-Dose	Standard-Dose	Difference*
Vaccine Cost**	$31.81	$5.84	**$25.97**
Direct Medical Costs *(Non-routine/urgent care visits, prescription medication, and hospitalizations)*	$645.76	$718.88	**-$73.12**
TOTAL DIRECT MEDICAL COST	**$677.57**	**$724.72**	**-$47.15**
Productivity Costs (Including non-prescription medication)	$137.04	$149.79	**-$12.75**
TOTAL SOCIETAL COSTS	**$814.61**	**$874.52**	**-$59.91**

Per-Patient Canadian Resource Consumption, High-Dose vs Standard Dose (expressed as $CAD)[1]:

*Difference = FLUZONE® HD – FLUZONE®
**Vaccine prices: FLUZONE® HD – US price, SD – Canadian price

Canadian cost estimates were representative of what the Ontario government would have incurred. Hospital costs were collected from the Ontario Case Costing Initiative (OCCI) database; all other costs came from standardized Ontario government fee schedules.
Total Medical Cost = costs of vaccine + ER visits + non-routine/urgent care visits + RI-related prescriptions medications + hospitalizations.
Total societal cost = direct health care costs + cost of non-prescription RIs-related medications + indirect costs.

References:
1. Becker DL, et al. (2016). Human Vaccines & Immunotherapeutics, 12(12), 3036-3042.

Limitations

- No laboratory data to confirm influenza
- HD:SD relative benefit on A(H1N1) may underestimate difference when other strains dominate, especially A(H3N2)

Gravenstein S, et al. *Lancet Respir Med* 2017.

Summary

- HD vaccine reduces influenza and hospitalization among ***outpatient elderly***
- 2013-2014 season is of special interest: a ***nursing home*** population
  - A(H1N1) predominates
    - A(H1N1) has not been considered particularly pathogenic for older adults
  - A relatively low influenza attack rate to comparison seasons
  - NNT design with over 15% of population unvaccinated
- HD may afford some herd immunity in the LTC setting
- The influenza impacts cardiovascular outcomes; vaccine could help with these
- FFS claims differences consistent with biologic plausibility of effect on hospitalization based on diagnoses, and specifically cardiorespiratory outcomes
- The Vaccine confers a cost benefit

Reference:
1. http://www.cartoonistgroup.com/subject/The-Influenza-Comics-and-Cartoons.php/0 accessed 30Mar2018

What is happening in Canada?

- Manitoba provides TIIV HD to LTC facilities
- Ontario has announced a publicly funded program – part of Seniors Action Plan
- Other provinces and territories announcements pending