Aging & the Immune System: Rethinking Vaccines for Older Adults

A collaboration between:

CDC's Current Issues in Immunization NetConference

NVPO's UpShot Webinar Series

Today's Agenda

Introduction

Andrew Kroger, MD, MPH, Medical Officer, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention

The Research Behind Immunosenescence: Understanding How the Immune System Changes with Age

Albert C. Shaw, MD, PhD, Associate Professor of Medicine (Infectious Diseases), Yale School of Medicine

Translation of Efficacy into Effectiveness: Influenza Revisited

Stefan Gravenstein, MD, MPH, Professor of Medicine, Warren Alpert Medical School and Brown School of Public Health, Brown University and Adjunct Professor of Medicine, University Hospitals Cleveland Medical Center, Case Western Reserve University

Learning Objectives

1. Describe an emerging immunization issue
2. List a recent immunization recommendation made by the Advisory Committee on Immunization Practices
3. Locate resources relevant to current immunization practice
4. Implement disease detection and prevention health care services (e.g., smoking cessation, weight reduction, diabetes screening, blood pressure screening, immunization services) to prevent health problems and maintain health

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Do You Have A Question?

Please enter your question into the Q&A pod

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The findings and conclusions in this presentation are those of the authors and do not necessarily represent the views of CDC or HHS.

NVPO and the National Vaccine Plan

- The National Vaccine Plan (NVP) is the nation's leading roadmap for a 21st century vaccine and immunization enterprise.
- The NVP has five overarching goals:
  - Develop new and improved vaccines
  - Enhance the vaccine safety system
  - Support communications to enhance informed vaccine decision-making
  - Ensure a stable supply of, access to, and better use of recommended vaccines in the United States
  - Increase global prevention of death and disease through safe and effective vaccination

Goal 1: Develop New and Improved Vaccines

- Vaccine research and development has led to the eradication and elimination of several serious infectious diseases.
- Continued research and development—**including research that advances our understanding of the immune system**—is necessary to develop new vaccines against emerging threats and to improve the effectiveness of existing vaccines.

The Research Behind Immunosenescence:

Understanding How the Immune System Changes with Age

Albert C. Shaw, MD, PhD, FIDSA, Associate Professor of Medicine (Infectious Diseases), Yale School of Medicine

The Research Behind Immunosenescence: Understanding How the Immune System Changes with Age

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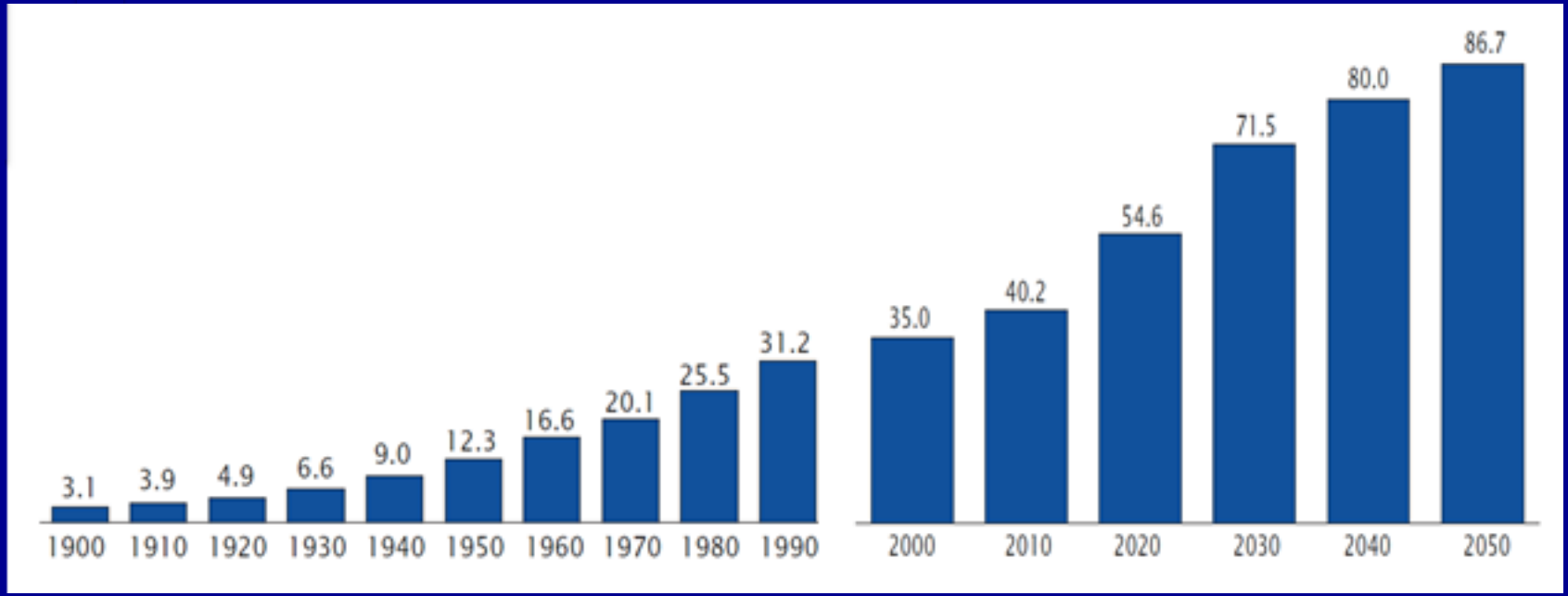
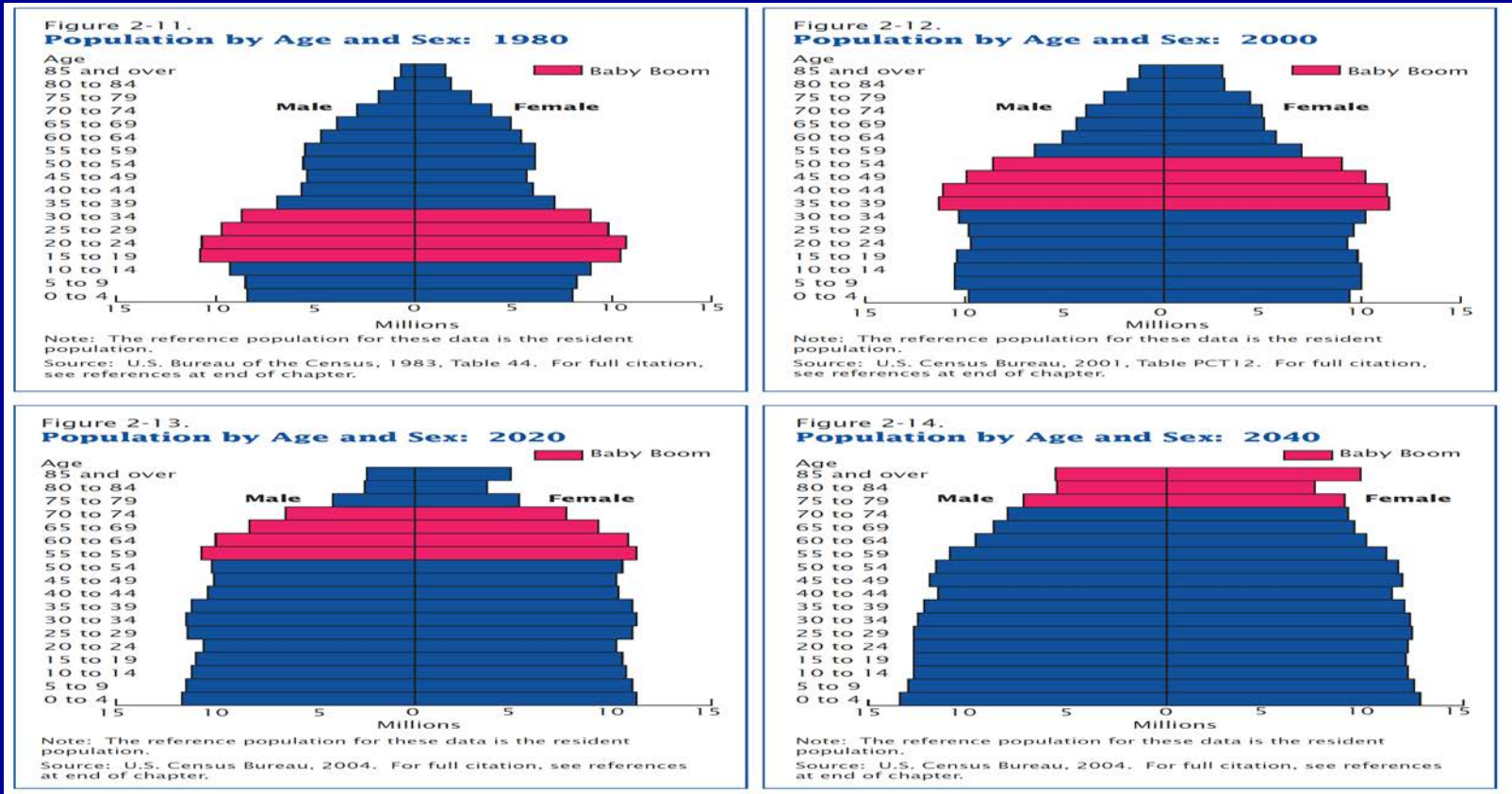
Associate Professor of Medicine
Yale School of Medicine
Section of Infectious Diseases

The Geriatric Demographic Imperative: U.S. Population Over Age 65 (millions)



Individuals over age 65 who currently comprise about 12% of the U.S. population account for over 35% of visits to general internists, 34% of prescription drug use, 50% of hospital stays, and 90% of nursing home residents (CDC, 2005).

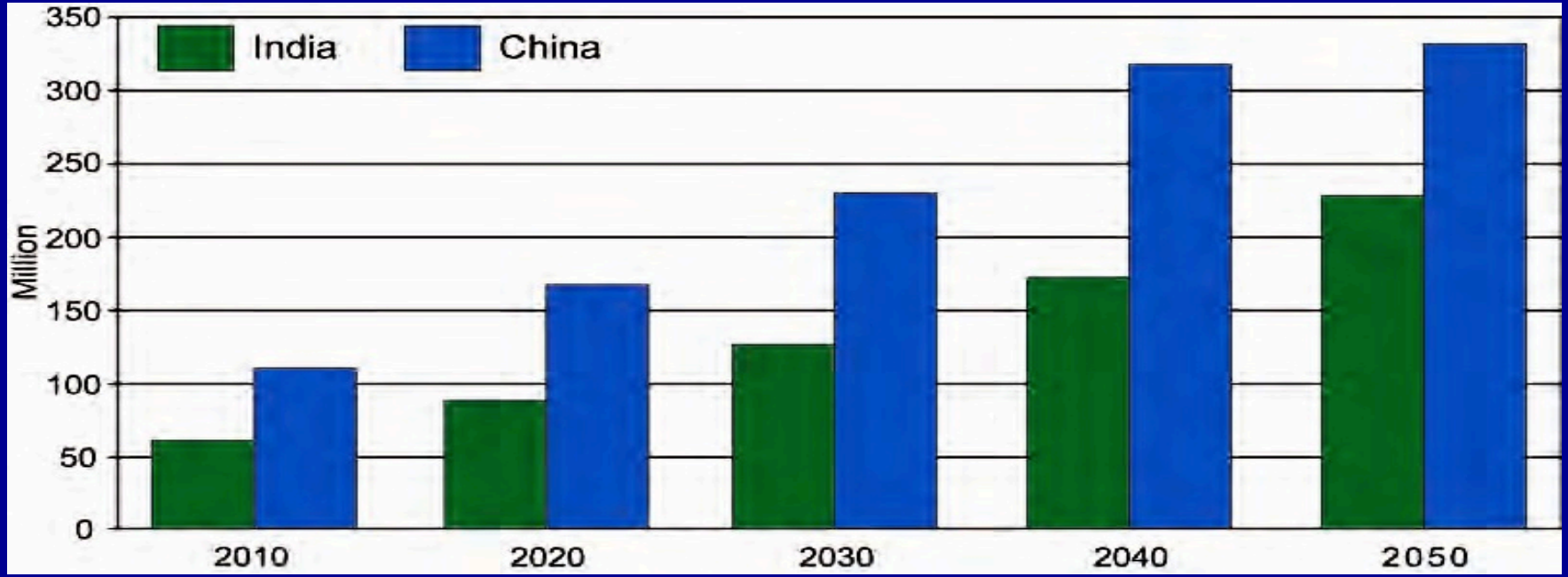
Aging of the Baby Boom Generation (1946-1965)



Reference:

U.S. Census Bureau, “65+ in the United States,” 2005

Growth in Population Over Age 65: China and India



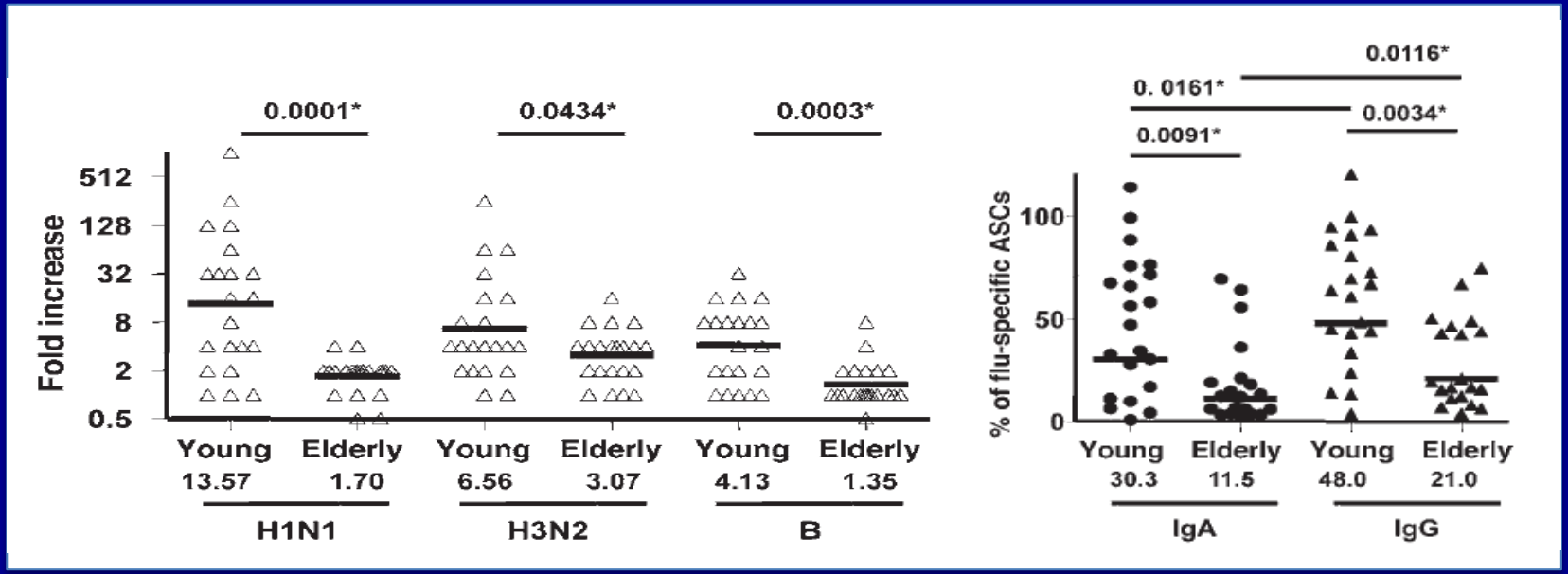
Reference:
http://www.nia.nih.gov/research/publication/global-health-and-aging/humanitys-aging#sthash.cWDbb3gE.dpuf

Relative Mortality Rates for Geriatric Infectious Diseases

Infectious Disease	Relative mortality rate compared to young adults
Pneumonia	3
Urinary Tract Infection	5-10
Appendicitis	15-20
Cholecystitis	2-8
Sepsis	3
Meningitis	3
Endocarditis	2-3
Tuberculosis	10

Reference:
Yoshikawa, 1997

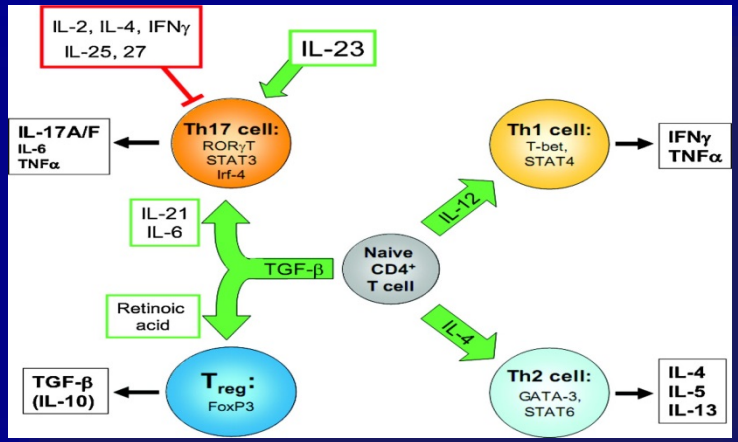
Adaptive Immunity in Aging: B Cells



- Decreased B cell repertoire diversity with age
- Decreased AID expression and decreased Ig heavy chain class switching

Reference:
Sasaki et al., 2011

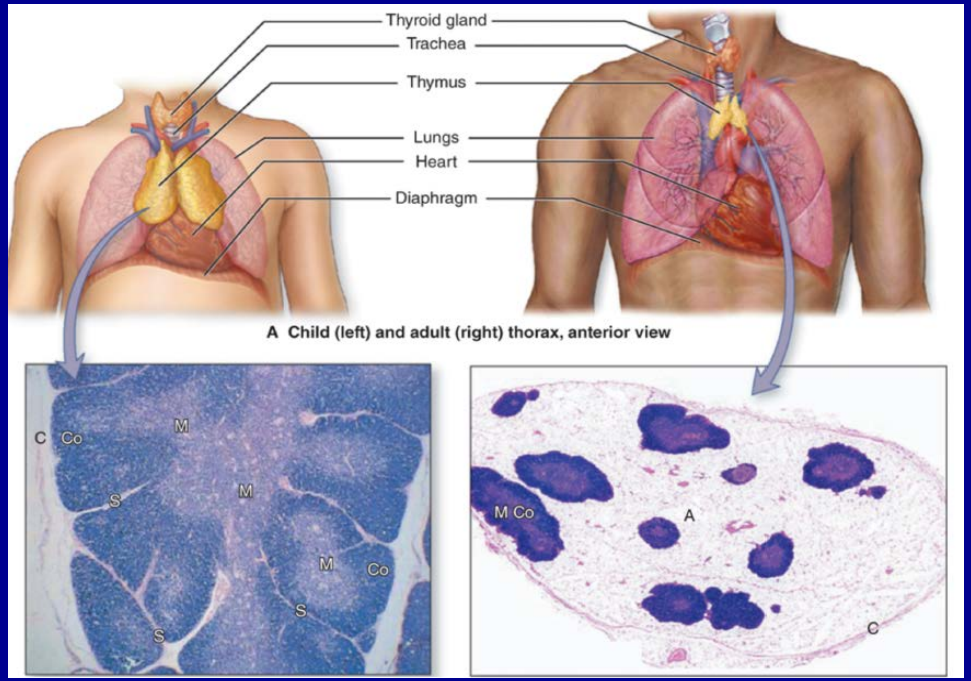
Adaptive Immunity in Aging: T Cells



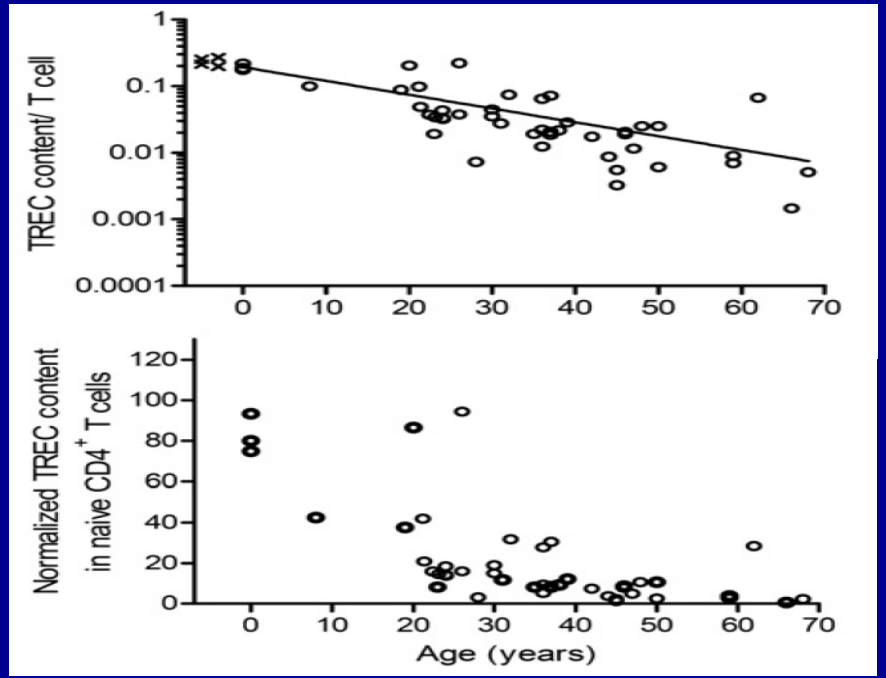
- DTH responses (e.g. PPD) clearly diminished in the elderly
- In human CD4 T cells, age-associated changes in signal transduction are seen, particularly in the ERK MAP kinase pathway.
- Changes in T cell receptor signaling strength with age could influence engagement of downstream pathways
- Some evidence for increased IL-17, Th17 polarization
- Decreased survival of memory T cells: age-associated increase in CD39 (ATPase) expression (Fang et al., 2016)

Adaptive Immunity in Aging: T Cells

With thymic involution, the human T cell compartment in adults is maintained almost exclusively (~90%) by peripheral expansion.

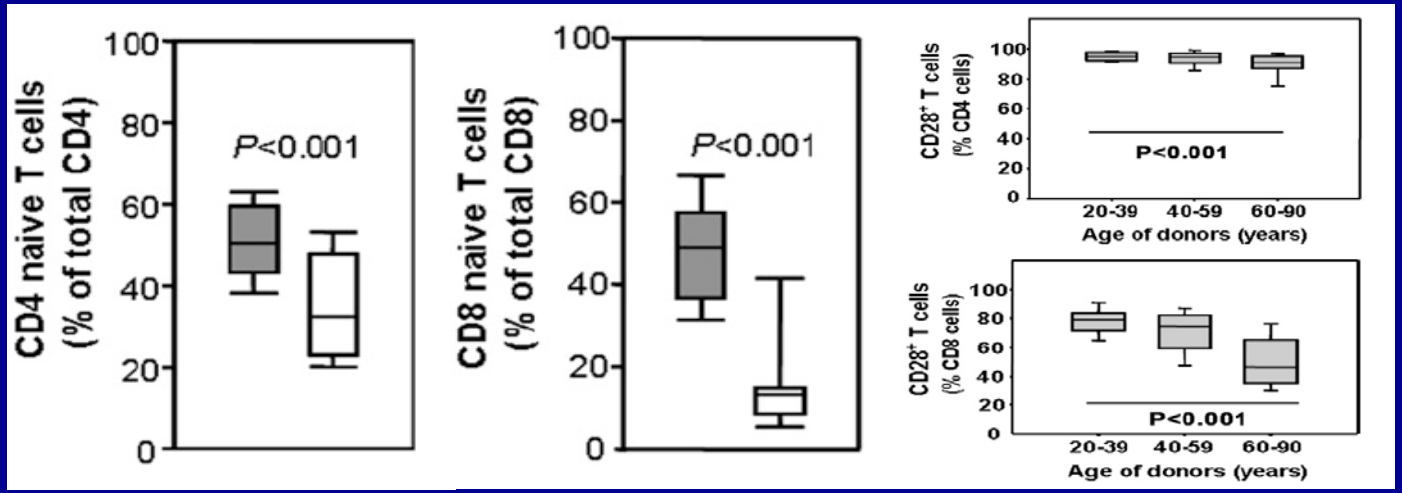


Hazzard's Geriatric Medicine and Gerontology



den Braber et al., 2012

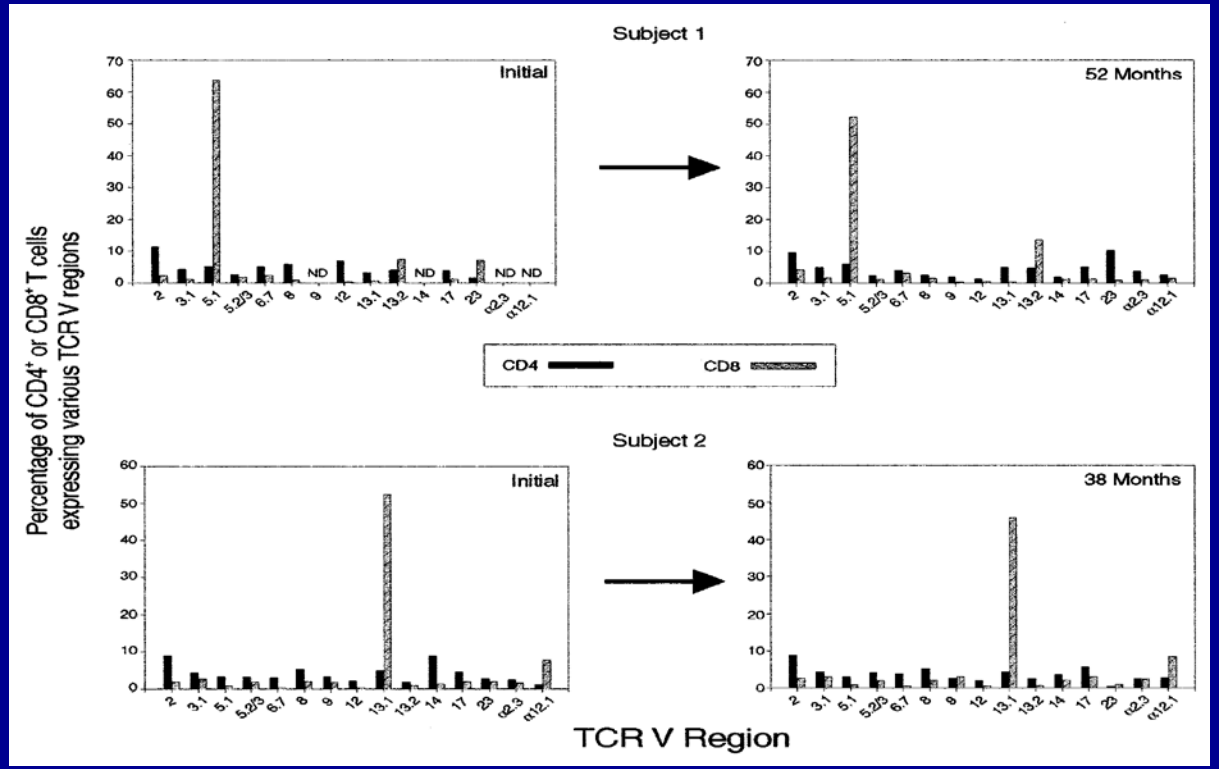
Adaptive Immunity in Aging: T Cells



- In older individuals, more T cells show a "memory" phenotype ($CD45RO^+$) than a "naïve" phenotype ($CD45RA^+$)
- Marked decrease in CD28 expression in CD4+ and (mainly) $CD8^+$ T cells from elderly donors
- CD28- T cells have shortened telomeres
- CD28- T cells overproduce cytokines (e.g. IL-6)

Reference:
Czesnikiewicz-Guzik et al., 2008

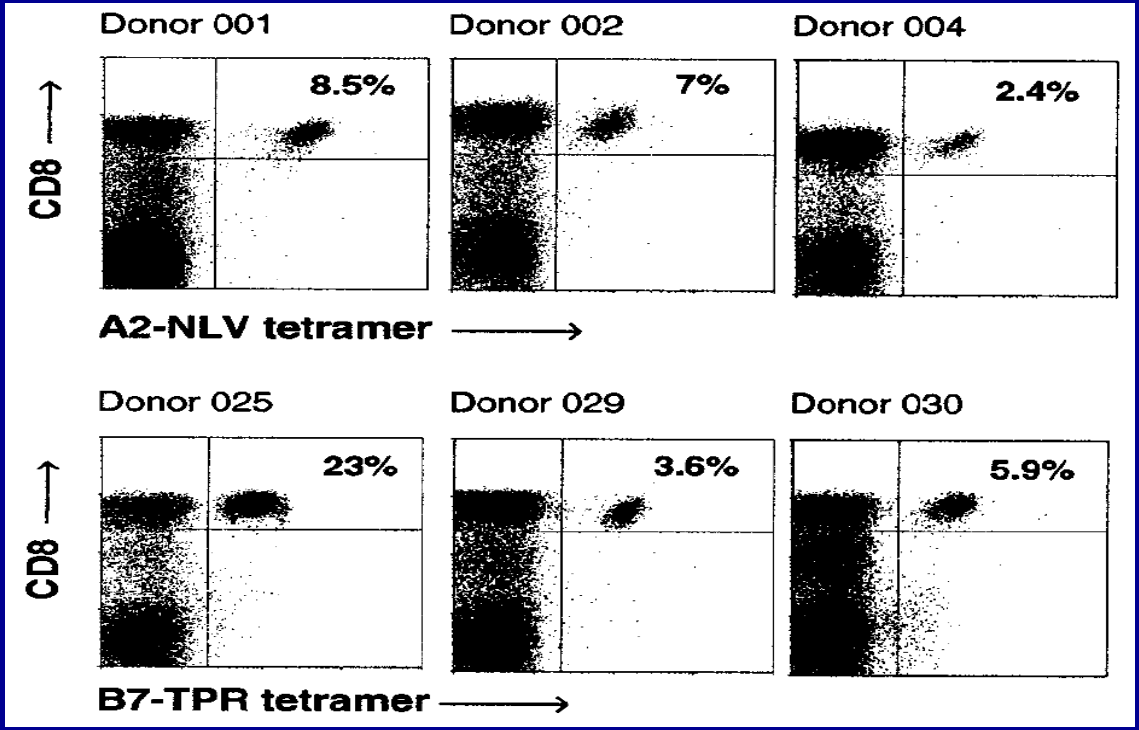
Adaptive Immunity in Aging: T Cells



- Long-lived, clonal expansion of T cells (mostly CD8+) in healthy elderly individuals, possibly from chronic antigen stimulation
- ? Restriction of T cell repertoire

Reference:
Chamberlain et al., 2000

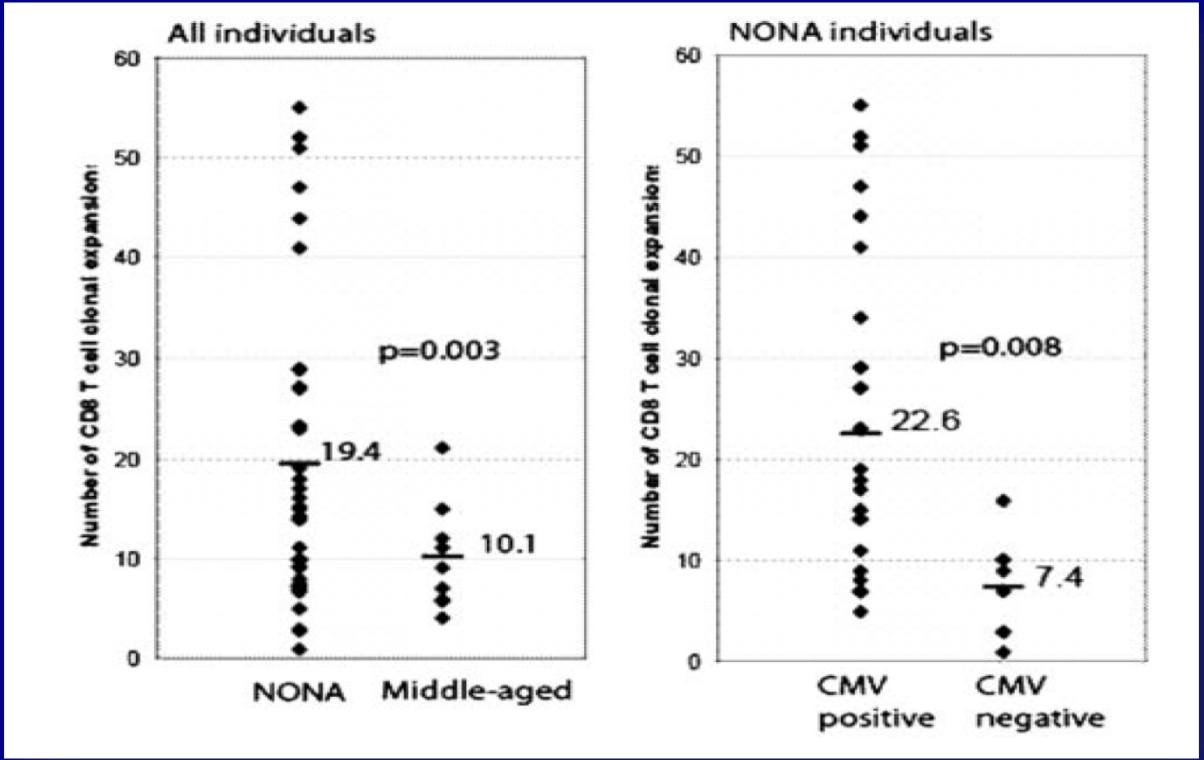
A Substantial Proportion of CD8+ CD28- T Cells Recognize CMV



- Age-associated accumulation of CMV-specific effector memory CD8+ T cells
- Likely reflects the broad tissue expression of CMV and the frequency of asymptomatic reactivation throughout life

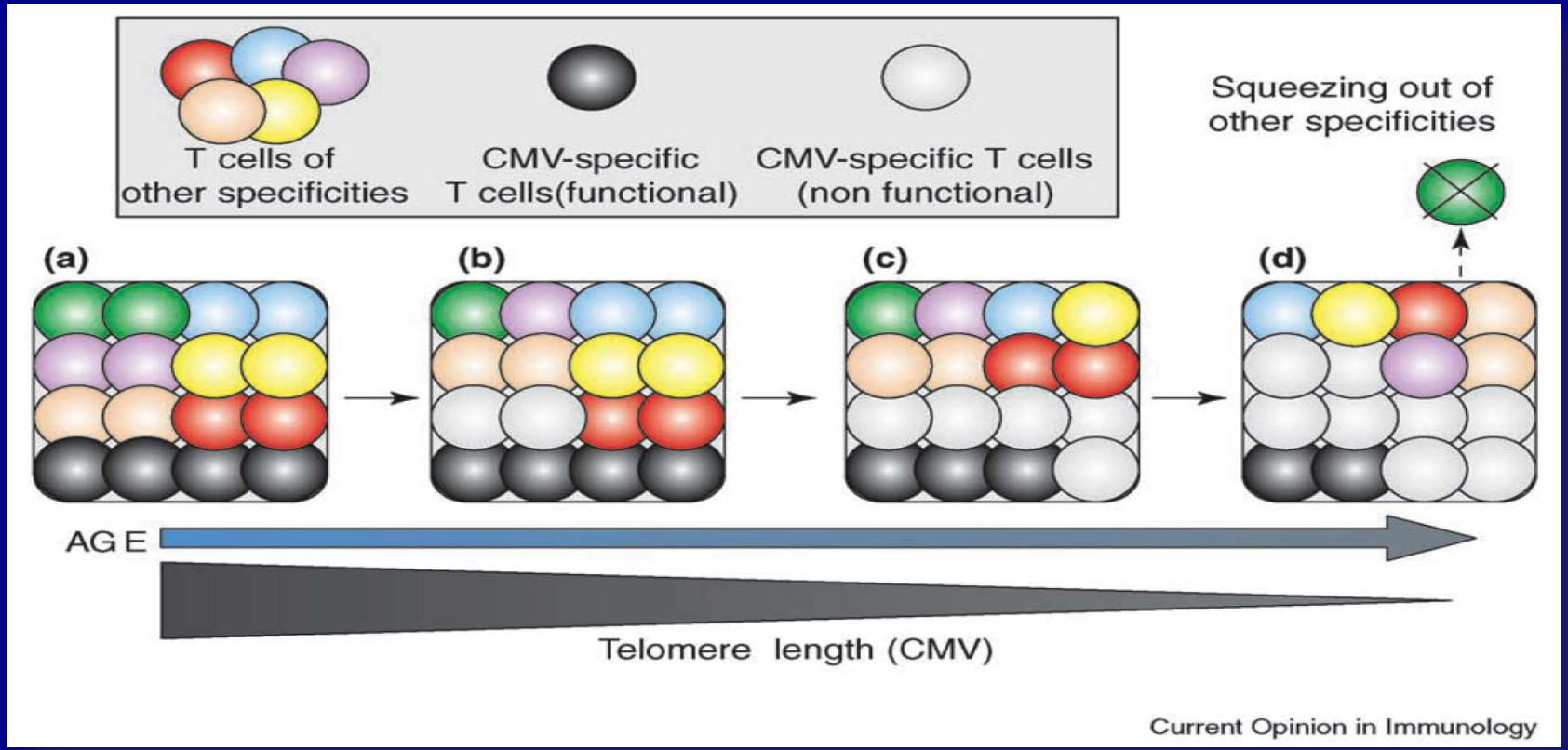
Reference:
Khan et al., 2002

CD8 T Cell Expansions are Associated with CMV Seropositive Status



Reference:
Hadrup et al., 2006

Immunosenescence: An Infectious Disease?

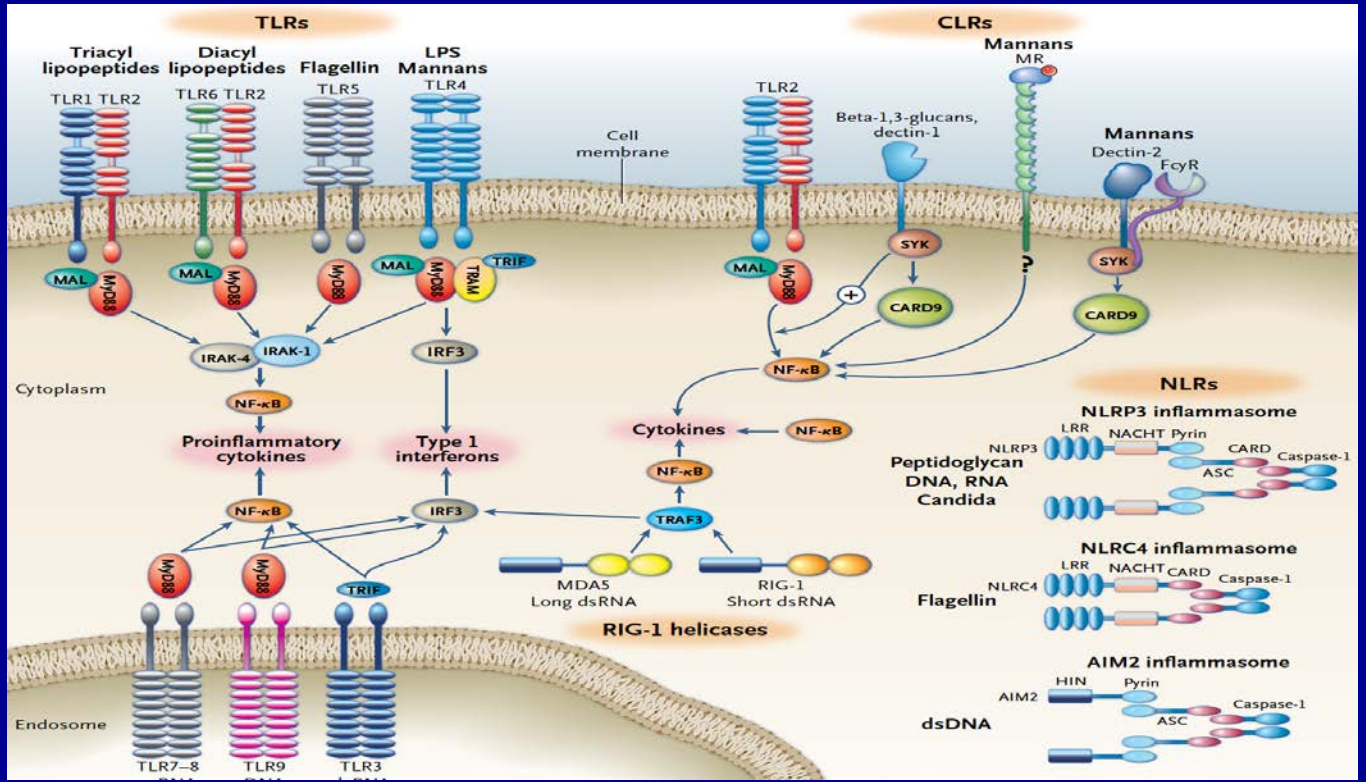


Reference:
Akbar and Fletcher, 2005.

Innate Immunity

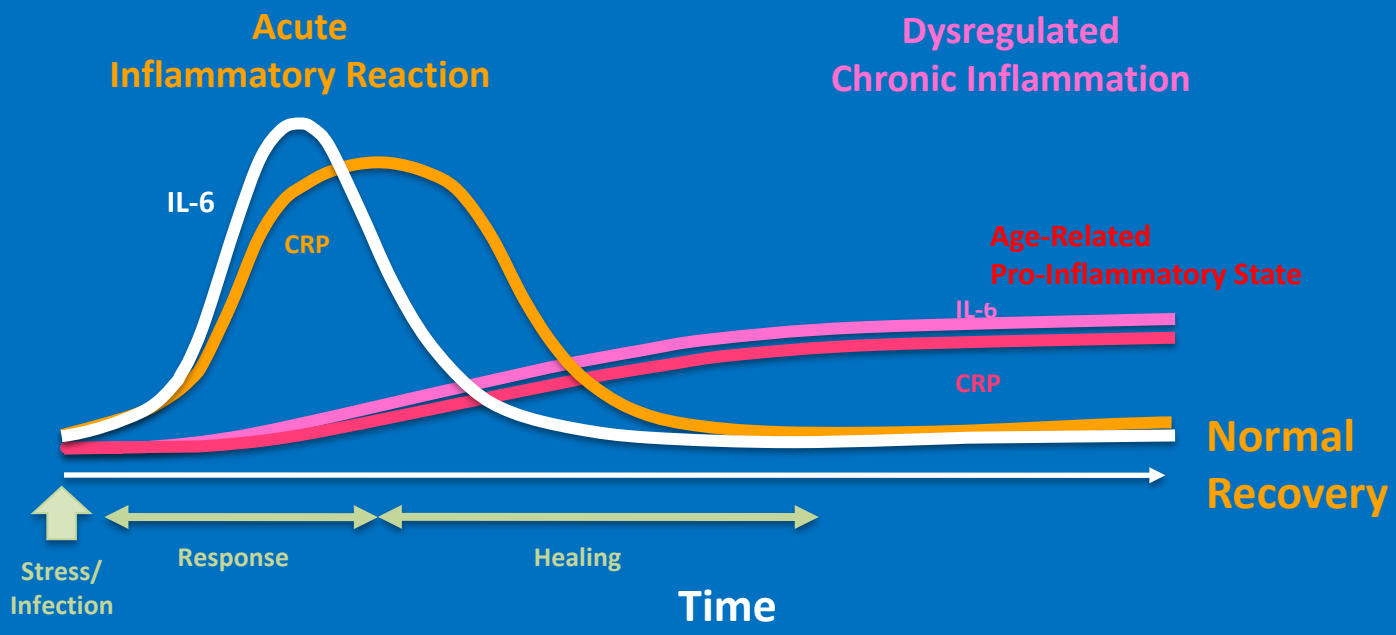
- Rapid onset—mediated by macrophages, NK cells, dendritic cells, mast cells
- Complement pathways, iron sequestration
- Phagocytosis
- Innate immune activation results in inflammatory responses
- Pattern recognition receptors, but not as specific as the slower onset adaptive immune response mediated by B and T cells

Pathogen Recognition Receptors in the Innate Immune System



Reference:
Netea and van der Meer, 2011

Acute vs. Dysregulated Chronic Inflammation



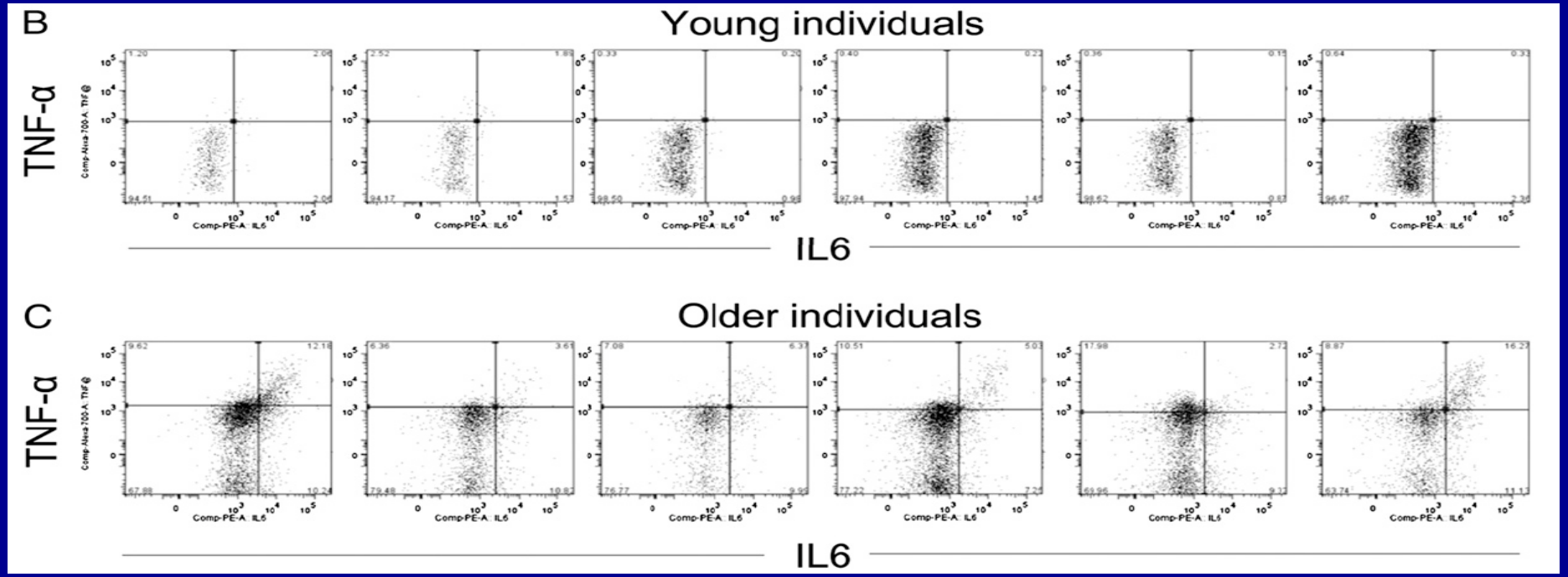
Immune Activation in Aging: Inflamm-Aging

- Though overall immune function and defense against infection is impaired with aging, an age-associated pro-inflammatory milieu has been observed (Fagiolo et al., 1993; Franceschi et al., 2007).

- Elevated levels of cytokines (e.g. IL-1β, IL-6, IL-8, TNF-α), acute phase reactants (e.g. CRP) and clotting factors have been observed.

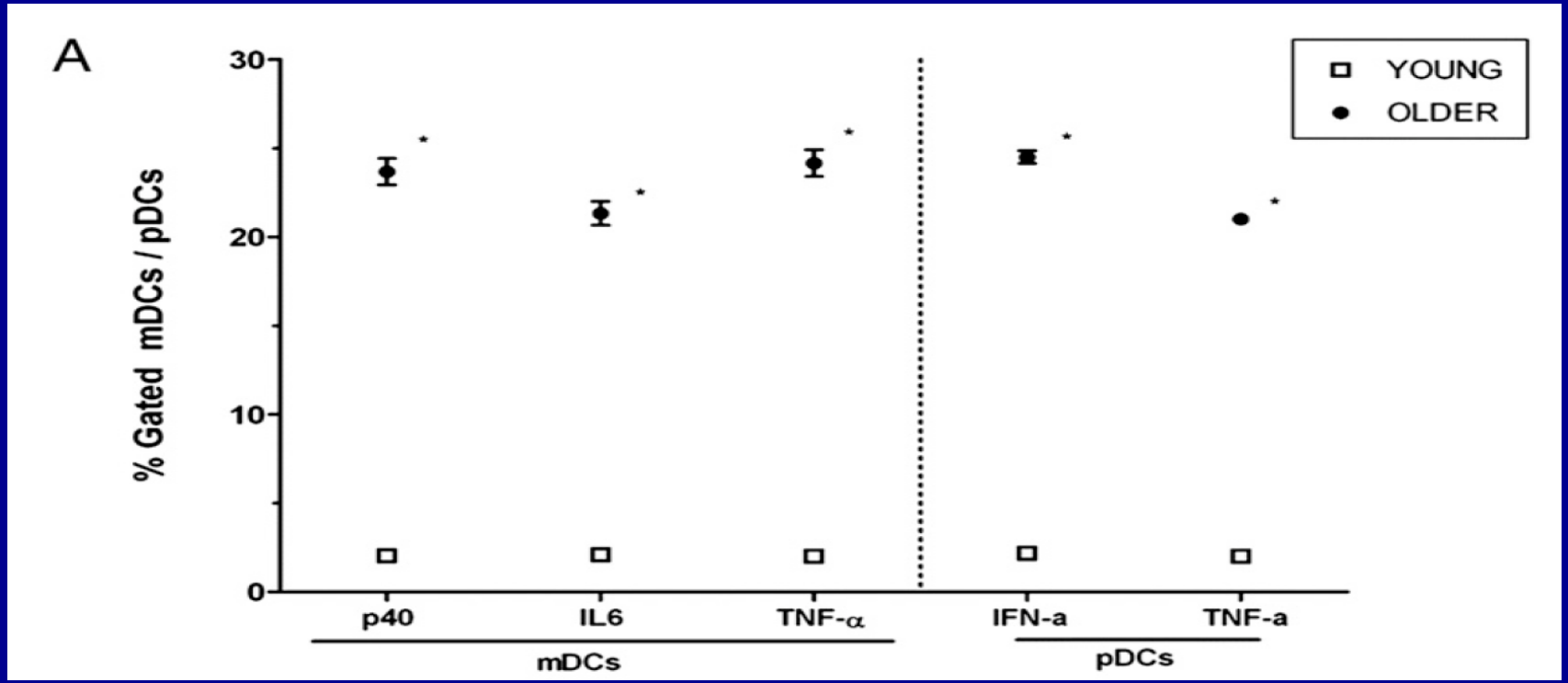
- Source for these inflammatory markers incompletely understood—possibilities include:
  - Control of chronic viral infections such as CMV
  - Engagement of PRRs by endogenous DNA
  - Release of pro-inflammatory cytokines following DNA damage
  - Age-associated shift toward myeloid HSC differentiation

Age-associated Increase in Basal Cytokine Production in Dendritic Cells



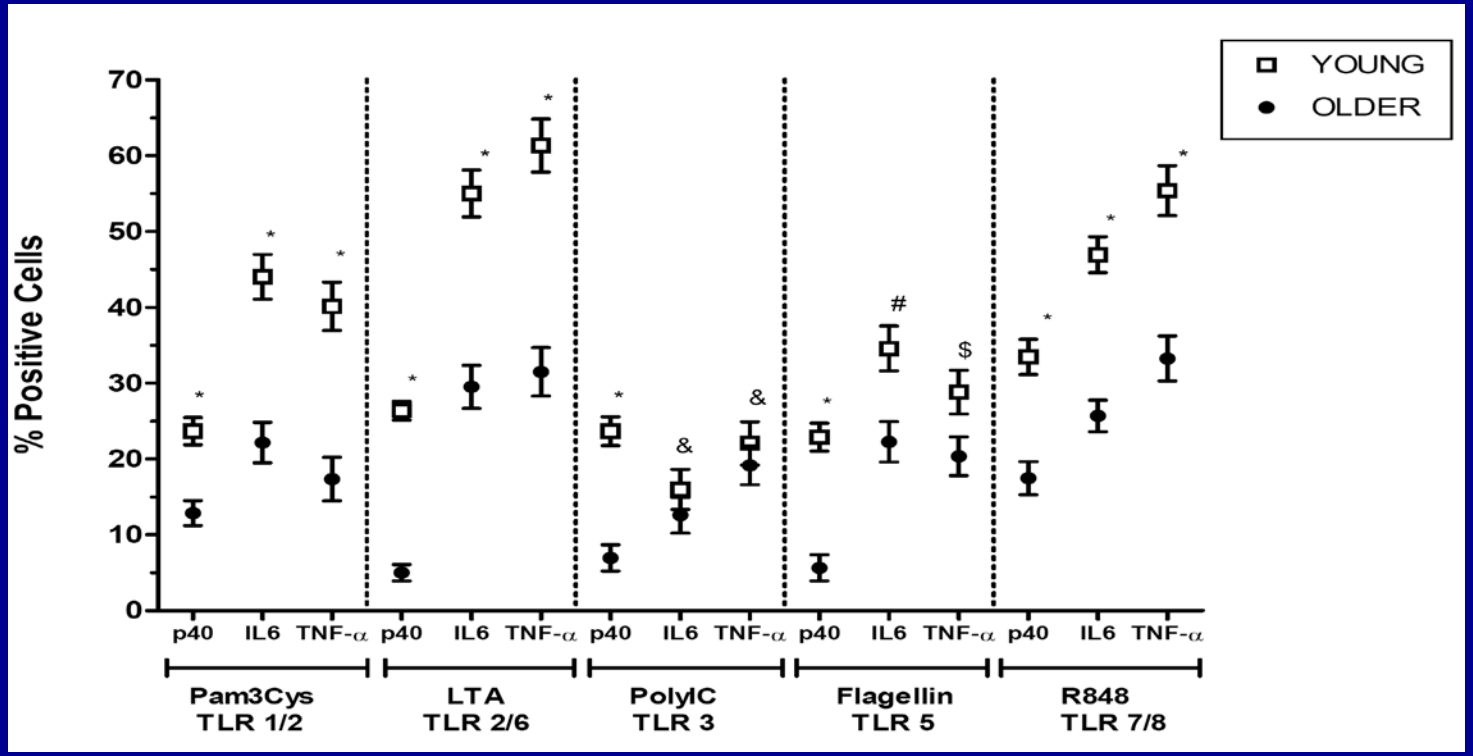
Reference:
Panda, Qian et al., 2010

Age-associated Increase in Basal Cytokine Production in Dendritic Cells (n=104)



Reference:
Panda, Qian et al., 2010

Age-associated Alteration in TLR-induced Cytokine Production in Myeloid DCs

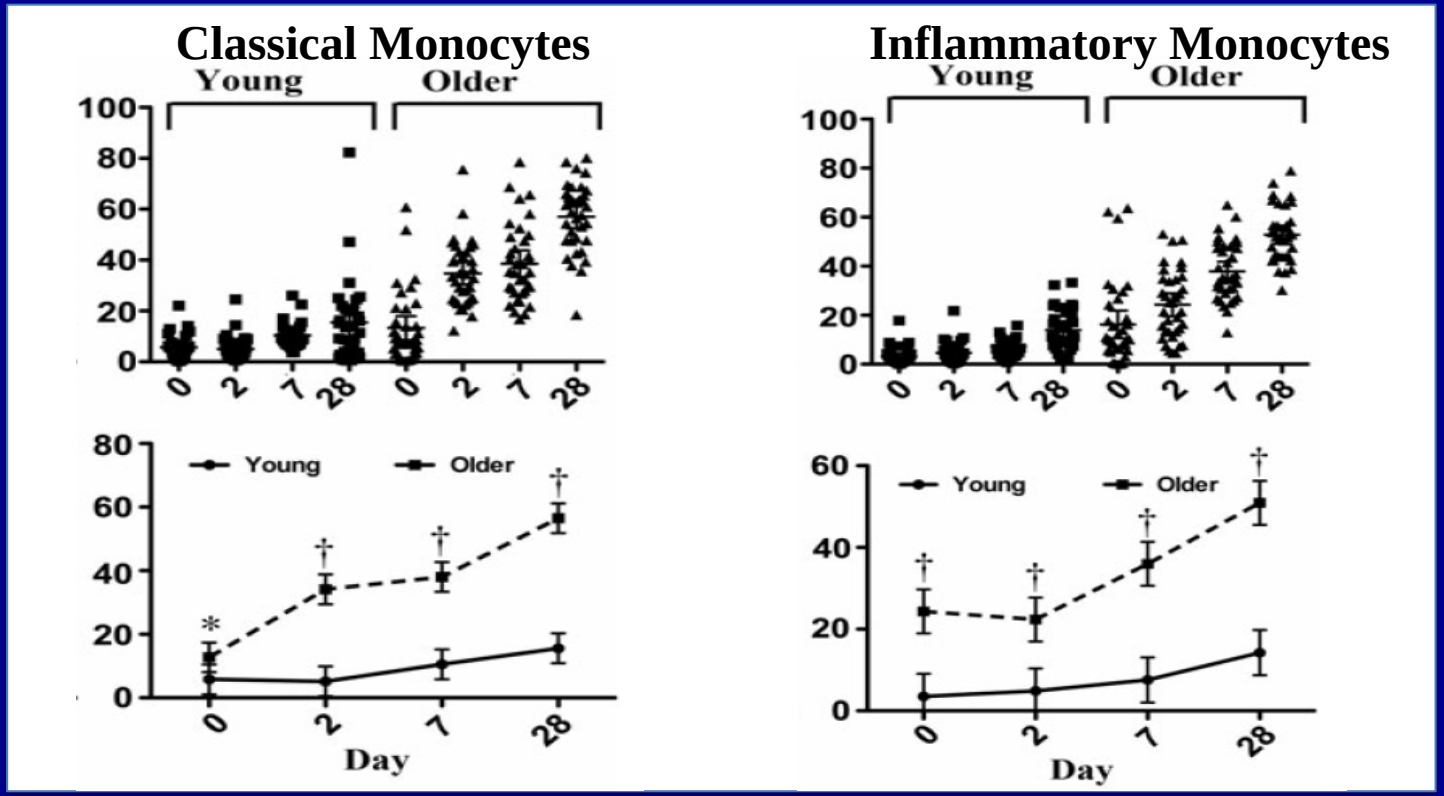


*< 0.0001, #<0.01, $<0.05, &<NS. P values adjusted for gender, race, BMI, number of comorbid conditions n=104

Reference:

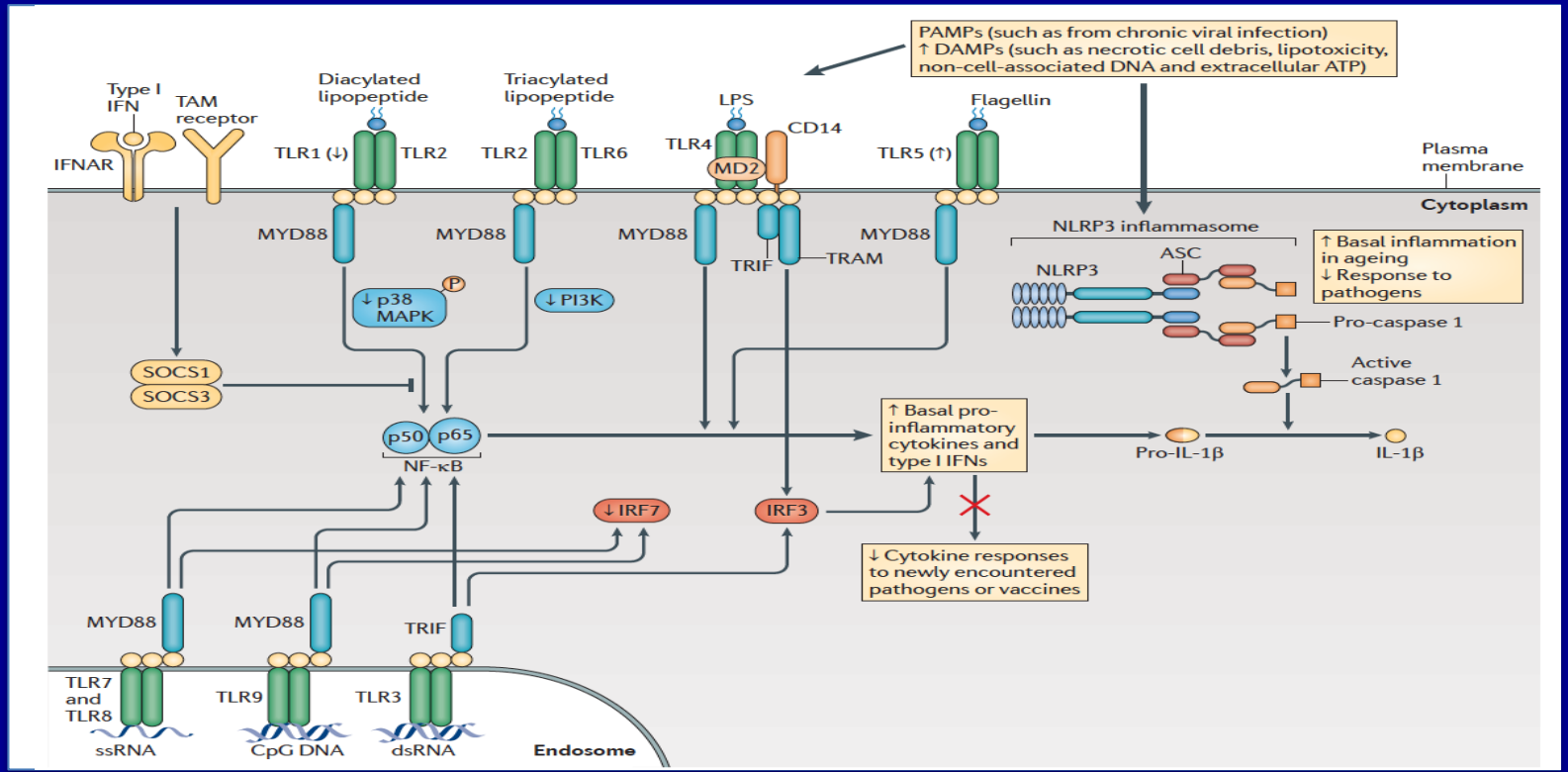
Panda, Qian et al., 2010

Age-associated Alteration in Intracellular IL-10 Production following Influenza Vaccine



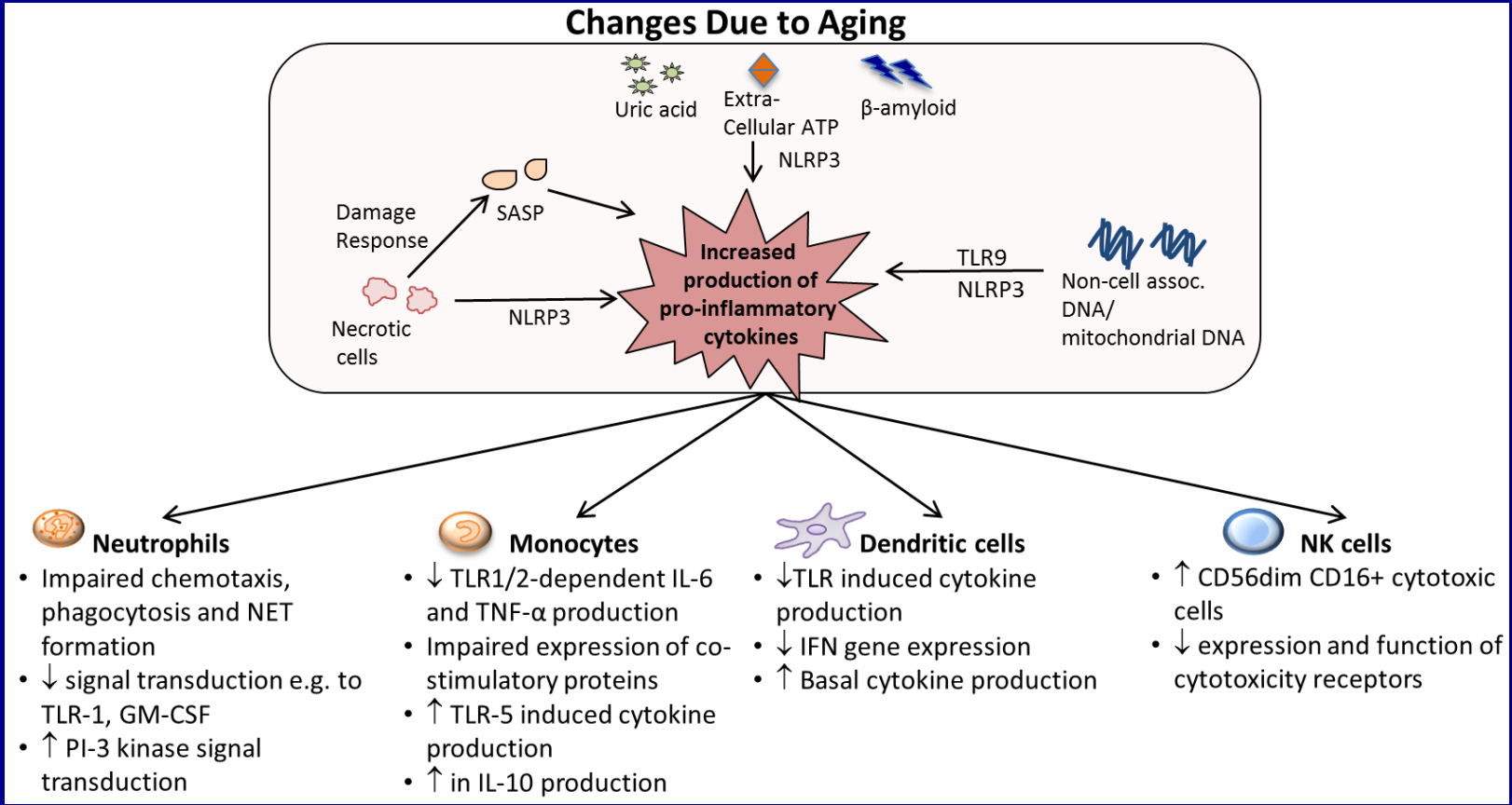
Reference:
Mohanty et al., 2015

Dysregulated Inflammation and Innate Immune Failure in Aging



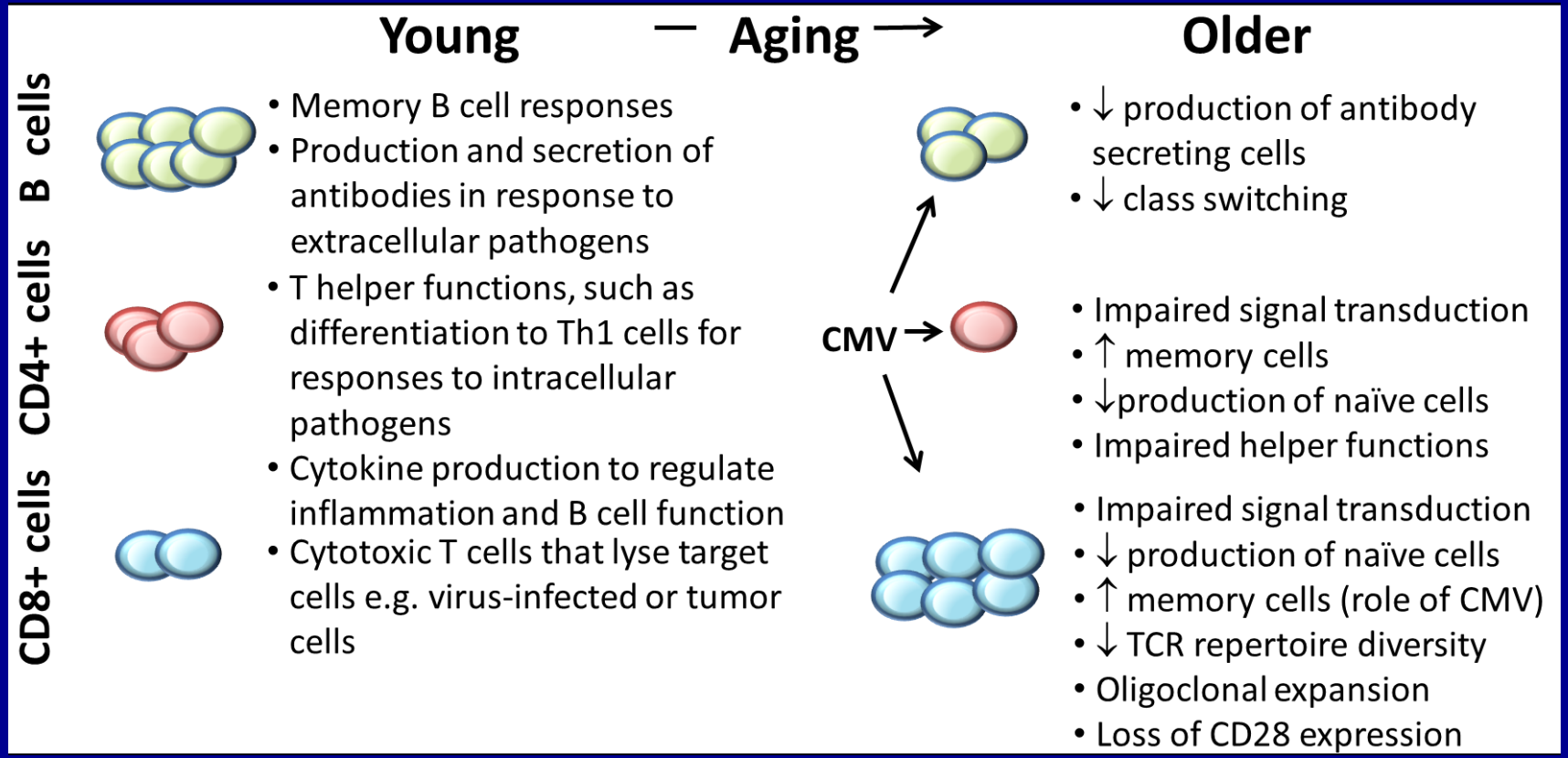
Reference:
Shaw et al., 2013

Age-Associated Alterations in Innate Immunity



Reference:
Shaw and Bandaranayake 2016

Age-Associated Alterations in Adaptive Immunity



Reference:
Shaw and Bandaranayake 2016

Translation of Efficacy into Effectiveness:

Influenza Revisited

Stefan Gravenstein, MD, MPH, Professor of Medicine, Warren Alpert Medical School and Brown School of Public Health, Brown University and Adjunct Professor of Medicine, University Hospitals Cleveland Medical Center, Case Western Reserve University

Translation of Efficacy into Effectiveness: Influenza Revisited

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Professor of Medicine and Health Services Policy and Practice
Brown University
Adjunct Professor of Medicine
University Hospitals Cleveland Medical Center and Case Western Reserve University

Objectives

- Comment on the influence of age on influenza outcomes
  - Especially in the context of inflammation and vascular outcomes
- Evidence of influenza vaccine impact on vascular outcomes
- Discuss a cluster-randomized approach to get from efficacy to effectiveness in a long-term care setting

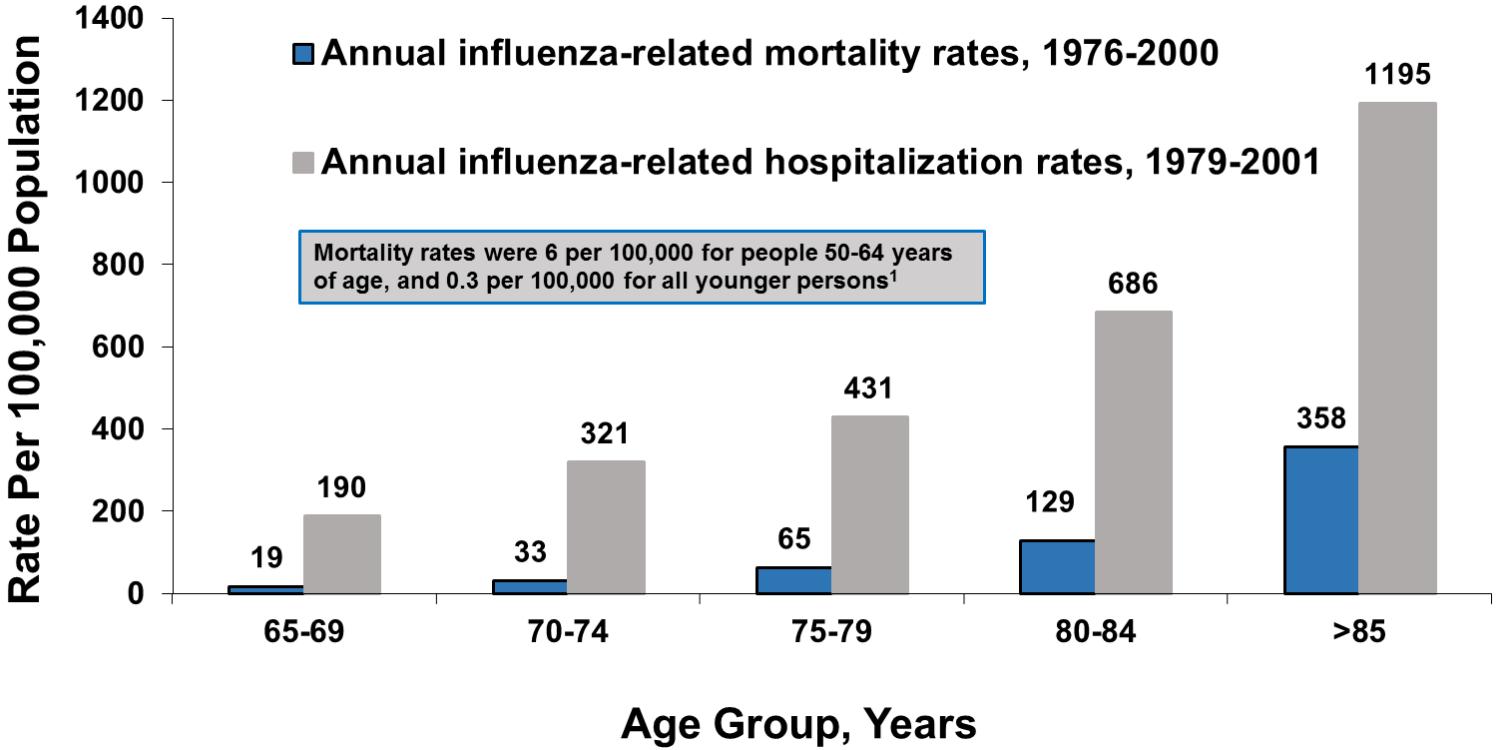
Review: Immune Senescence

- More permissive for infection, including pneumonia[1]
  - More permissive for severe infection that can result in hospitalization
- Lowers vaccine response[1,2]
  - Need better vaccines to overcome declining response
  - Age-related changes in T-cell subsets and cytokine production profiles affect the magnitude, quality, and persistence of antibody responses to vaccines[3,4]
- Slows recovery from infection

References:

1. Zheng B, et al. *J Immunol*. 2007;179(9):6153-6159.
2. Doria G, et al. *Mech Ageing Dev.* 1997;96(1-3):1-13.
3. Siegrist CA. Vaccine immunology. In: Plotkin SA, et al, eds. *Vaccines*. Sixth edition. Philadelphia, PA: Saunders Elsevier; 2012:17-36.
4. Goronzy JJ, Weyand CM. *Nature Immunol.* 2013;14(5):428-436.

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.

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.

Herpes Zoster (HZ) and Risk for Vascular Event: Increased with Myocardial Infarction and Cerebrovascular Accident

- Kim et al (2017) report hazard ratios
  - Myocardial infarction following HZ is 1.59 overall, and increases with age
  - Cerebrovascular event after HZ is 1.35 overall, and decreases with age

- Erskine et al (2017) meta-analysis of 12 studies
  - Cerebrovascular event risk increases after HZ ophthalmicus
    - OR 1.39-4.42 depending on statistical approach in 1st 3 months
  - Cerebrovascular event risk increases by 1.22-1.34 generically in the year following HZ
  - Myocardial infarction risk increases after HZ generically within a year (OR 1.19) or longer

References:
1. Kim et al, *Letters*, J A C C 2017, 7 0(2):293–300.
2. Erskine et al, *PLoS One*. 2017; 12(7): e0181565.

Influenza Vaccination and Vascular Outcomes in Older Adults

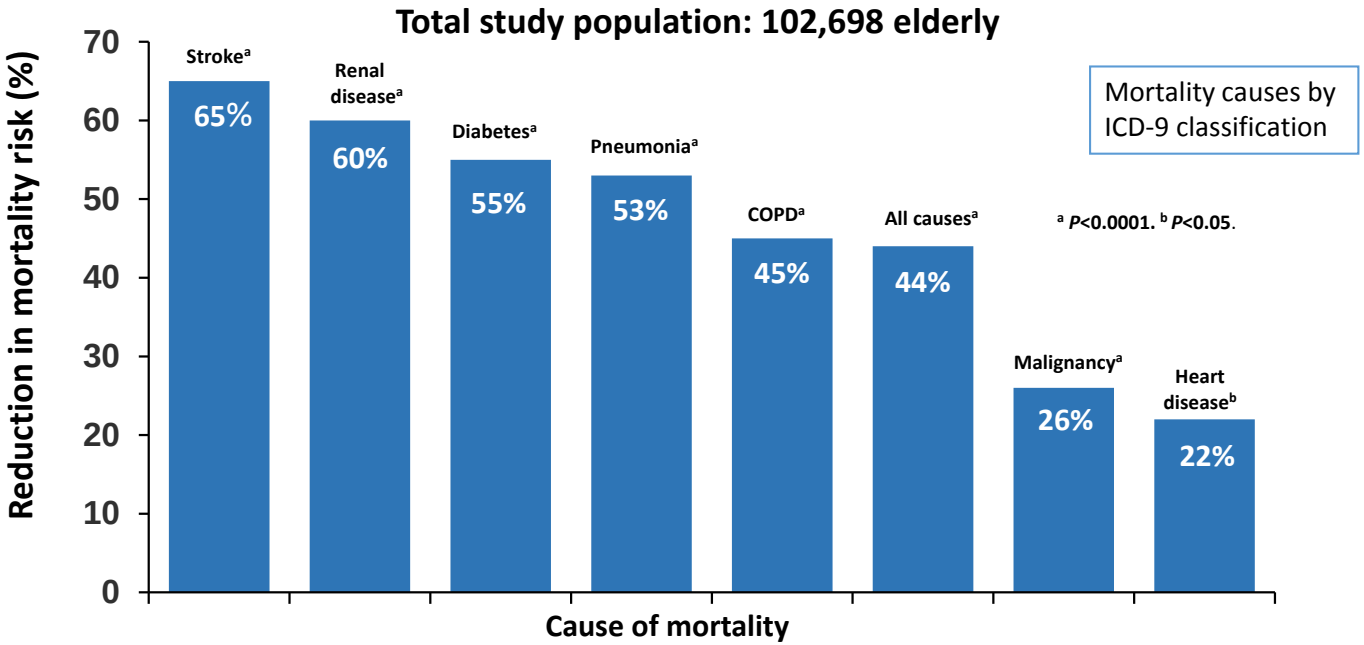
Influenza Vaccination Also Can Lower the Risk of Major Cause-Specific Mortality[1]

- Study in Taiwan in >100,000 residents ≥65 years of age
- **Six of 8 major causes of mortality evaluated were not directly related to lung disease**
- >10-month follow-up of 35,637 vaccinated and 67,061 unvaccinated seniors
- High-risk was defined as having
  - A chronic disease
  - Residence in long-term care, or
  - A history of recent (prior 3 years) hospital admission
- 80% of the full study population were not classified as high-risk

Study objective:
"To understand more thoroughly whether influenza vaccination was effective for reducing major cause-specific mortality (other than lung diseases) in a county-wide population study with large sample sizes"

Reference:
1. Wang CS, et al. *Vaccine.* 2007;25(7):1196-1203.

Influenza Vaccination Also Can Lower the Risk of Major Cause-Specific Mortality[1] *(cont.)*



"Influenza vaccine is strongly associated with a lower mortality risk, not only for pneumonia and COPD, but also for other major cause-specific mortalities, which indicates that influenza vaccination might reduce the domino effects of complications from influenza in the elderly."

Reference:

1. Wang CS, et al. *Vaccine.* 2007;25(7):1196-1203.

Influenza Vaccine and Cardiovascular Events[1]

- Meta-analysis of 5 clinical trials of >6,000 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.

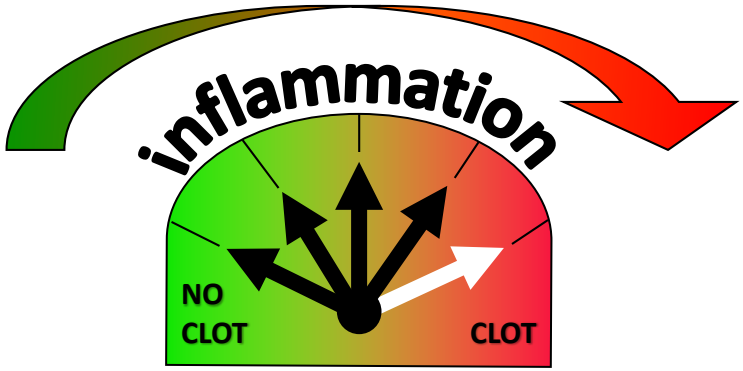
The Range of Efficacy of Coronary Interventions Compared With Influenza Vaccination

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

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

“Thrombometer” – The Propensity to Clot



LOW

CRP
IL-1, 6
TNF-alpha

HIGH

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

Summary

- Immune senescence conflates with underlying inflammation 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 should overcome some of these considerations in the populations at greatest risk

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

Efficacy vs. Effectiveness

- For efficacy, typically a precise subject definition limits study participants
  - Healthier, often affecting ability to access study site, and cognitively able to consent
  - Systematically may exclude various underlying diseases

- Efficacy RCTs can guide precise likelihood of response *in those studied*

- Effectiveness implies a treatment as it is applied to a population
  - Reduced systematic exclusion
  - Often intent-to-treat, so if low adherence due to tolerance, for example, even an efficacious drug could prove to be ineffective
  - More generalizable

- Cluster-randomized trials can more closely determine *effectiveness* depending on the ”cluster” selected

Influenza Vaccine and Nursing Home Residents

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Background

- **Diaz Granados, et al:** Outpatient RCT with 24% reduction in influenza

- **Nace, et al, nursing home RCT for immunogenicity:** GMTs higher for high dose than standard dose for all comparisons (A/H1N1, A/H3N2, and B) both seasons at 30 and 180 days except 2012-3 for A/H1N1 at 30 days

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

David A. Nace,[1] Chyongchiou Jeng Lin,[2] Ted M. Ross,[3] Stacey Saracco,[1] Roberta M. Churilla,[1] and Richard K. Zimmerman[2]

[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

(See the editorial commentary by Lindley and Bridges on pages 1860–1.)

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

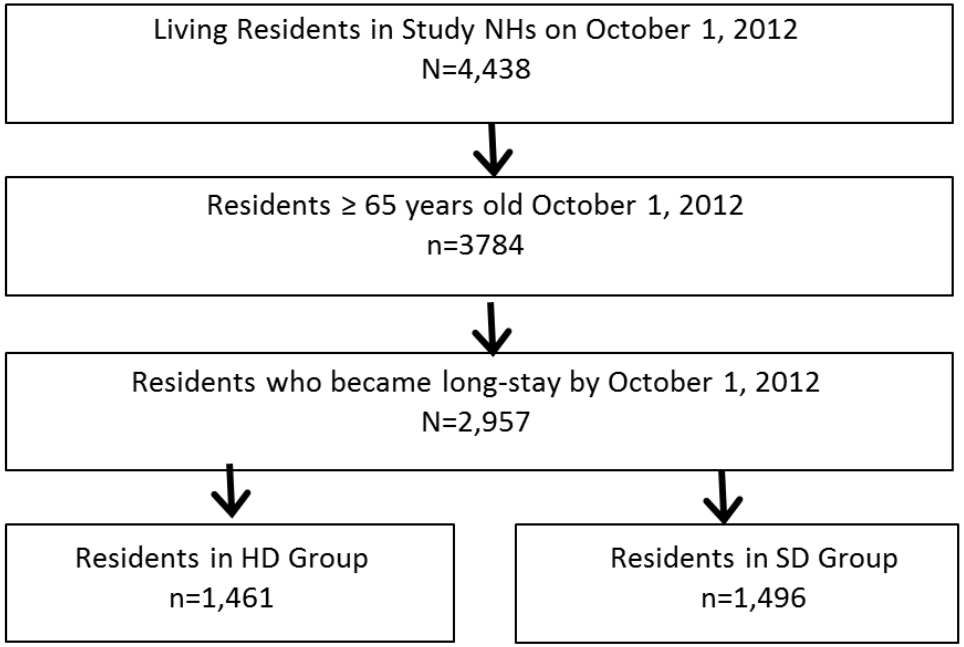
References:
Diaz Granados, et al, NEJM 2014:371.
Nace, et al, JID 2015:211 (15 June)

Objectives

- Review results from pilot study undertaken in 39 nursing facilities during the 2012-13 influenza season

- Review results 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
  - Primary outcomes of respiratory and all-cause hospitalizations
  - Secondary outcomes of cardiovascular hospitalizations

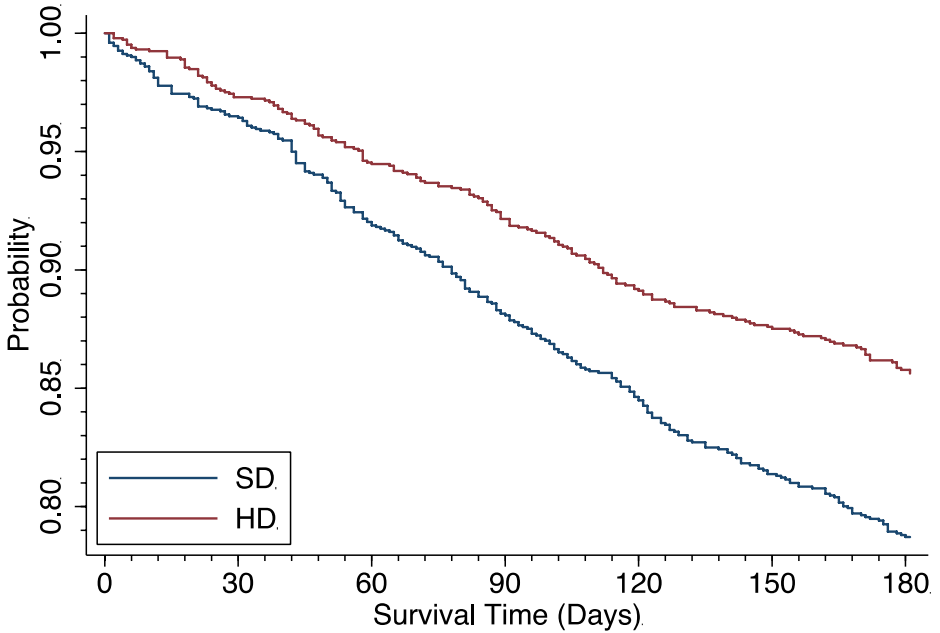
Feasibility Study: Methods
Patient Eligibility and Selection



[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.

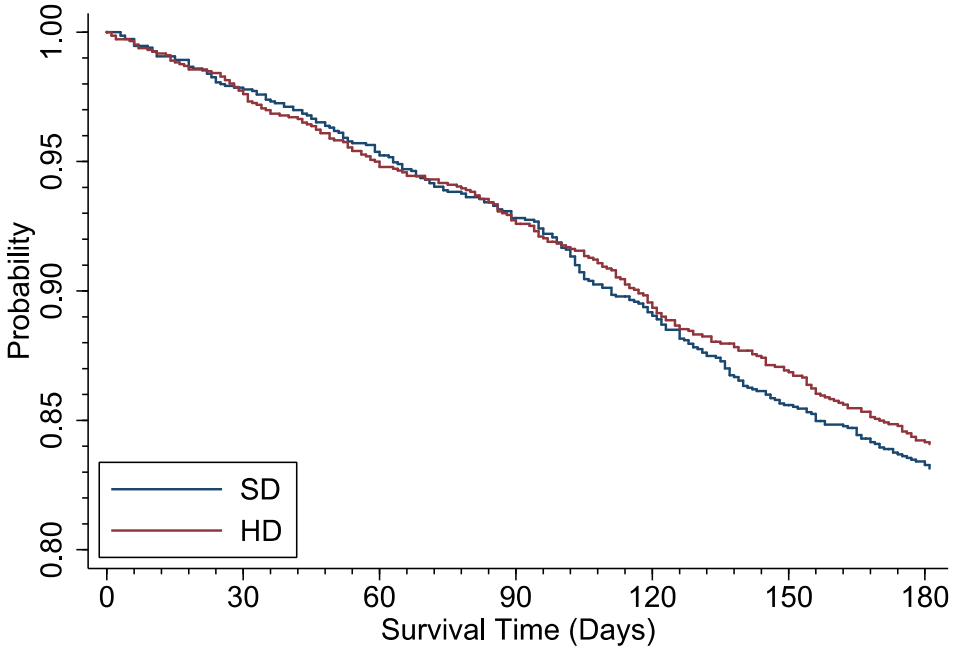
Feasibility Study:
Ever Hospitalized in an A/H3N2 Season



Number at risk

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

Feasibility Study: Mortality in an A/H3N2 Season



Number at risk

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

Feasibility Study 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

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 U.S. 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 United States, this is the **Medicare Fee for Service** claims)

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

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

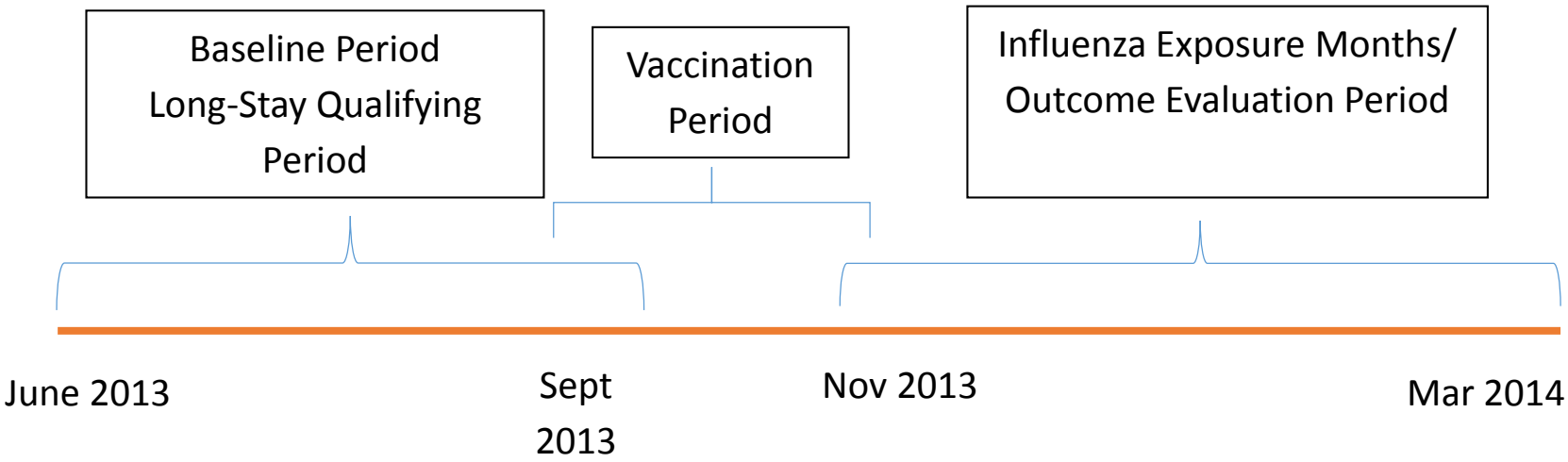
Pragmatic Cluster RCT of HD in Nursing Homes (NHs)

- 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

Reference:
Gravenstein et al, *Lancet Respir Med* 2017



Reference:
Gravenstein et al, *Lancet Respir Med* 2017

Outcome Determination

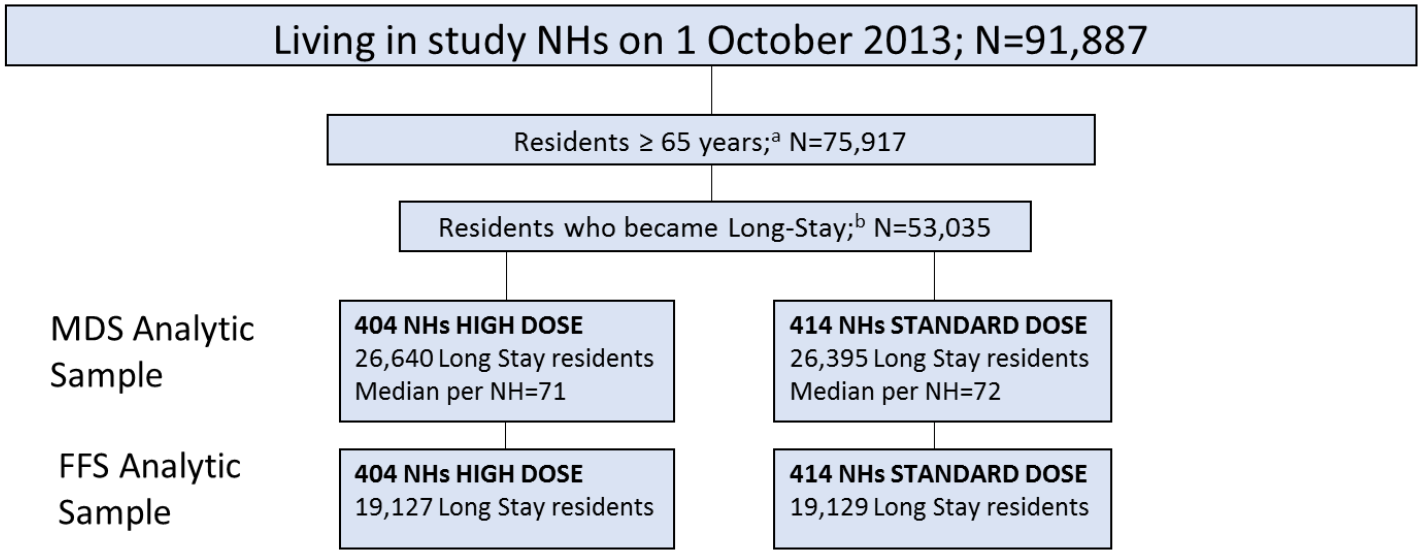
- PRIMARY: **Medicare FFS** permanent NH residents; number of hospitalizations due to P&I per patient day:[1]
  - ✓ P&I hospitalization defined as:
    - ✓ ICD9-CM codes 460–466, 480–488, 490–496, 500–518
- ALL permanent NH residents (90+ days), mortality
- ALL permanent NH residents, total hospitalizations 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

References:

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

Reference:
Gravenstein et al, *Lancet Respir Med* 2017

Analytic Approach

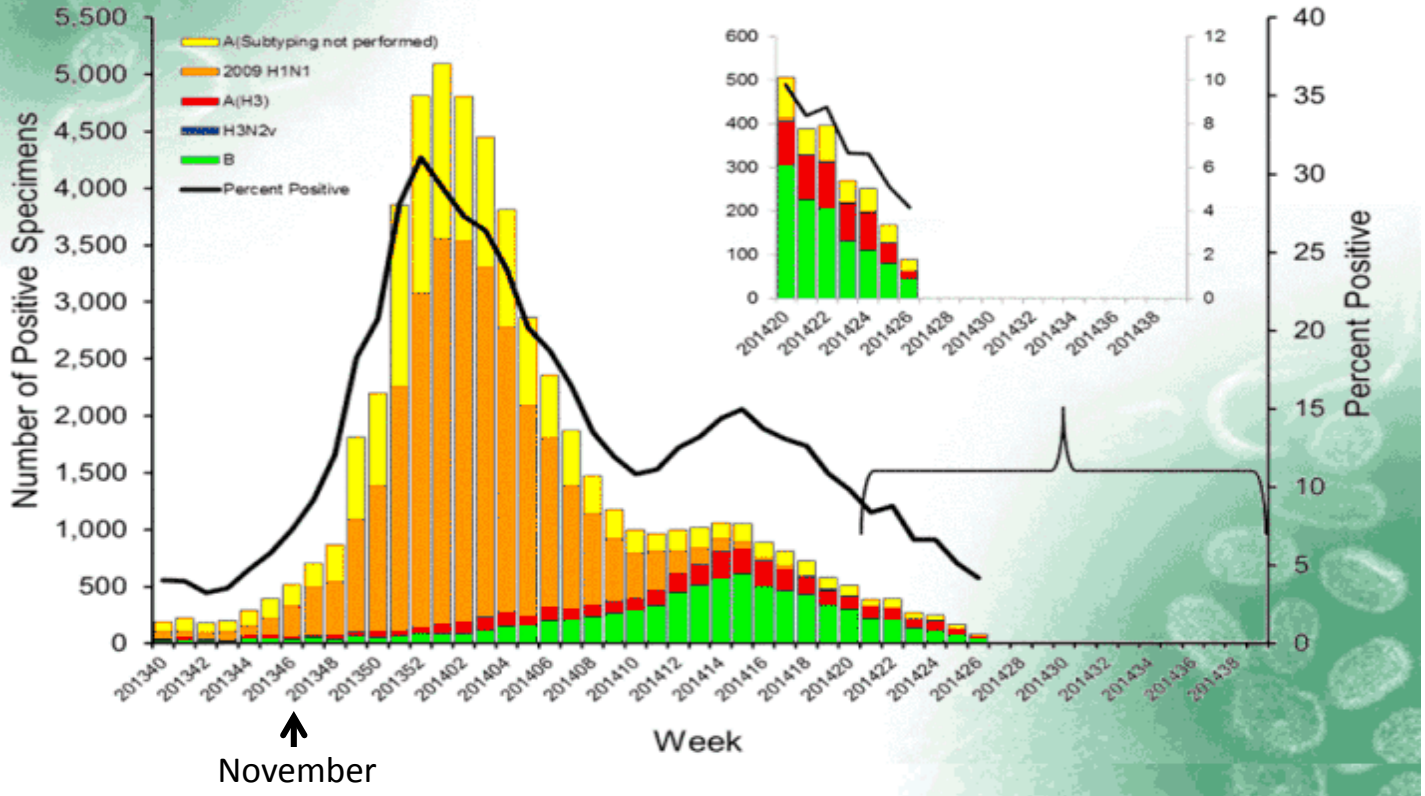
- Unit of analysis: individual residents
  - Adjusted for clustering by NHs using robust variance estimates
- Multivariable logistic, Poisson, and Cox regression
  - Initial model assessed interaction between treatments
  - Adjusted for pre-specified NH- and resident-level covariates
- Analysis by Intention-to-Treat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

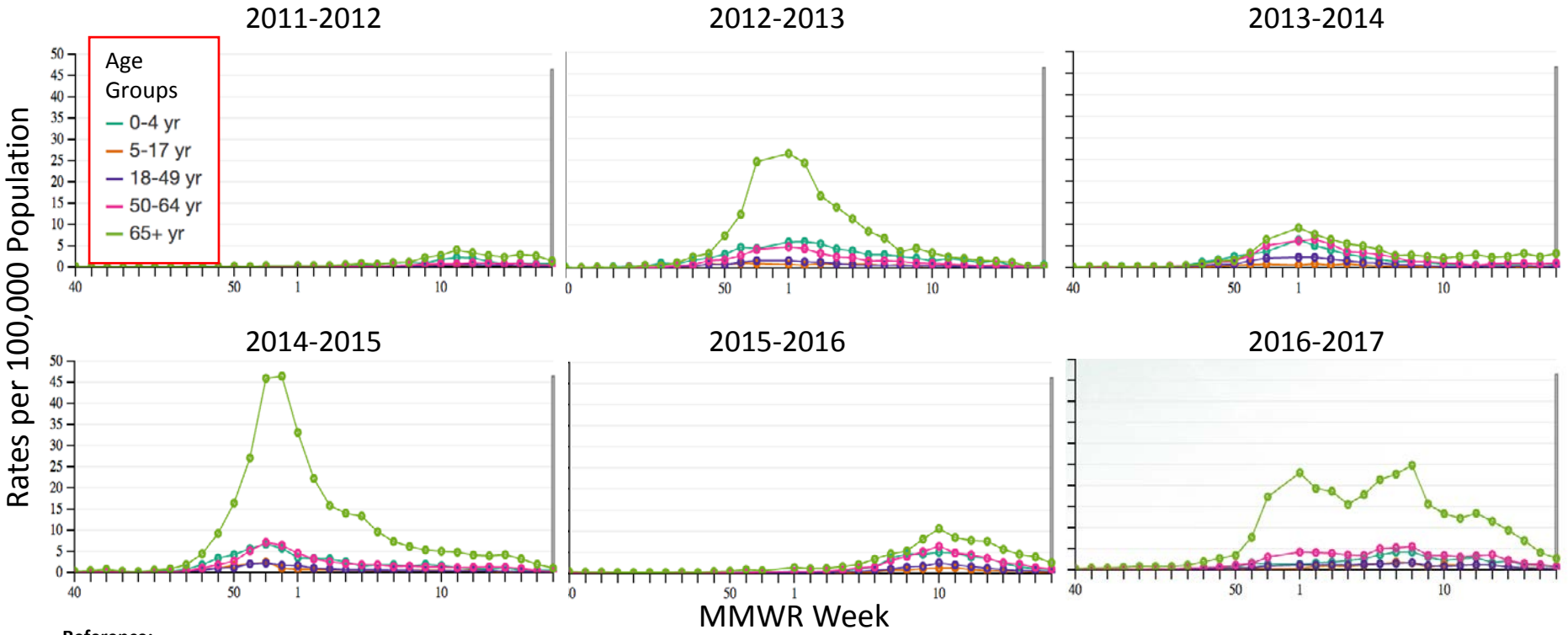
Influenza Positive Tests Reported to CDC by U.S. WHO/NREVSS Collaborating Laboratories, National Summary, 2013-14



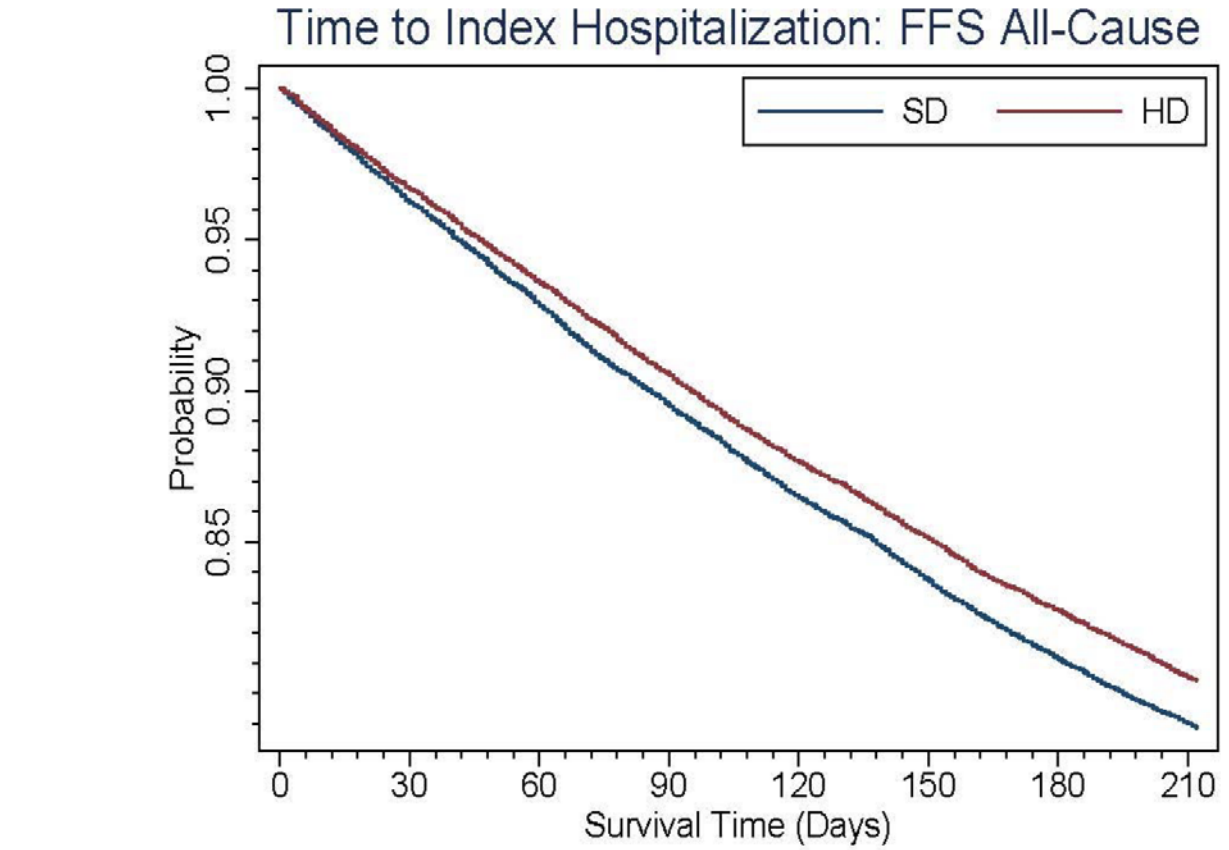
Weekly CDC Surv-NET Lab-Confirmed Flu Hospitalizations by Age and Season 2011-2017

Feasibility Study
A/H3N2 Predominant Season

Full Study
A/H1N1 Predominant Season



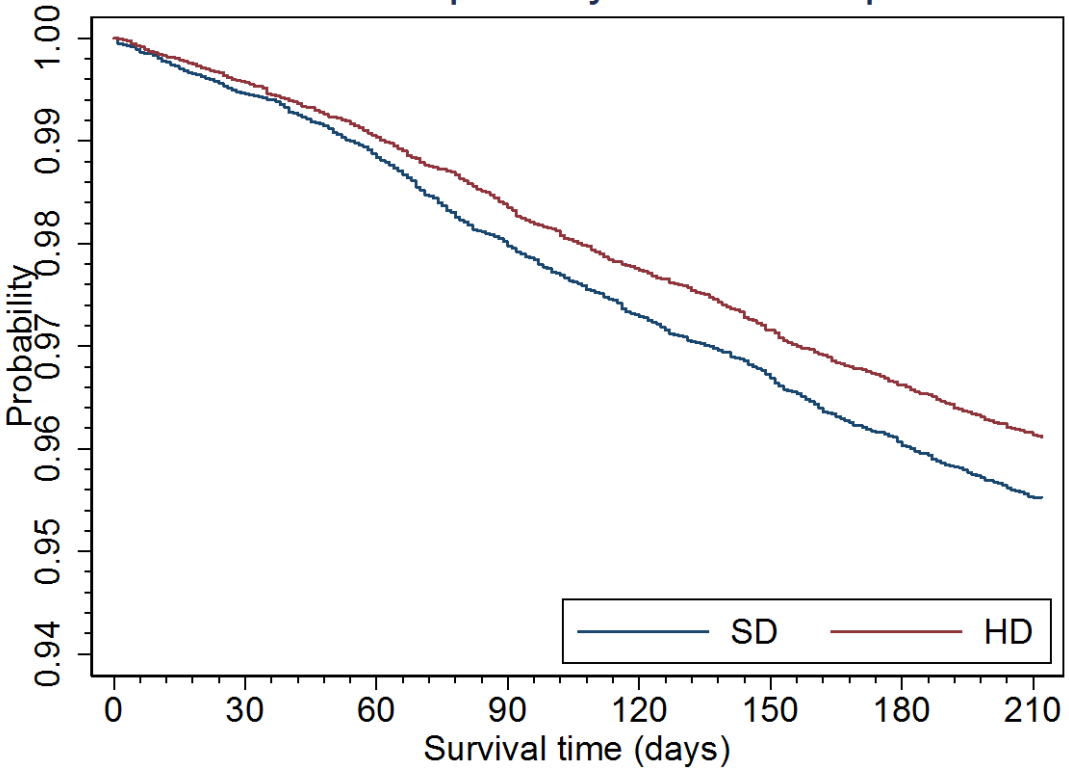
Reference:
https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html; Downloaded 20 JUN 2017



Reference:

Gravenstein et al, *Lancet Respir Med* 2017

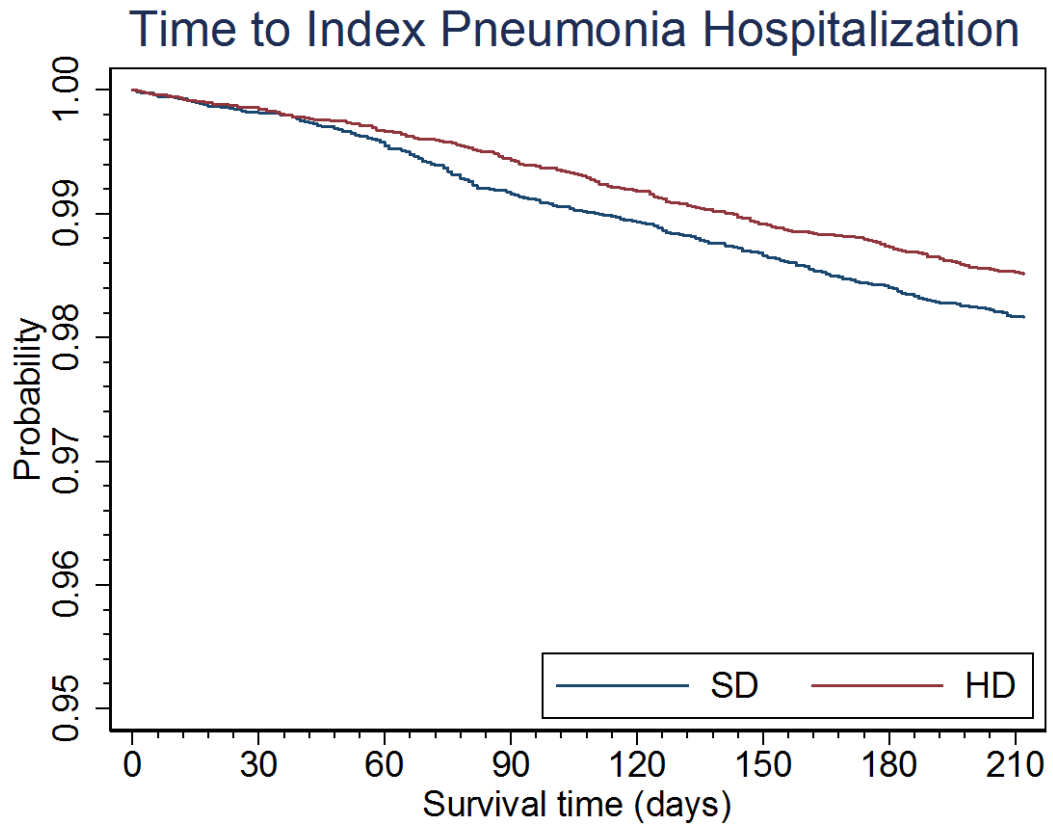
Time to Index Respiratory Illness Hospitalization



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

Reference:

Gravenstein et al, *Lancet Respir Med* 2017



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

Reference:

Gravenstein et al, *Lancet Respir Med* 2017

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

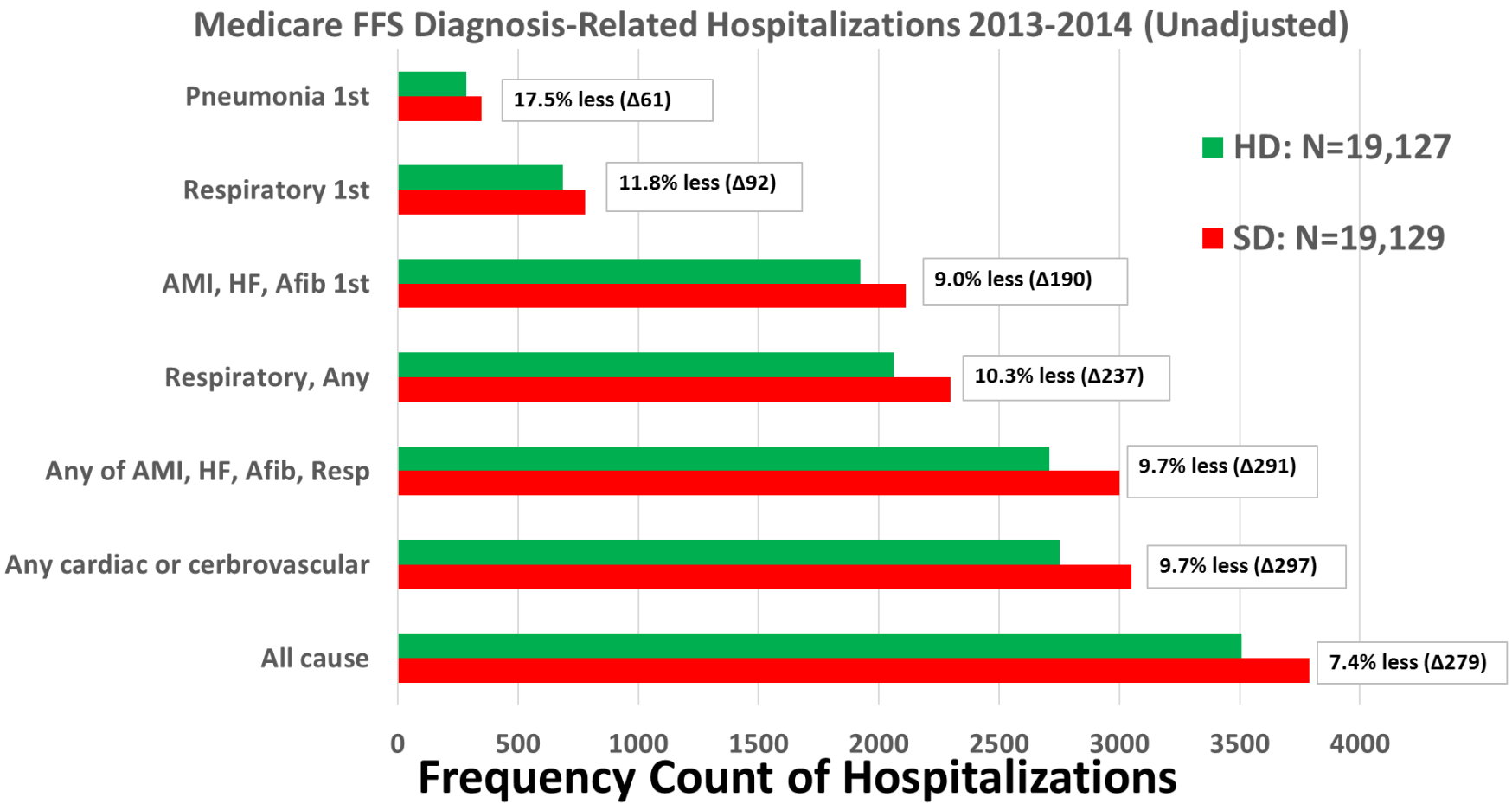
NNT = 1/ARR where ARR = CER – EER [a]

69, FFS sample

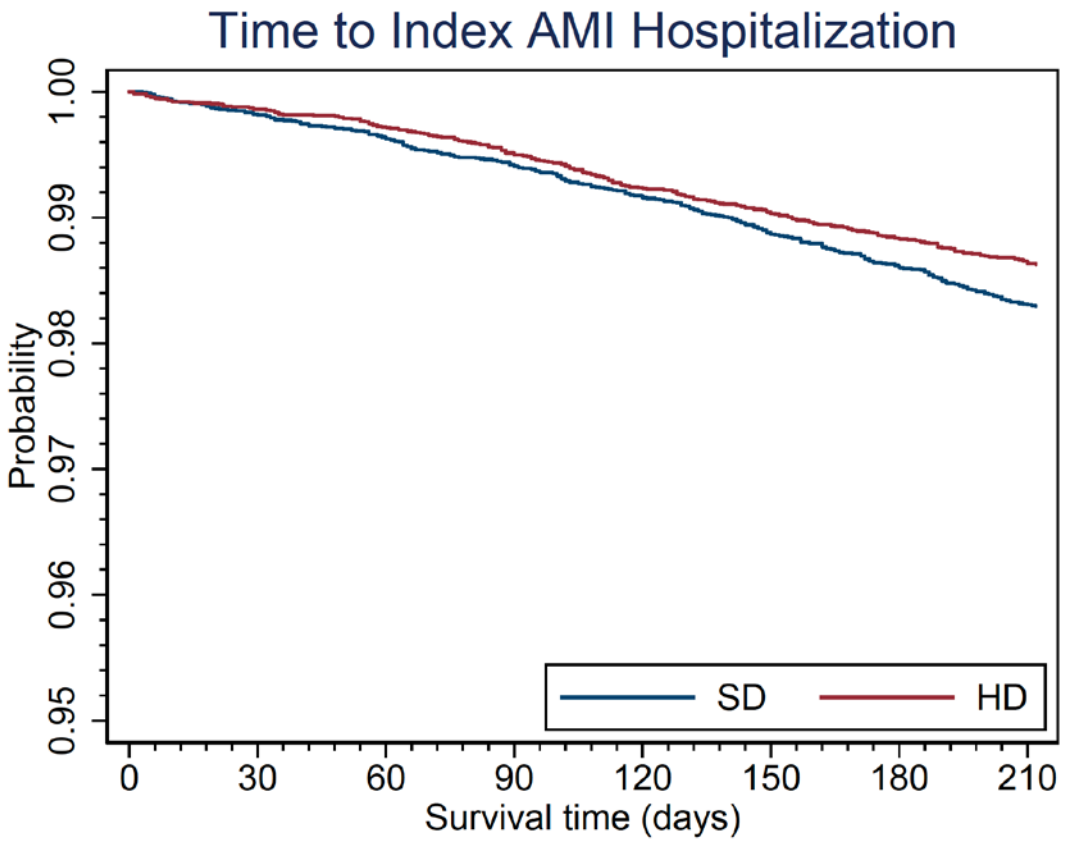
To prevent 1 hospitalization, 69 long-stay NH residents 65+ years of age need to be vaccinated with high-dose influenza vaccine compared to standard dose vaccine.

[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)

Reference:
Gravenstein et al, *Lancet Respir Med* 2017



Reference:
Gravenstein, et al, IAGG San Francisco, July 2017



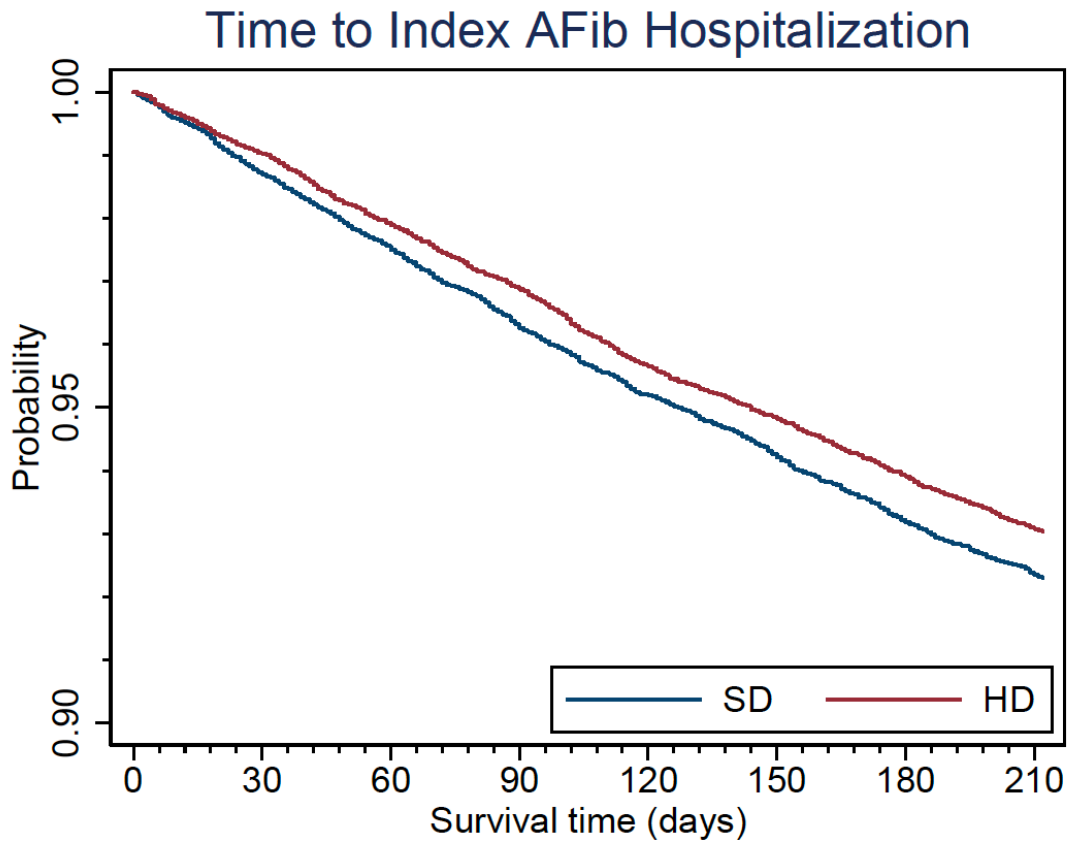
*p=0.017

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

Reference:

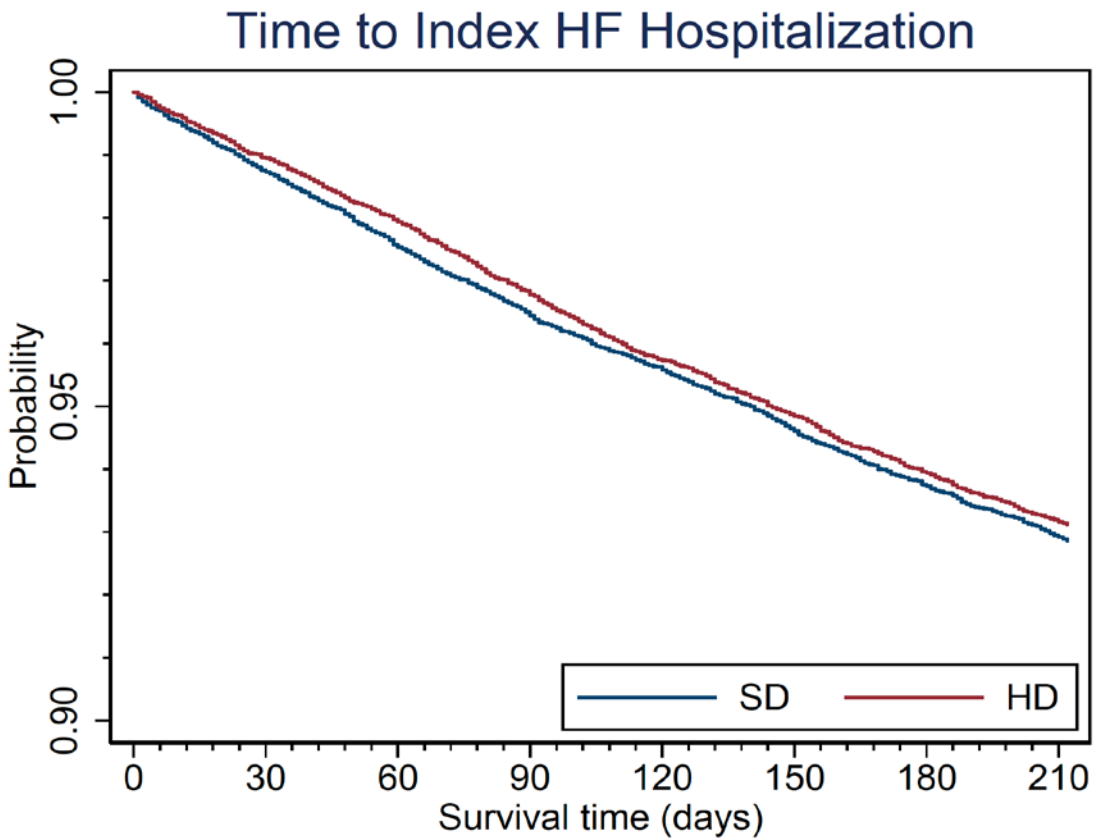
Gravenstein, et al, IAGG San Francisco, July 2017



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

Reference:

Gravenstein, et al, IAGG San Francisco, July 2017



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

Reference:

Gravenstein, et al, IAGG San Francisco, July 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	0.699-1.02	0.0799	817 38,225	0.825	0.634-0.995	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.

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

Summary

- HD vaccine reduces laboratory-confirmed influenza and hospitalization among ***outpatient elderly*** in several RCTs

- 2013-2014 season is of special interest because it offers a conservative estimate of relative benefit of HD vs. SD in preventing cardiorespiratory hospitalization in a ***nursing home*** population
  - A(H1N1) predominates, and relative benefit of HD vaccine for this strain in a NH population has been unknown
    - 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

- FFS claims differences consistent with biologic plausibility of effect on hospitalization based on diagnoses, and cardiorespiratory outcomes

MF59 Adjuvanted Flu Vaccine and Elderly

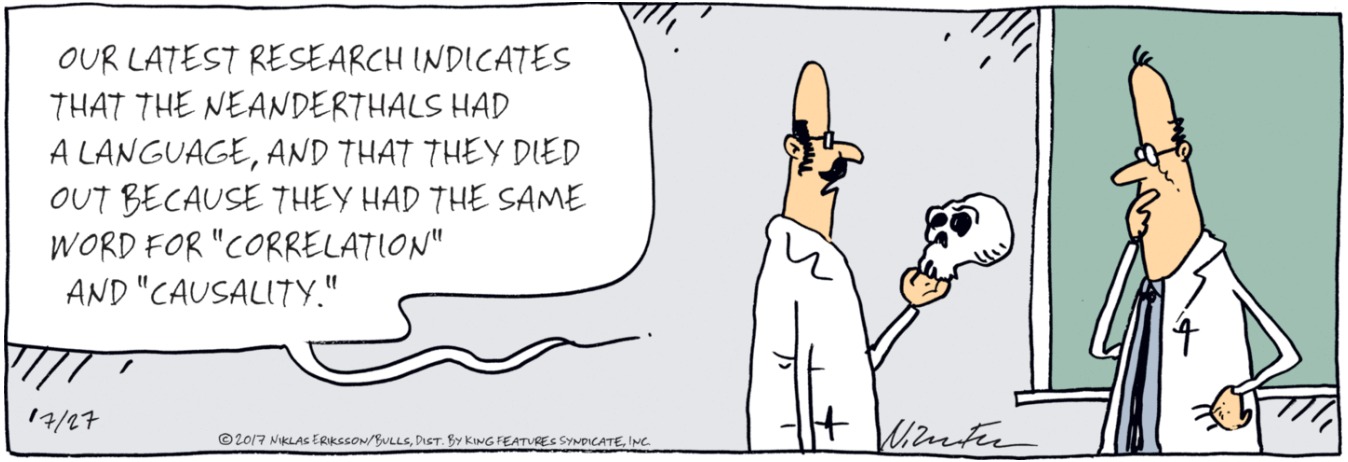
- Available in Europe since 1997; U.S. licensed in 2015 for age 65 years and older
  - Over 150 million doses
- Uses M59 oil emulsion of squalene from sharks
- Requires less antigen (3.75 vs 15 µg/antigen/standard dose and 60 µg for high dose)
- Improves cross-reactivity
- Non-RCT evidence of reduced hospitalization risk in elderly
  - Large cohort study: 25% reduction over 3 seasons[1]
  - 80% protected vs 57% with standard dose in a long-term care population[2] and better protection in case control study in NH population[3]

References:
1. Mannino S et al. *Am J Epidemiol*. 2012;176:527-533. (B)
2. Iob A et al. *Epidemiol Infect*. 2005;133:687-693. (B)
3. Van Buynder PG et al. *Vaccine*. 2013;31:6122-6128. (B)

Overall Summary

- **Aging** and multi-morbidity increase risk for influenza complications
- Influenza is much more than just a respiratory disease in older adults
- More immunogenic vaccines can offer better protection
- Effectiveness studies can inform about more generalizable performance of a vaccine
  - Nursing home cluster-randomized trials are an example of this

Earliest Evidence that Research Skills in Public Health Have Value



Continuing Education Information

- For CE credit go to:

  www2a.cdc.gov/TCEOnline

- CE credit expires: **October 30, 2017**
- Course Code: **WC2661-092616**
- Instructions available in the resource pod

Q&A

Thank You!

Extra Slides

Secondary Prevention of CV Events with Influenza Vaccination

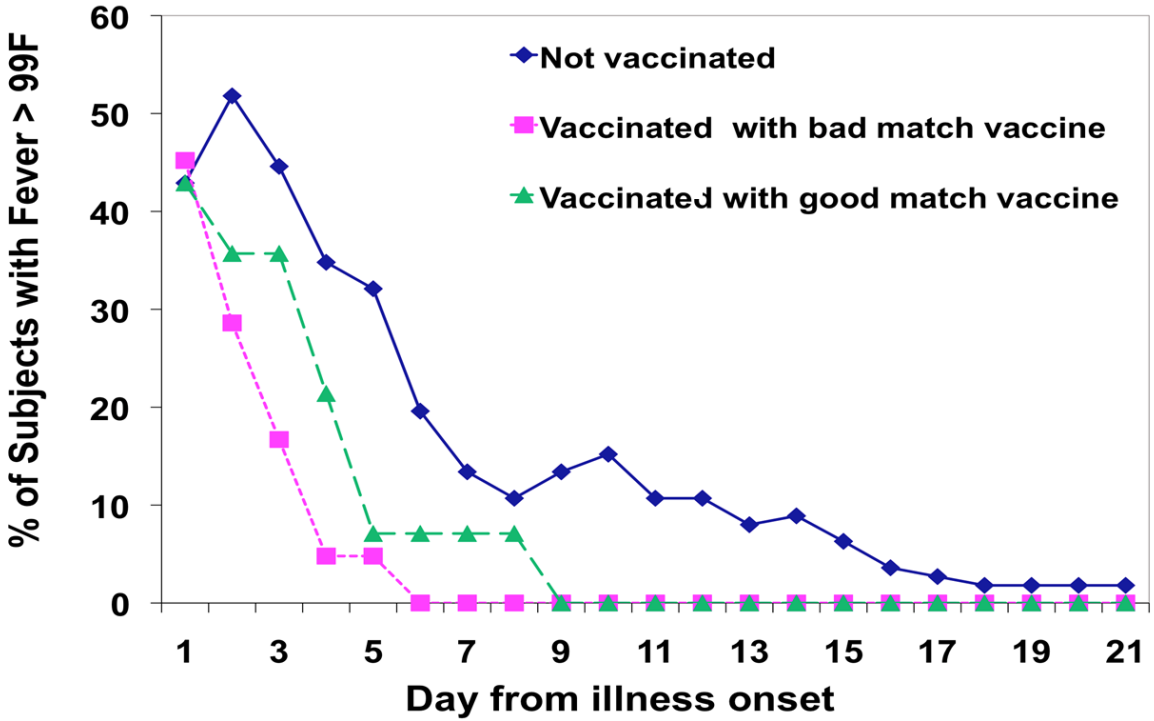
Study	Population Studied	Primary End Point	Results
FLUVACS[1,2a] (Argentina)	200 AMI patients; 100 with planned PCI[b] 151 vaccinated 150 controls	CVD death at 1 year	**CVD deaths:** **6% (vaccinated) vs. 17% (controls)** **RR = 0.34**
FLUCAD[3c] (Poland)	658 optimally treated patients with CAD 375 vaccinated 333 controls	CVD death at 1 year	**Primary end point: No impact** **Secondary end point:** **Coronary ischemic events significantly less** **6.02% (vaccinated) vs. 9.97% (controls)**
PROBE study[4d] (Thailand)	439 patients >50 yrs of age admitted with ACS 221 vaccinated 218 controls	Rate of MACE[e] at 1 year	**MACE:** **9.5% (vaccinated) vs. 19.3% (controls)** **RR = 0.70**

[a] FLUVACS = Flu Vaccination Acute Coronary Syndromes; [b] PCI = Percutaneous coronary intervention;
[c] FLUCAD = Flu and Coronary Artery Disease; [d] PROBE = Prospective randomized open with blinded endpoint;
[e] MACE = Major adverse cardiovascular events.

References:

1. Gurfinkel EP, et al. *Eur Heart J*. 2004;25(1(:25-31.
2. Gurfinkel EP, et al. *Tex Heart Inst J.* 2004;31(1):28-32.
3. Ciszewski A, et al. *Eur Heart J*. 2008;29(11):1350-1358.
4. Phrommintikul A, et al. *Eur Heart J*. 2011;32(14):1730-1735.

In LTC, Residents' Fever from Flu is Less, and is Attenuated More if Vaccinated[1]

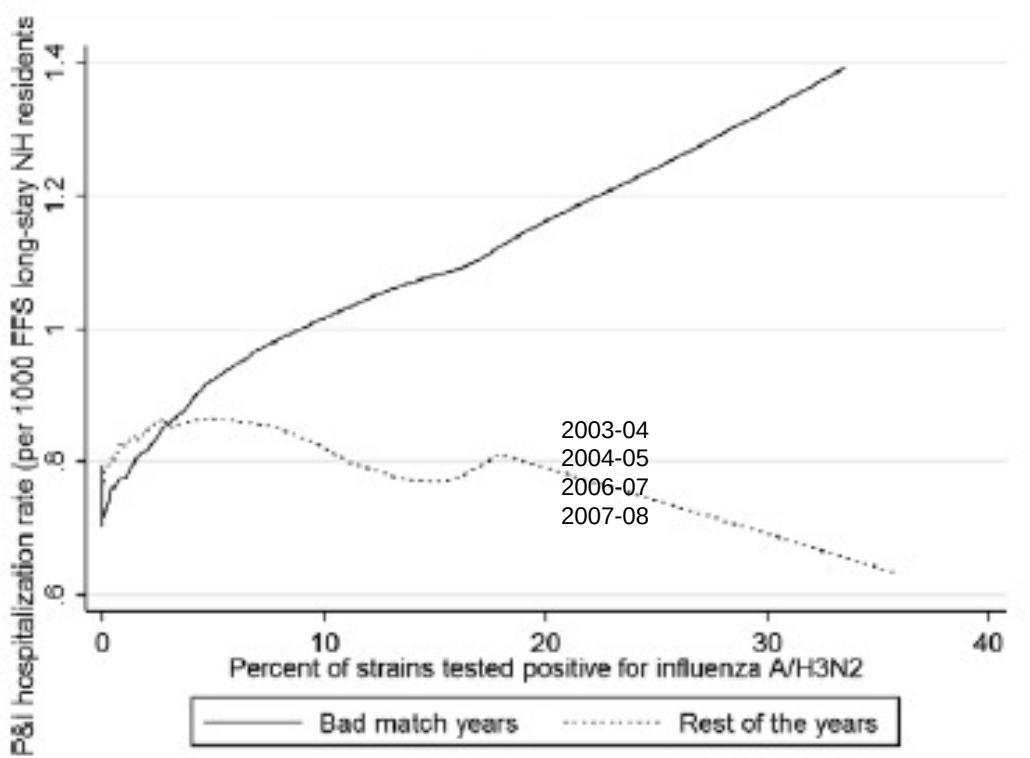


Reference:

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.

Effect of Influenza Vaccination on Hospitalization and Mortality in Long-Term Care[1]

Match Matters
Symptoms, hospitalization, and death are all lower in years where vaccine is a good match than in bad-match years



Reference:
1. Pop-Vicas A, et al. *J Am Geriatr Soc.* 2015;63(9):1798-1804.

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

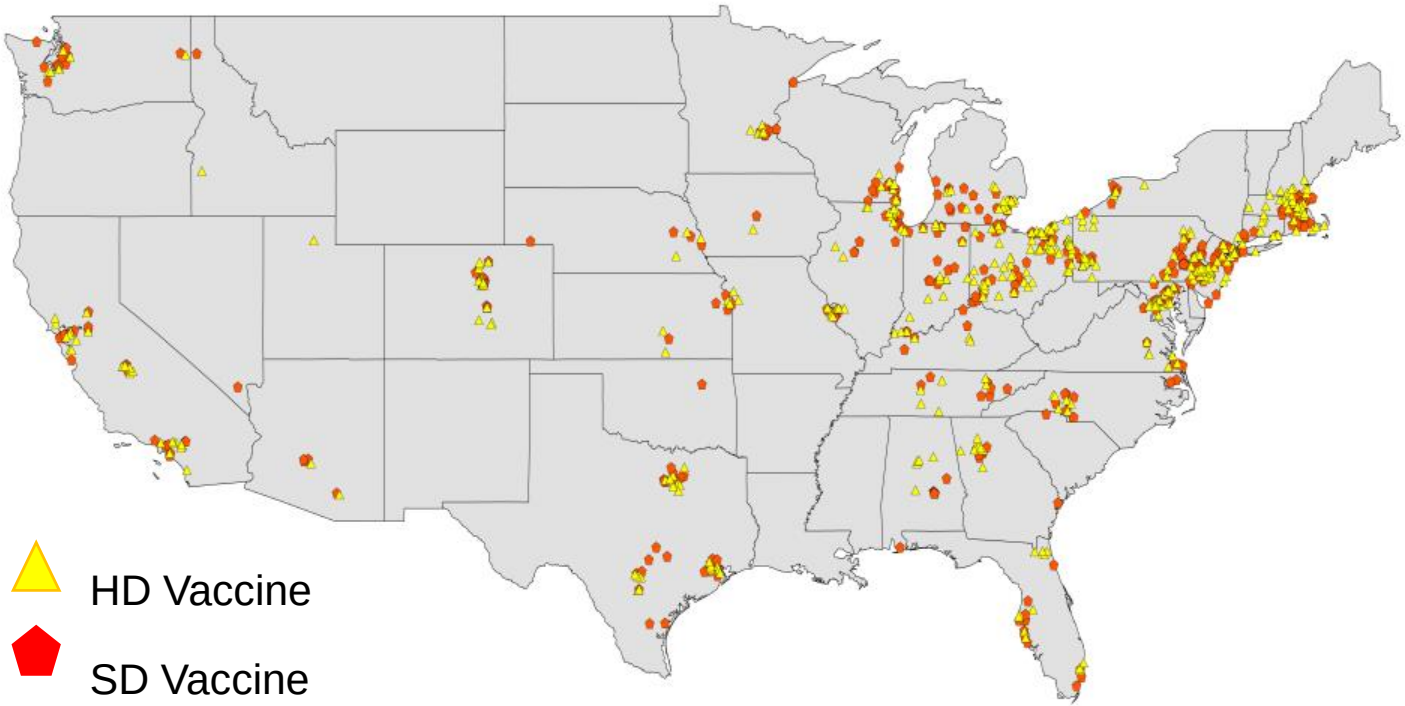
Effects of Influenza Vaccine on Major Adverse Cardiovascular Events[1]

Endpoints	Vaccine (n=221)	Control (n=218)	Unadjusted HR (95% CI)	*P*-value (unadjusted HR)	Adjusted HR (95% CI)	*P*-value (adjusted HR)
MACE, n (%)	21 (9.5)	42 (19.3)	0.70 (0.57- 0.86)	0.004	0.67 (0.51-0.86)	0.005
Death, n (%)	6 (2.7)	12 (5.5)	0.73(0.50-1.03)	0.156	0.62 (0.34-1.12)	0.113
Hospitalization for ACS, n (%)	10 (4.5)	23 (10.6)	0.73 (0.55-0.91)	0.032	0.68 (0.47-0.98)	0.039
Hospitalization for HF, n (%)	4 (1.8)	10 (4.6)	0.69 (0.49-1.01)	0.111	0.62 (0.19-2.04)	0.136
Hospitalization for stroke, n (%)	1 (0.5)	0	—	1.0	—	

Hazard ratios were adjusted for age, sex, serum creatinine, treatment with angiotensin-converting enzyme inhibitors, and coronary revascularization.
MACE, major adverse cardiovascular events; ACS, acute coronary syndrome; HF, heart failure.

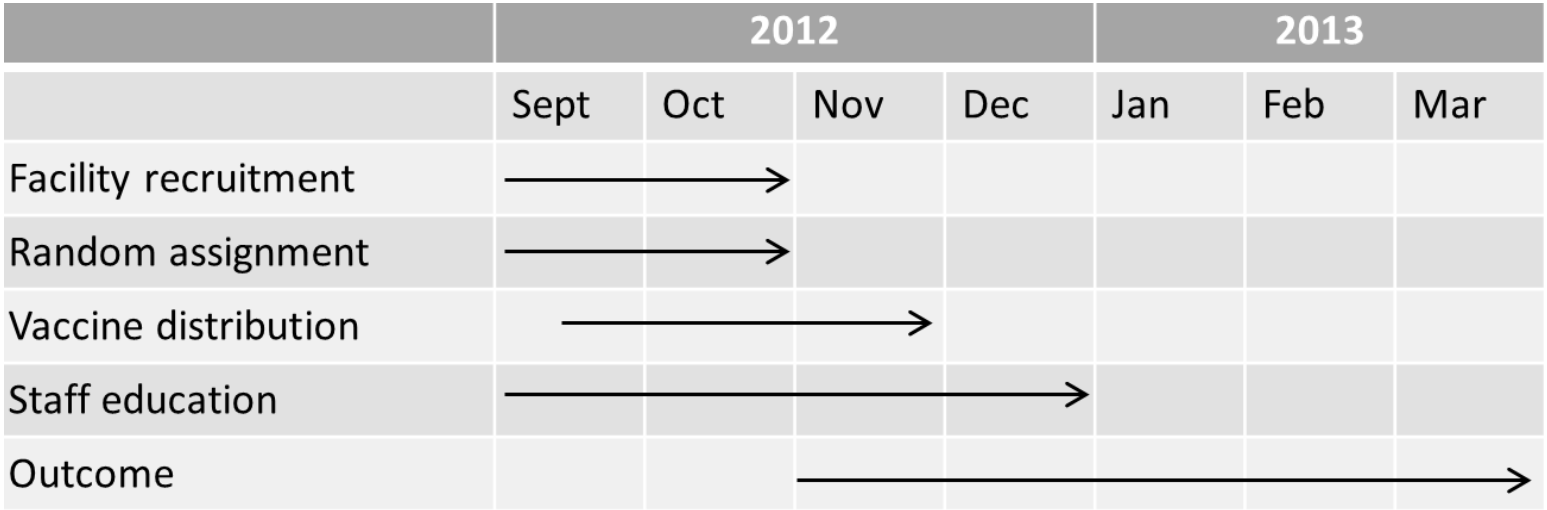
Reference:
1. Phrommintikul A, et al. *Eur Heart J.* 2011;32(14):1730-1735.

Participating NHs by State (n=823)



Reference:
Gravenstein et al, *Lancet Respir Med* 2017

Pilot Study: Methods



- **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

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.

Reference:
Gravenstein et al, *Lancet Respir Med* 2017

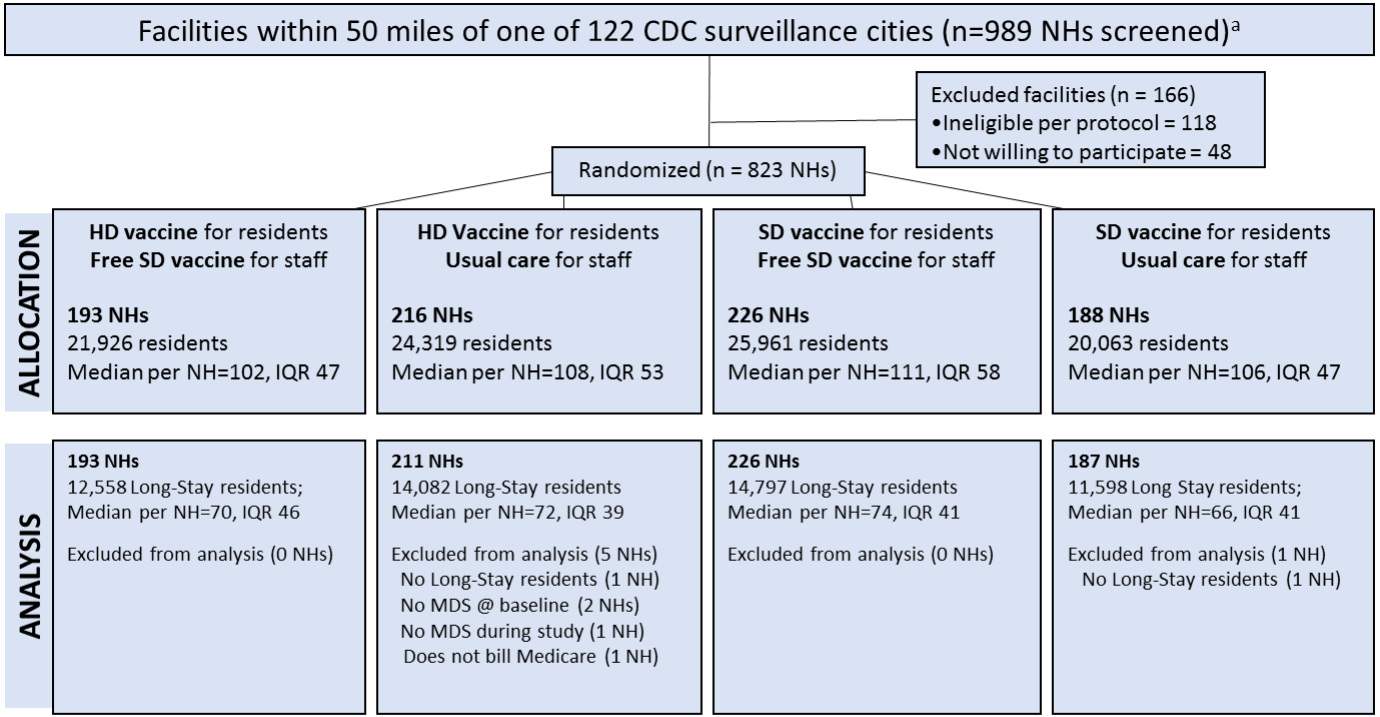
Exclusion Criteria

- Excluded facilities:
  - ✓Already using HD influenza vaccination
  - ✓Having fewer than 50 permanent residents
  - ✓Hospital-owned NHs
  - ✓More than 20% of residents UNDER 65 years of age

- Excluded residents:
  - ✓Under 65 years of age
  - ✓Less than 90 days stay in NH prior to vaccination
  - ✓For clinical outcomes, those not Medicare fee-for-service (FFS)

Reference:
Gravenstein et al, *Lancet Respir Med* 2017

NH Facilities Selection and Randomization



[a] 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

Reference:
Gravenstein et al, *Lancet Respir Med* 2017

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)

[a]Minimum Dataset (MDS).
[b]From OSCAR (online survey and certification).

NH Resident Groups Are Similar (n=53,035)

	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 years old	12,558	14,082	14,797	11,598
Age (mean, SD)	83.3 (8.7)	83.1 (8.8)	83.1 (8.8)	83.1 (8.9)
Female	9,020 (71.8)	10,234 (72.7)	10,689 (72.2)	8,351 (72.0)
African American	1,803 (14.4)	2,083 (14.8)	2,195 (14.8)	1,782 (15.4)
White	9,481 (75.5)	10,679 (75.8)	11,156 (75.4)	8,706 (75.1)
Hispanic	713 (5.7)	683 (4.9)	782 (5.3)	509 (4.4)
Married	2,332 (18.7)	2,693 (19.5)	2,777 (19.0)	2,240 (19.6)
Heart Failure	2,551 (20.3)	2,864 (20.3)	3,126 (21.1)	2,341 (20.2)
Stroke/ CVA/ TIA	2,454 (19.5)	2,802 (19.9)	3,094 (20.9)	2,312 (19.9)
Hypertension	9,969 (79.4)	11,142 (79.1)	11,713 (79.2)	9,151 (78.9)
Diabetes Mellitus	4,235 (33.7)	4,816 (34.2)	5,163 (34.9)	4,039 (34.8)
Asthma/COPD/CLD	2,406 (19.2)	2,859 (20.3)	3,097 (20.9)	2,337 (20.2)

Reference:
Gravenstein et al, *Lancet Respir Med* 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	0.699-1.02	0.0799	817 38,225	0.825	0.634-0.995	0.0438
All-cause hospitalization MDS cohort	818 53,008	0.936	0.874 - 1.000	0.0573	817 52,968	0.933	0.884 - 0.985	0.0117
ADL (functional decline of at least 4 points)	818 48,468	1.001	0.958 - 1.047	0.9452	817 48,429	0.996	0.956 - 1.038	0.8599
Mortality (all-cause)	818 53,008	0.982	0.931 – 1.036	0.5063	817 52,968	0.985	0.931 – 1.038	0.5674

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.

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

NNT for Respiratory VS Afib Hospitalization

	Atrial fibrillation (in any discharge diagnosis position)		Respiratory Illness (primary admission diagnosis)	
AGE	NNT	N	NNT	N
Young (65-77)	77	4833	99	4877
Young old (78-85)	260	5236	256	5419
Old (86-90)	235	4305	293	4203
Old-old (91+)	37	4755	88	7628

Reference:
Gravenstein, et al, IAGG San Francisco, July 2017