

Influenza in the Elderly

Stefan Gravenstein, MD, MPH

Professor of Medicine and Health Services Policy and Practice

Gerontology Center

Brown University

VA COIN

Providence Veterans Administration Hospital

Adjunct Professor of Medicine

University Hospitals Cleveland Medical Center and Case Western Reserve University

Disclosures

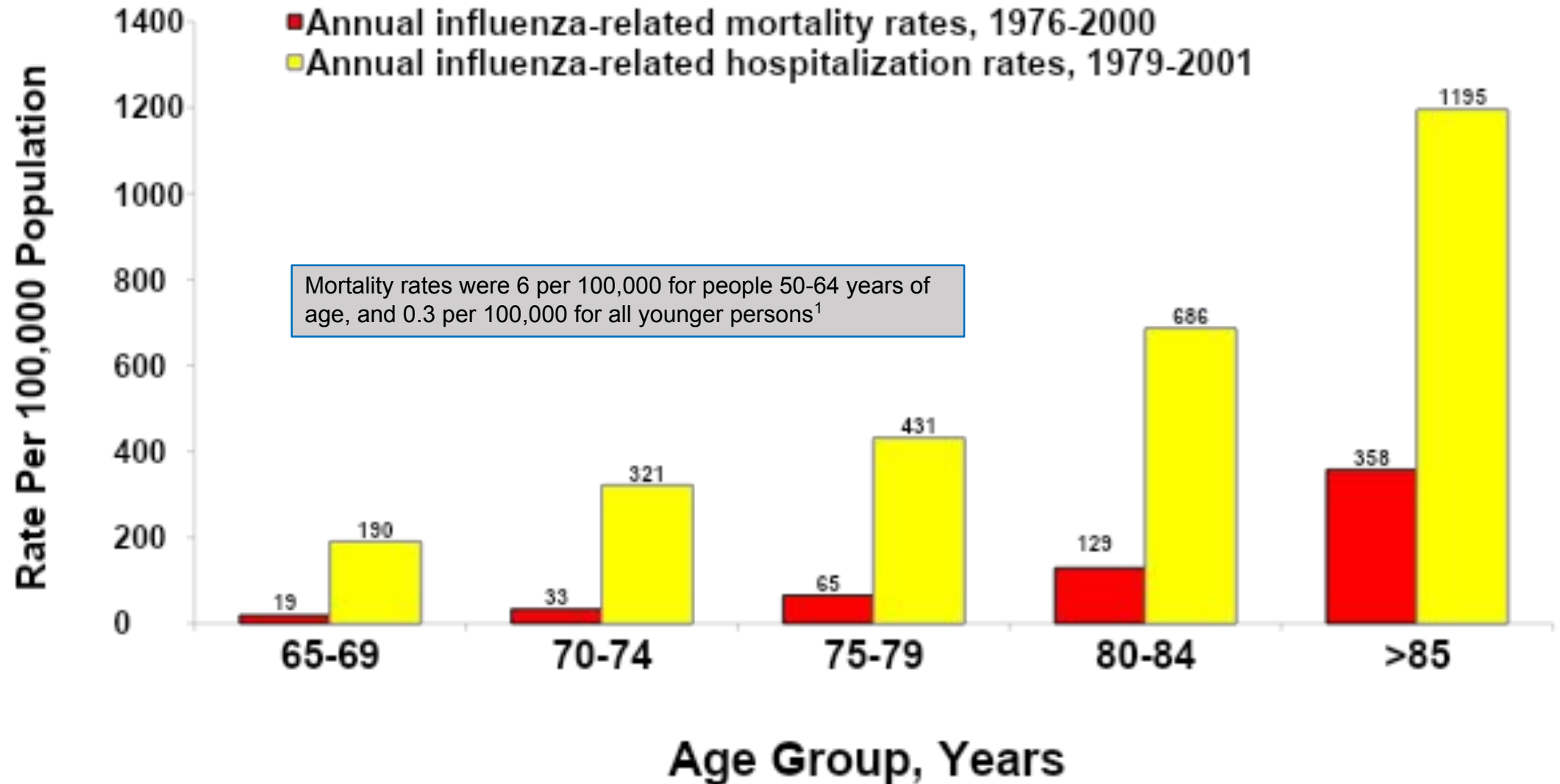
- Grant and contract support from Centers for Disease Control, Centers for Medicare and Medicaid, National Institutes of Health, Pfizer, Sanofi Pasteur, Seqirus
- Consulting with American Geriatrics Society, Gerontological Society of America, Longeveron, Merck, Novartis, Novavax, Pfizer, Janssen
- Speaker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

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

Objectives

- Influenza and immunosenescence
- Recognize direct and indirect effects of disease and vaccines
- Vaccine effectiveness

Influenza-Associated Hospitalizations and Death Rates Increase With Age¹



Reference:

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

Chronic Conditions in Adults Hospitalized with Laboratory-Confirmed Influenza¹

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.

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Reference:

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

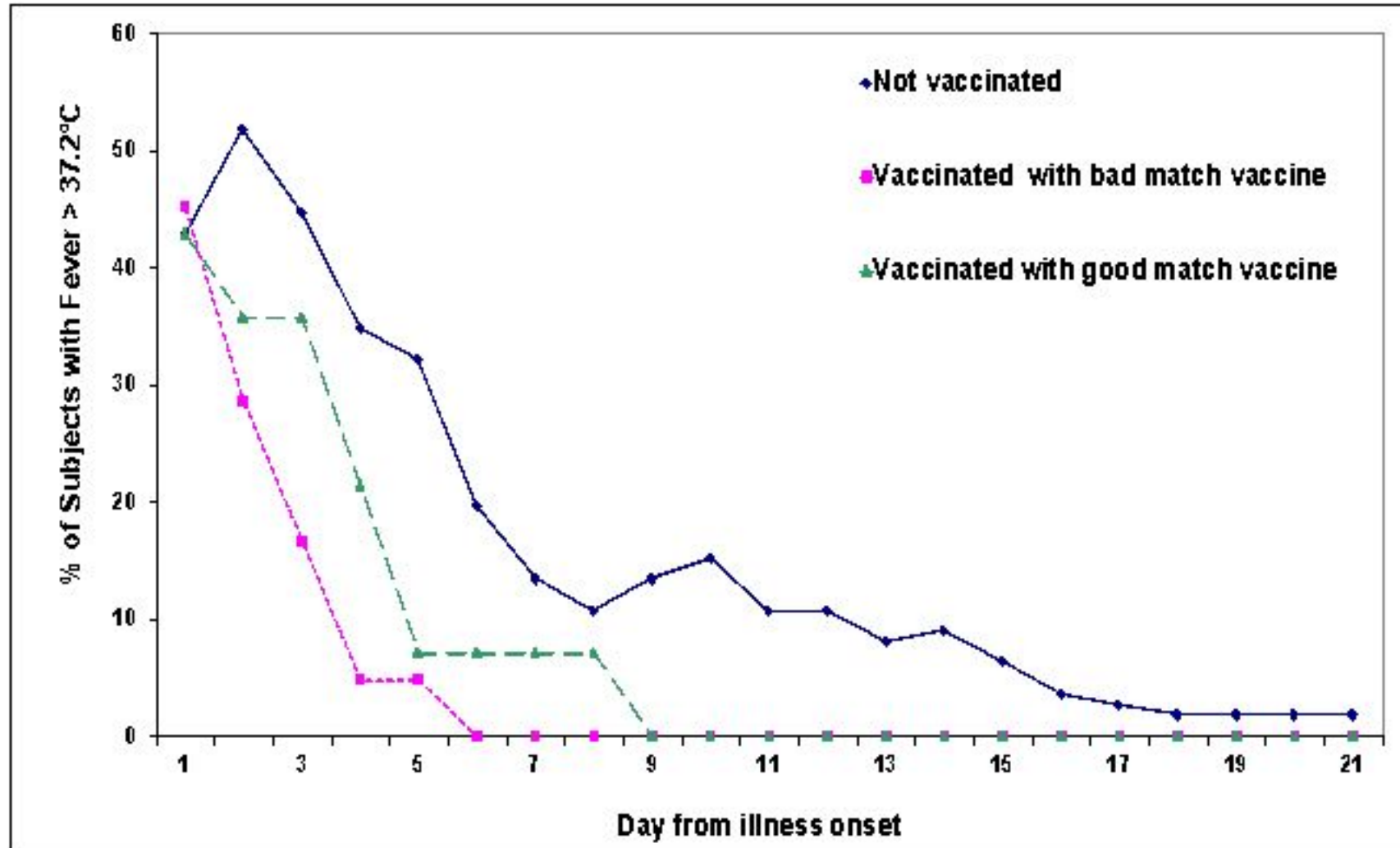
Influenza vaccine is effective in older adults

- Globally, flu causes 3-5 million severe illnesses, and 250-500k deaths
- National UK retrospective observational cohort study, 2000-2009¹
 - Propensity matched/adjusted: sex, age, SES, clinical risks groups, prior vax
 - 1.8 mm person seasons of observations; 274k influenza vaccines targeting at-risk (256k), with 69% uptake by 65+ (179k vaccinations)
 - Laboratory confirmation by RT-PCR in 3.2k subset
 - 57% overall VE, 18% in 65+ against laboratory confirmed illness
 - 16% reduction in primary care consultations for influenza-like illness
 - 19% for preventing P&I hospitalizations
 - 38% effective in reducing death to influenza and pneumonia
- Europe (9 country) with A/H3N2 and B co-circulation 2017-2018
 - Test negative design for 65 and older with recent (≤ 7 day) acuter respiratory infection, RT-PCR
 - 3483 patients, 376 A/H3N2, 928 B, and 2028 controls
 - IVE 24% influenza A in 65-79 year olds; 14% in ≥ 80 year olds
 - IVE 30% influenza B in 65-79 year olds; 19% in ≥ 80 year olds despite vaccine mismatch

Reference:

1. Simpson CR, et al. Southampton (UK): NIHR Journals Library; 2013 Nov. PMID: 25642510.
2. Rose AMC, et al. Influenza Other Respir Viruses. 2020;14(3):302-310.

In LTC, Residents' Fever From Influenza Is Less, and Fever Is Attenuated More If Vaccinated¹



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.

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.

Pneumonia and cardiac events

- Review of this by Corrales-Medina et al 2013 with pneumonia followed by cardiovascular events
 - **“a quarter of adults admitted to hospital with pneumonia develop a major acute cardiac complication during their hospital stay, which is associated with a 60% increase in short-term mortality.”**
- Prospective study 2017 in 1182 CAP admissions, followed for 30 days
 - 32% cardiovascular event in <30 days (24% HF, 9% afib, 8% AMI)
 - 17.6% vs 4.5% mortality with vs w/o CVE (p<.001)

References:

Corrales-Medina VG et al, Lancet 2013
Violi F et al, Clin Infec Dis, 2017

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, 70(2):293–300.
2. Erskine et al, *PLoS One*. 2017; 12(7): e0181565.

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

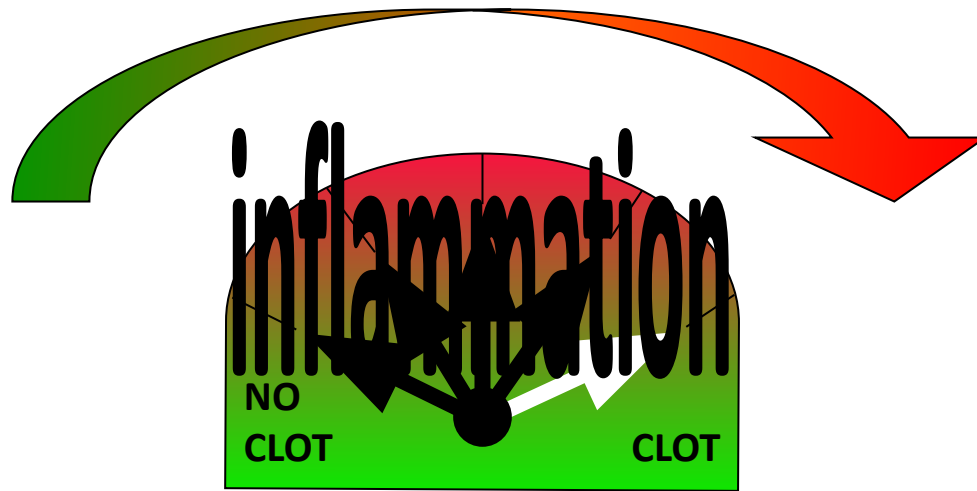
Reference:

1. 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)

“Thrombometer” – The Propensity to Clot



<u>LOW</u>	<u>HIGH</u>
CRP	DVT
IL-1, 6	Stroke
TNF-alpha	MI
	Delirium
	Dementia

Increases with age

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

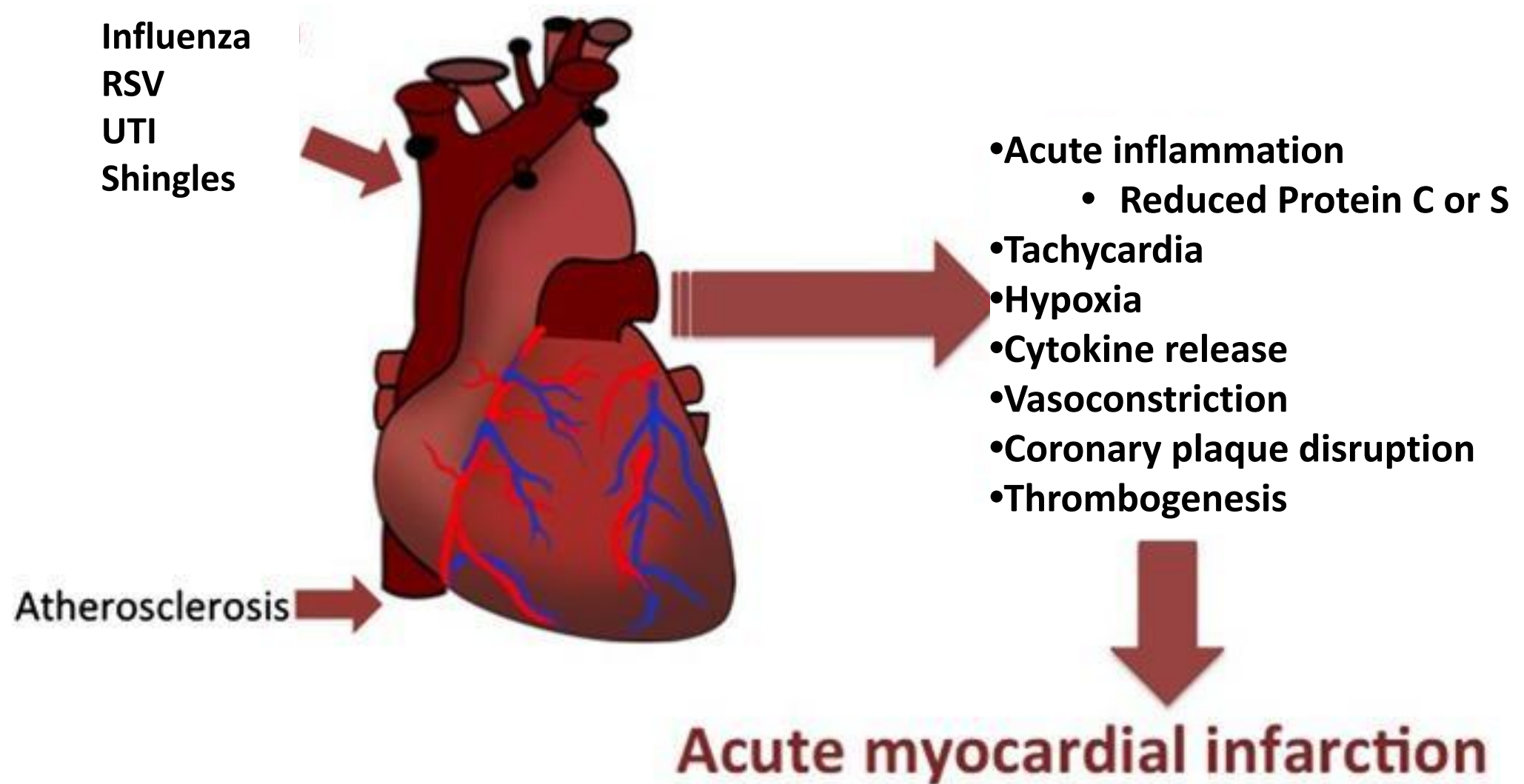
Increases with disease

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

Increases following infection

- Influenza, RSV
- Community acquired pneumonia
- Shingles
- Bladder infection
- Pressure sores

Influenza Infection Can Trigger Acute Myocardial Infarction



Adapted from:

1. MacIntyre CR, et al. *Heart*. 2016;102(24):1953-1956.

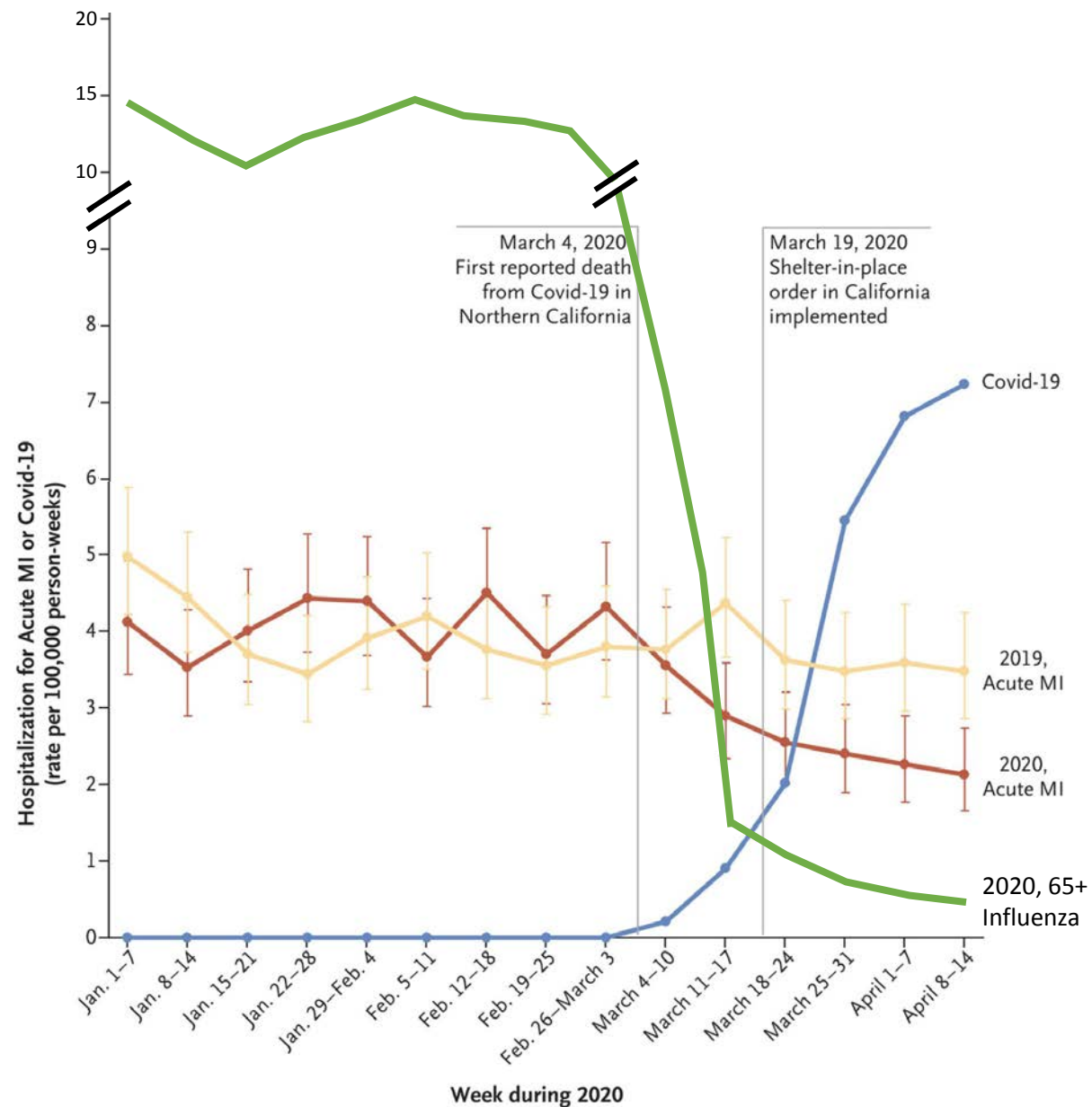
COVID, Flu & AMI

- COVID associated with strokes and heart attacks due to coagulopathy, viral invasion
- Kaiser Permanente Northern California with 4.4 million lives¹
 - January through April 2020 (red), weekly AMI (STEMI and NSTEMI) hospitalization compared to 2019 (yellow)
 - AND COVID-19 incidence rates (blue)
 - 48% decrease in AMI hospitalization during COVID-19, both STEMI and NSTEMI
- Laboratory-confirmed influenza hospitalization (green) declined by over 90% in March
 - Opposite the increase in COVID-19 hospitalization

Figure adapted from CDC's FluView and Solomon et al.^{1,2}

References:

1. Sawlani V, et al. Clin Radiol. 2020:S0009-9260(20)30392-5. PMID: 33023738.
2. Jørstad, H.T., Piek, J.J. Neth Heart J (2020). Editorial
3. Basso C, et al. Eur Heart J. 2020;. Epub ahead of print. PMID: 32968776
4. Solomon MD, et al., N Engl J Med 2020; 383:691-693 DOI: 10.1056/NEJMc2015630
5. <https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html> accessed 9 OCT 2020



No. of Patients

2019, Acute MI	140	125	104	97	110	118	106	100	107	106	123	102	98	101	98
2020, Acute MI	118	101	115	127	126	105	129	106	124	102	83	73	69	65	61
2020, Covid-19	0	0	0	0	0	0	0	0	0	6	26	58	156	195	207

The Range of Efficacy of Coronary Interventions Compared With Influenza Vaccination

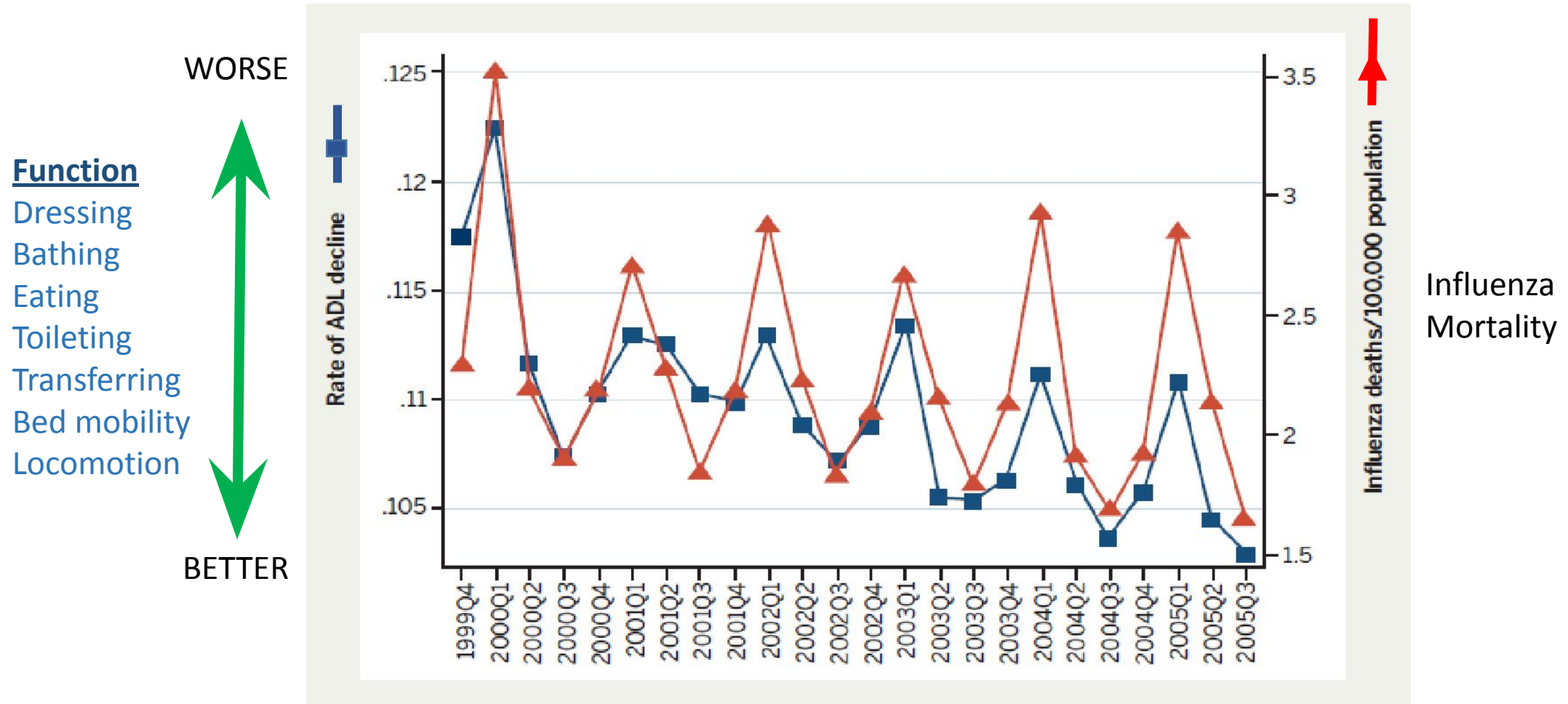
Table 1 Efficacy of accepted coronary interventions and influenza vaccine in the prevention of myocardial infarction

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:

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

Influenza Negatively Affects Functional Status in Nursing Home Residents



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.

Older Adults Have Decreased Immunologic Responses to Vaccines

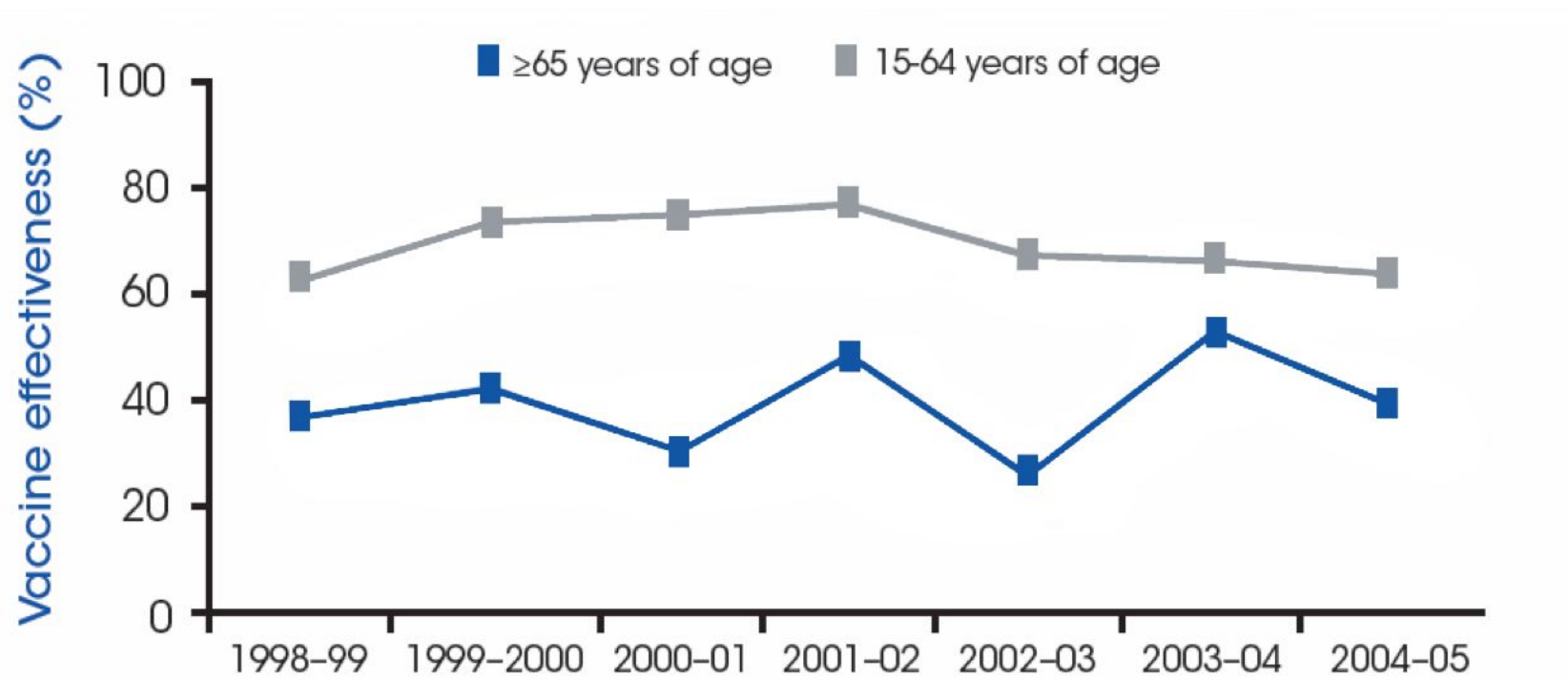
Age Affects the Antibody Response to Influenza Vaccination¹

- Review of 31 vaccine antibody response studies conducted from 1986 to 2002
 - Adults 65 years and older had significantly lower antibody responses to vaccination than younger adults
 - For all influenza antigens
 - Both measures studied were 2- to 4-fold less in older adults
 - Seroconversion and seroprotection
 - The results “highlight the need for more immunogenic vaccine formulations for the elderly”

Reference:

1. Goodwin K, et al. *Vaccine*. 2006;24(8):1159-1169.

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.

Immune Senescence

- More permissive for infection, including pneumonia¹
 - 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
- Changes symptom presentation with age

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.

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?

High dose flu vaccine reduces clinical flu in outpatient elderly

ORIGINAL ARTICLE

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

Carlos A. DiazGranados, M.D., Andrew J. Dunning, Ph.D., Murray Kimmel, D.O., Daniel Kirby, B.Sc., John Treanor, M.D., Avi Collins, B.Sc.N., Richard Pollak, D.P.M., Janet Christoff, R.N., John Earl, M.D., Victoria Landolfi, M.Sc., M.B.A., Earl Martin, D.O., Sanjay Gurunathan, M.D., Richard Nathan, D.O., David P. Greenberg, M.D., Nadia G. Tornieporth, M.D., Michael D. Decker, M.D., M.P.H., and H. Keipp Talbot, M.D., M.P.H.
N Engl J Med 2014; 371:635-645 | [August 14, 2014](#) | DOI: 10.1056/NEJMoa1315727

- 31,989 volunteers at 126 centers US/Canada
- Intent-to-treat, 50/50, 2011-2013
- Titers higher in HD group
- Relative efficacy, ILI 24.2%; (95% CI 9.7 to 36.5)
 - Relative efficacy ILI hospitalization 30% (95% CI 9 to 46)

INFLUENZA SEASON 2013-2014

LARGE TRIAL (823 NHs)



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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[http://dx.doi.org/10.1016/S2213-2600\(17\)30235-7](http://dx.doi.org/10.1016/S2213-2600(17)30235-7)

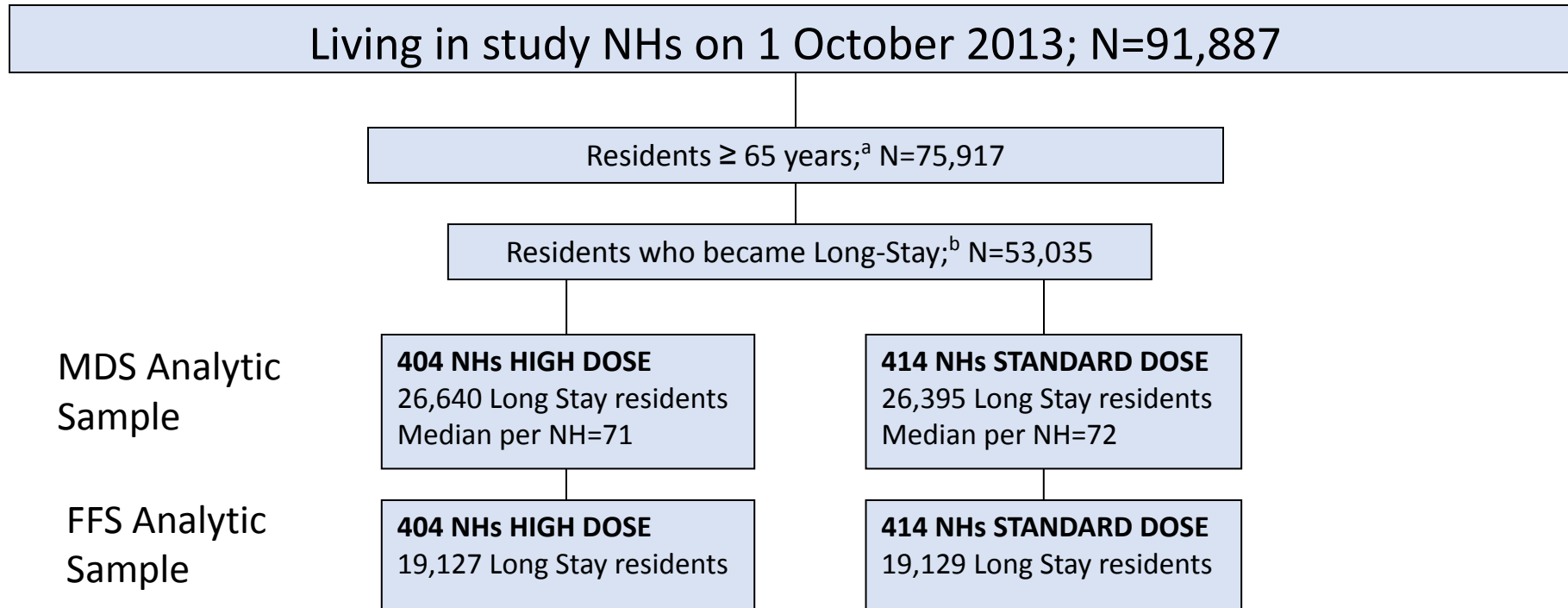
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[http://dx.doi.org/10.1016/S2213-2600\(17\)30290-4](http://dx.doi.org/10.1016/S2213-2600(17)30290-4)

[http://dx.doi.org/10.1016/S2213-2600\(17\)30290-4](http://dx.doi.org/10.1016/S2213-2600(17)30290-4)

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)]

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

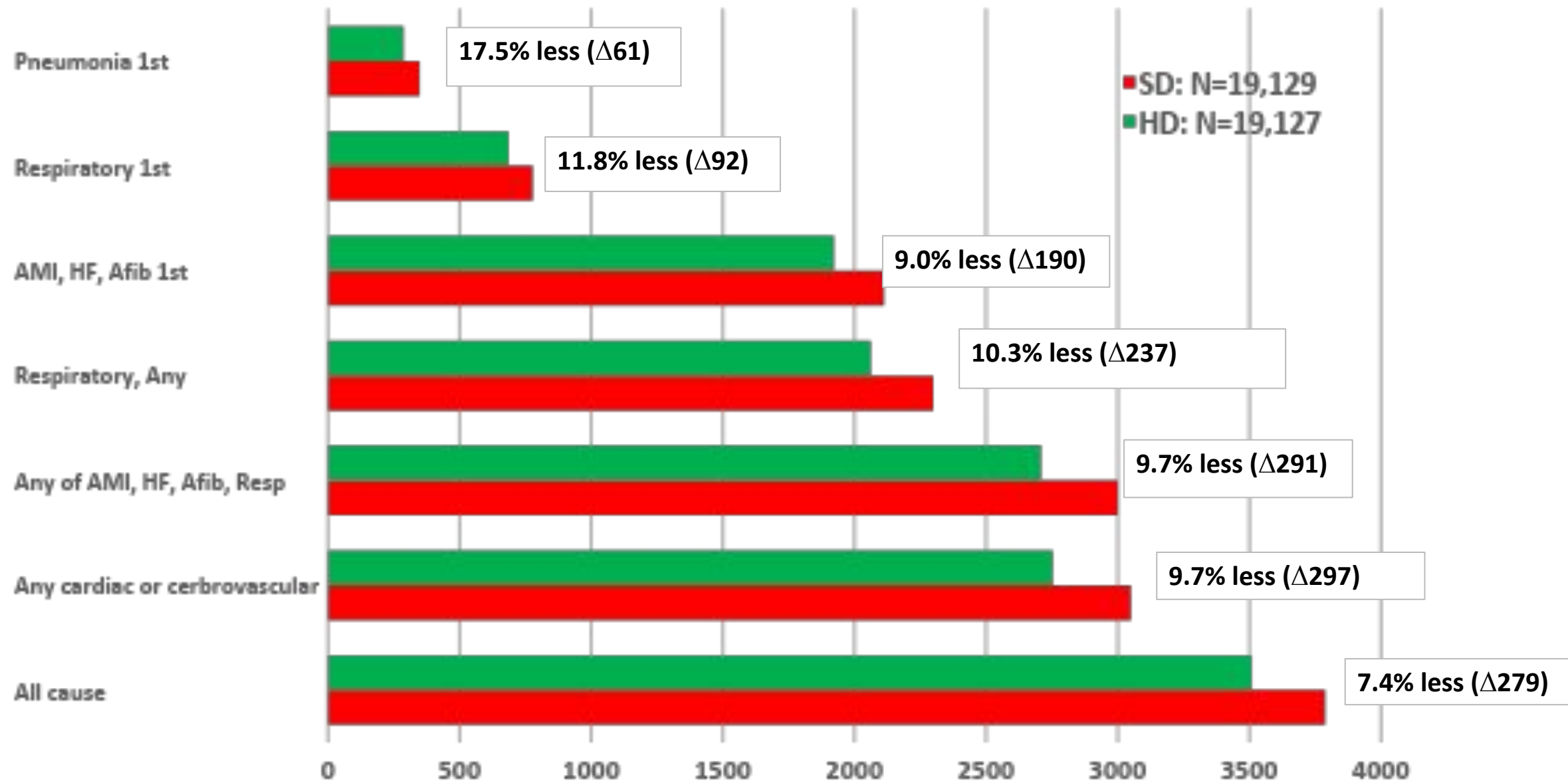
$$\text{NNT} = 1/\text{ARR} \text{ where } \text{ARR} = \text{CER} - \text{EER}^a$$

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)

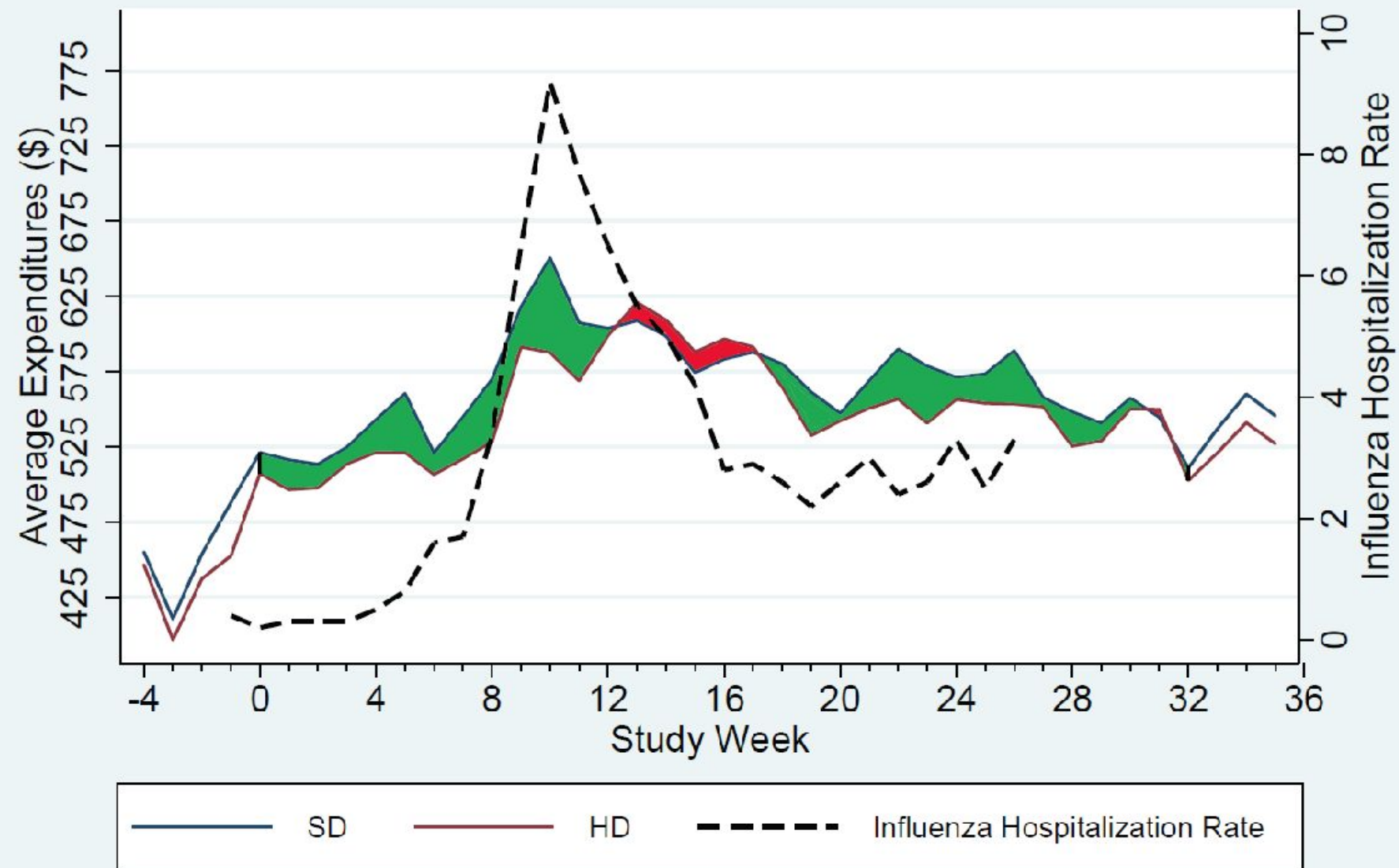
Medicare FFS Diagnosis-Related Hospitalizations 2013-2014 (Unadjusted)



Frequency Count of Hospitalizations

Average Weekly Expenditures

FFS: Full Trial



MF59 Adjuvanted Flu Vaccine and Elderly

- Available in Europe since 1997; US licensed in 2015 for 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/antigen for high dose)
- Improves cross-reactivity
- Non-RCT evidence of reduced hospitalization risk in elderly
 - Large cohort study: 25% reduction over 3 seasons¹
 - 80% protected vs 57% with standard dose in a long-term care population² and better protection in case control study in NH population³

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)

Cluster-randomized Trial of Adjuvanted Versus Nonadjuvanted Trivalent Influenza Vaccine in 823 US Nursing Homes

Kevin W. McConeghy^{1,2,*}, H. Edward Davidson³, David H. Canaday^{4,5,6}, Lisa Han³, Elie Saade^{4,5,6}, Vince Mor^{1,2,7}, and Stefan Gravenstein^{1,2,7}

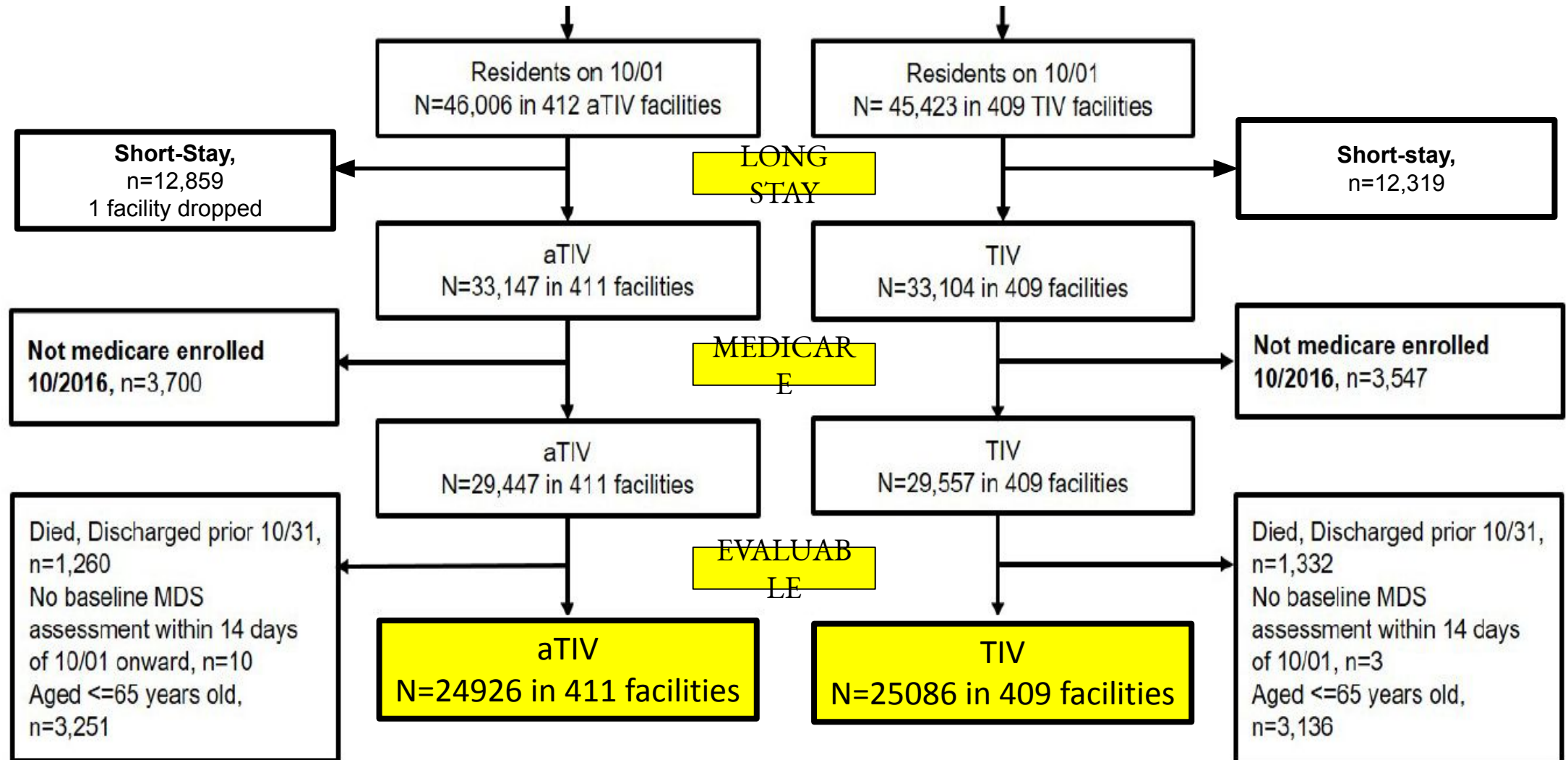
¹Center on Innovation in Long-Term Services and Supports, Veterans Administration Medical Center, Providence, Rhode Island, USA; ²School of Public Health, Brown University, Providence, Rhode Island, USA; ³Department of Preventive Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; ⁴Department of Infectious Diseases, University of Illinois at Chicago, Chicago, Illinois, USA; ⁵Department of Medicine, University of Illinois at Chicago, Chicago, Illinois, USA; ⁶Department of Public Health, University of Illinois at Chicago, Chicago, Illinois, USA; ⁷Department of Infectious Diseases, University of Illinois at Chicago, Chicago, Illinois, USA

- Cluster RCT in 832 nursing homes
- Similar in design to study with High Dose vaccine

Reference:

1. McConeghy KW, et al. Clin Infect Dis. 2020 Sep 4;ciaa1233. doi: 10.1093/cid/ciaa1233. Epub ahead of print. PMID: 32882710.

Residents in Analytic Sample



Reference:

1. McConeghy KW, et al. Clin Infect Dis. 2020 Sep 4;ciaa1233. doi: 10.1093/cid/ciaa1233. Epub ahead of print. PMID: 32882710.

Primary Analysis

Outcome	Unadjusted	Cov. Adjusted	Cov. and Race/Ethnicity
Hospitalization, all-cause	0.94 (0.87, 1.00) p-value = 0.05	0.94 (0.89, 0.99) p-value = 0.02	0.94 (0.89, 0.99) p-value = 0.03
Hospitalization, respiratory illness	0.93 (0.82, 1.04) p-value = 0.20	0.93 (0.82, 1.04) p-value = 0.19	0.91 (0.81, 1.02) p-value = 0.10
Hospitalization, Pneumonia / Influenza	0.79 (0.65, 0.97) p-value = 0.02	0.80 (0.66, 0.98) p-value = 0.03	0.79 (0.65, 0.96) p-value = 0.03
Mortality, all-cause	1.04 (0.98, 1.09) p-value = 0.18	1.05 (0.99, 1.10) p-value = 0.08	1.03 (0.98, 1.08) p-value = 0.23

Reference:

1. McConeghy KW, et al. Clin Infect Dis. 2020 Sep 4;ciaa1233. doi: 10.1093/cid/ciaa1233. Epub ahead of print. PMID: 32882710.

Adjuvanted Influenza Vaccine and Influenza Outbreaks in US Nursing Homes: Results From a Pragmatic Cluster-Randomized Clinical Trial

Stefan Gravenstein ✉, Kevin W McConeghy, Elie Saade, H Edward Davidson, David H Canaday, Lisa Han, James Rudolph, Nina Joyce, Issa J Dahabreh, Vince Mor

Clinical Infectious Diseases, ciaa1916, <https://doi.org/10.1093/cid/ciaa1916>

Published: 05 January 2021 **Article history** ▼

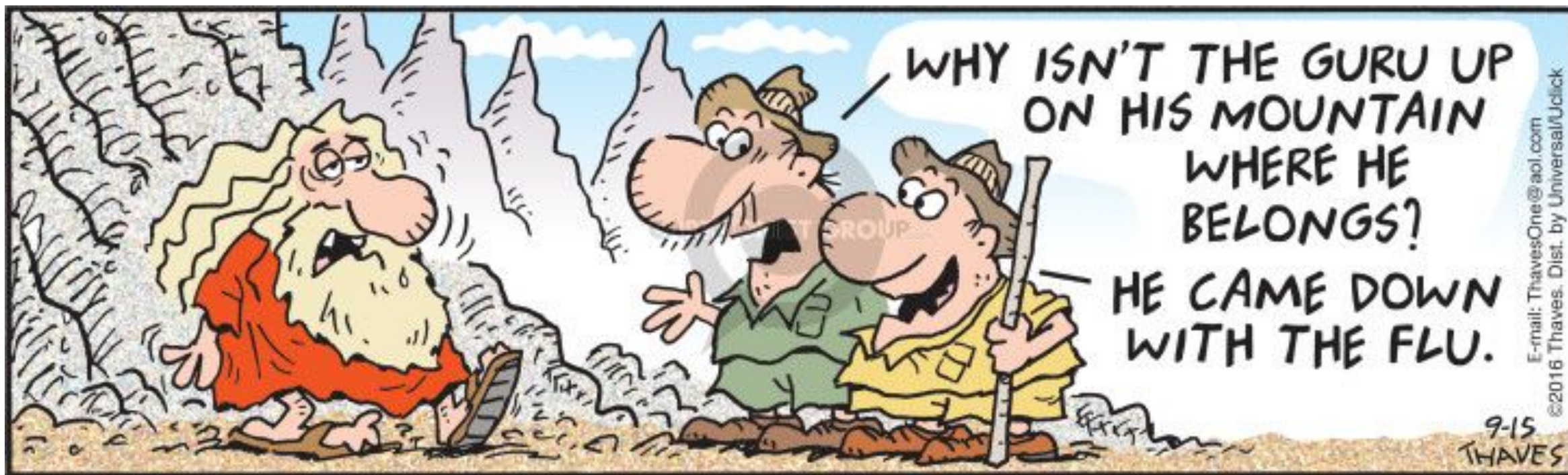
- Retrospective study of aTIV cluster RCT on 777 nursing homes reporting on outbreaks
- 133 aTIV vs 162 TIV facilities had influenza outbreaks
 - 17% unadjusted reduction; 21% adjusted reduction (0.79; 0.61-0.99)

Reference:

1. Gravenstein S, et al. Clin Infect Dis. 2021 Jan 5:ciaa1916. doi: 10.1093/cid/ciaa1916. Epub ahead of print. PMID: 33400778.

Summary

- **Aging** and multimorbidity increase risk for influenza complications
- Influenza is much more than just a respiratory disease in older adults
- **Vaccinate, good match or not, every year**
- More immunogenic vaccines can offer better protection



Reference:

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

Bonus slides

Earliest Evidence that Research Skills in Public Health Have Value

