Preparing for a Pragmatic Influenza Vaccine Clinical Trial: A One-shot Deal

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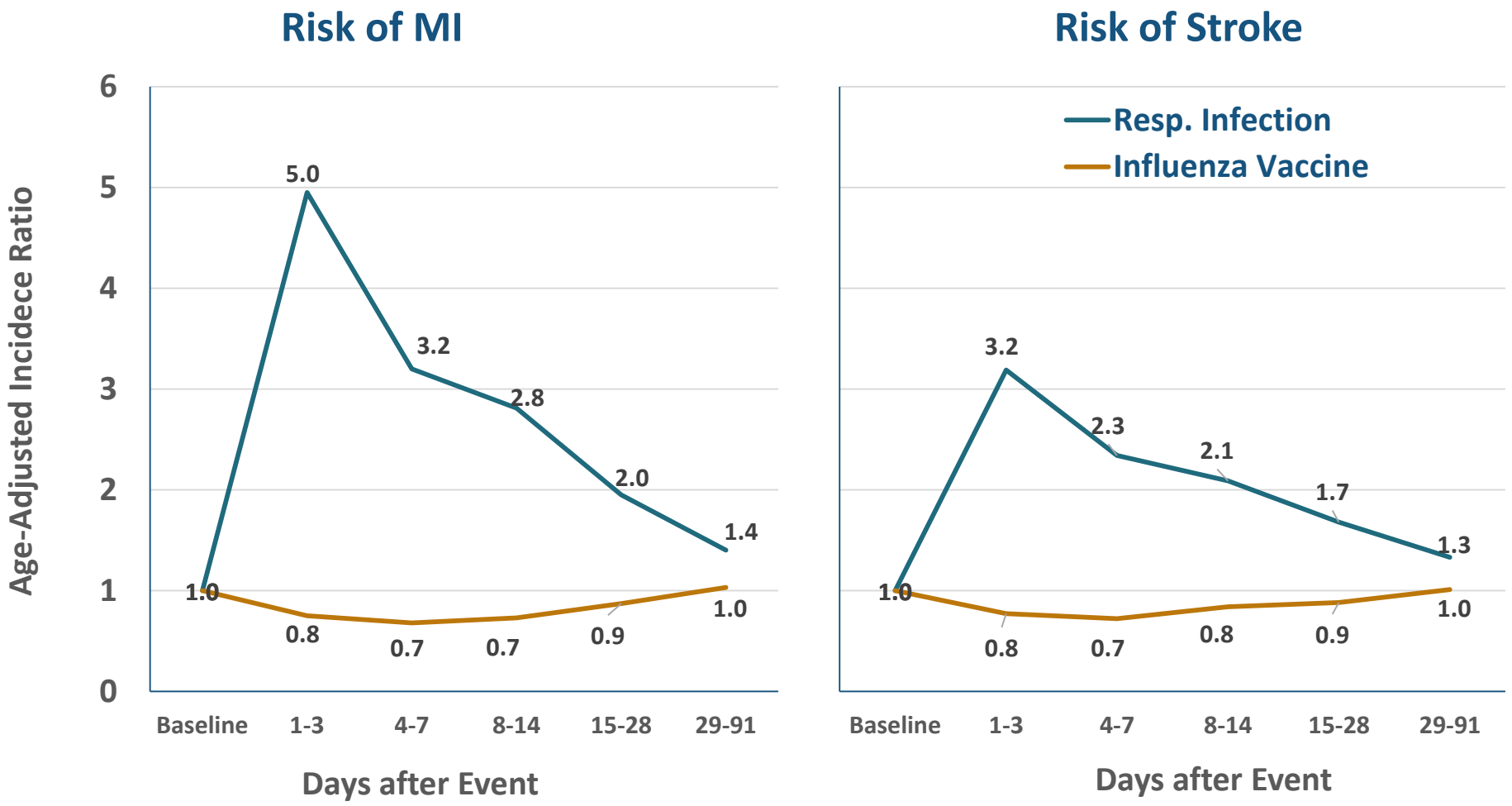
Impact of Influenza - United States

- Approximately 36,000 influenza-associated deaths during each influenza season
- Over 200,000 influenza-related excess hospitalizations
- Several analyses have documented an association between acute respiratory infections and cardiovascular events

Thompson et al JAMA. 2003;289:179-186
Thompson et al JAMA. 2004;292:1333-1340
Madjid et al. EHJ 2007(28):1205-1210

Influenza Infections Trigger Cardiovascular Events



- Self-controlled case series study design – patients acted as their own control in periods when they were not exposed to when they are exposed to an influenza-like illness event
- UK General Practice Research Database: N = 20,486 first MI; N = 19,063 first stroke

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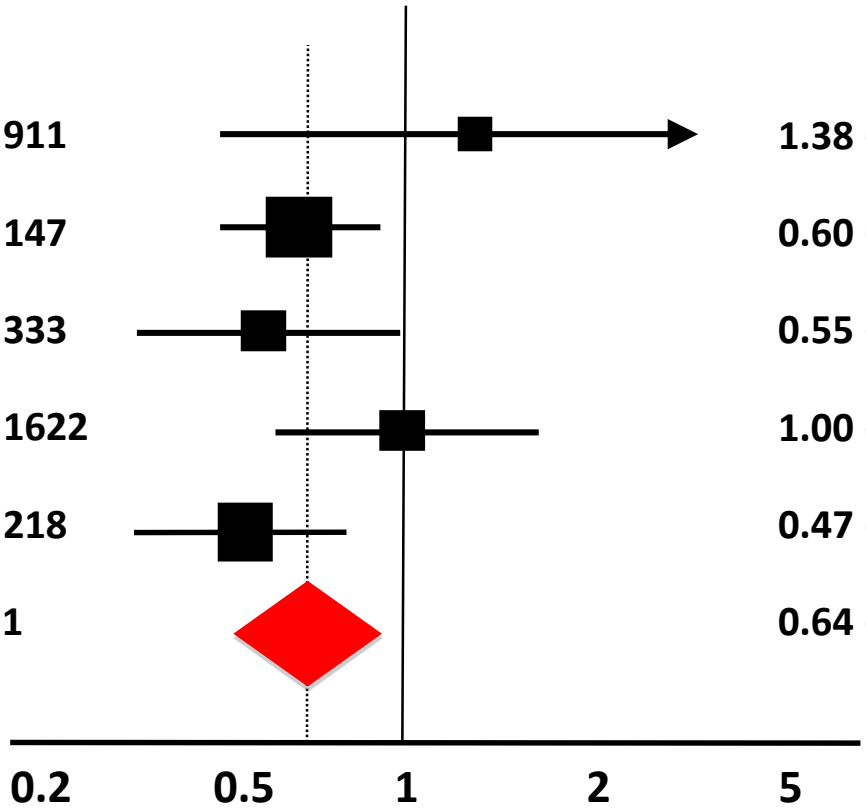
Smeeth L, et al. NEJM 2004;351(25):2611-8.

Influenza Vaccination Reduces CV Risk: A Meta-Analysis

Study	Influenza Vaccine Events	Influenza Vaccine Total	Placebo/ Control Events	Placebo/ Control Total	Risk Ratio (95% CI)
Govaert	7	927	5	911	1.38 (0.44 – 4.32)
FLUVACS	32	145	54	147	0.60 (0.41 – 0.87)
FLUCAD	16	325	30	333	0.55 (0.30 – 0.98)
DeVilliers	20	1620	20	1622	1.00 (0.54 – 1.85)
Phrommintikul	20	221	42	218	0.47 (0.29 – 0.77)
Total	95	3238	151	3231	0.64 (0.48 – 0.86)
	2.93%		4.67%		



Absolute Risk Difference: 1.74%
Number Needed to Treat: 58

Test for Heterogeneity I^2=28%
Overall P-Value = 0.003

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Udell JA, Zawi R, Bhatt DL et al… Farkouh ME, Cannon CP. JAMA 2013:310; 1711-1720.

Influenza Vaccine Preparations

- Influenza vaccine is an inactivated preparation
- Vaccine viral strains can change annually to reflect most commonly circulating strains in a given year (A/H1N1, A/H3N2, and B-type)
- Currently, there are trivalent and quadrivalent versions of the STANDARD dose (15 µg/strain) vaccine, and a trivalent version of a HIGH dose (60 µg/strain) vaccine

	Standard Dose	High Dose
Trivalent (2 A strains + 1 B strain)	✓ 15µg	✓ 60µg Approved for Medically Stable Individuals ≥ 65
Quadrivalent (2 A strains+ 2 B strains)	✓ 15µg	NO FORMULATION EXISTS

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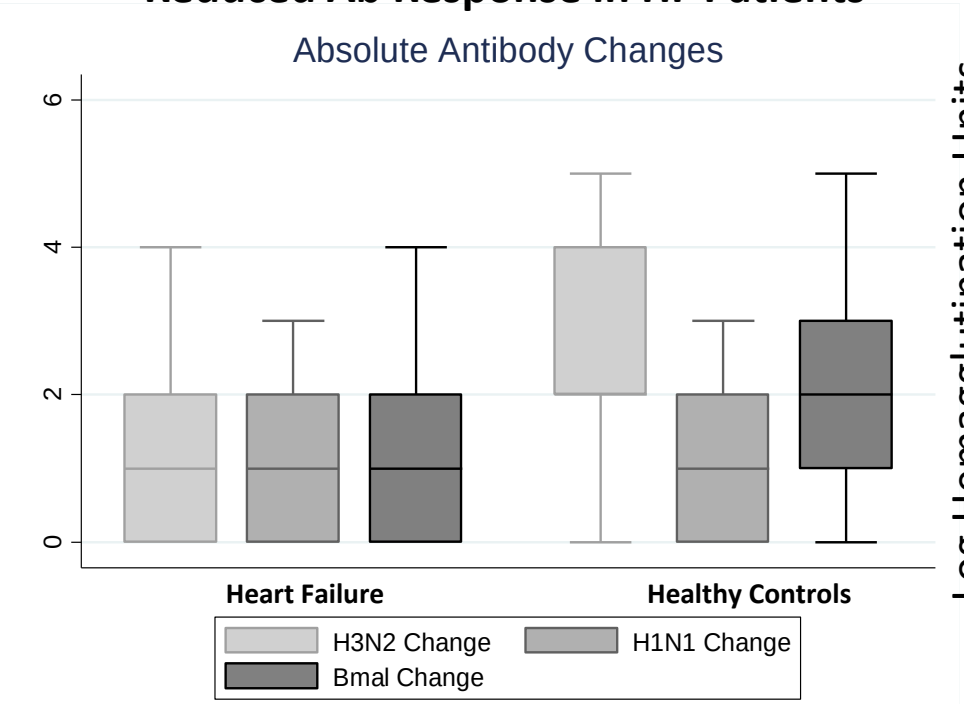
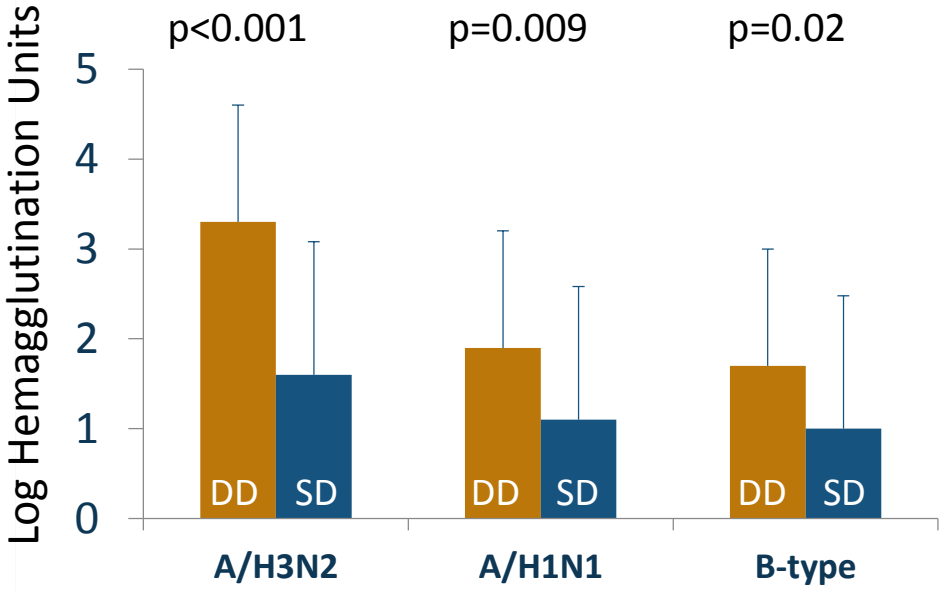
Patients with Heart Failure Exhibit *Reduced Immune Response* to Vaccine that can be *Overcome with a Higher Dose* of Vaccine

Reduced Ab Response in HF Patients



Vardeny et al. J Card Fail 2009;15:368-373

Increased Ab Titers with High Dose Vaccine



Pilot double-blind RCT of double dose (DD) vs. standard dose (SD) influenza vaccine

* Adjusted for baseline antibody titers

Vardeny et al. Eur J HF 2013;15(5):560-4

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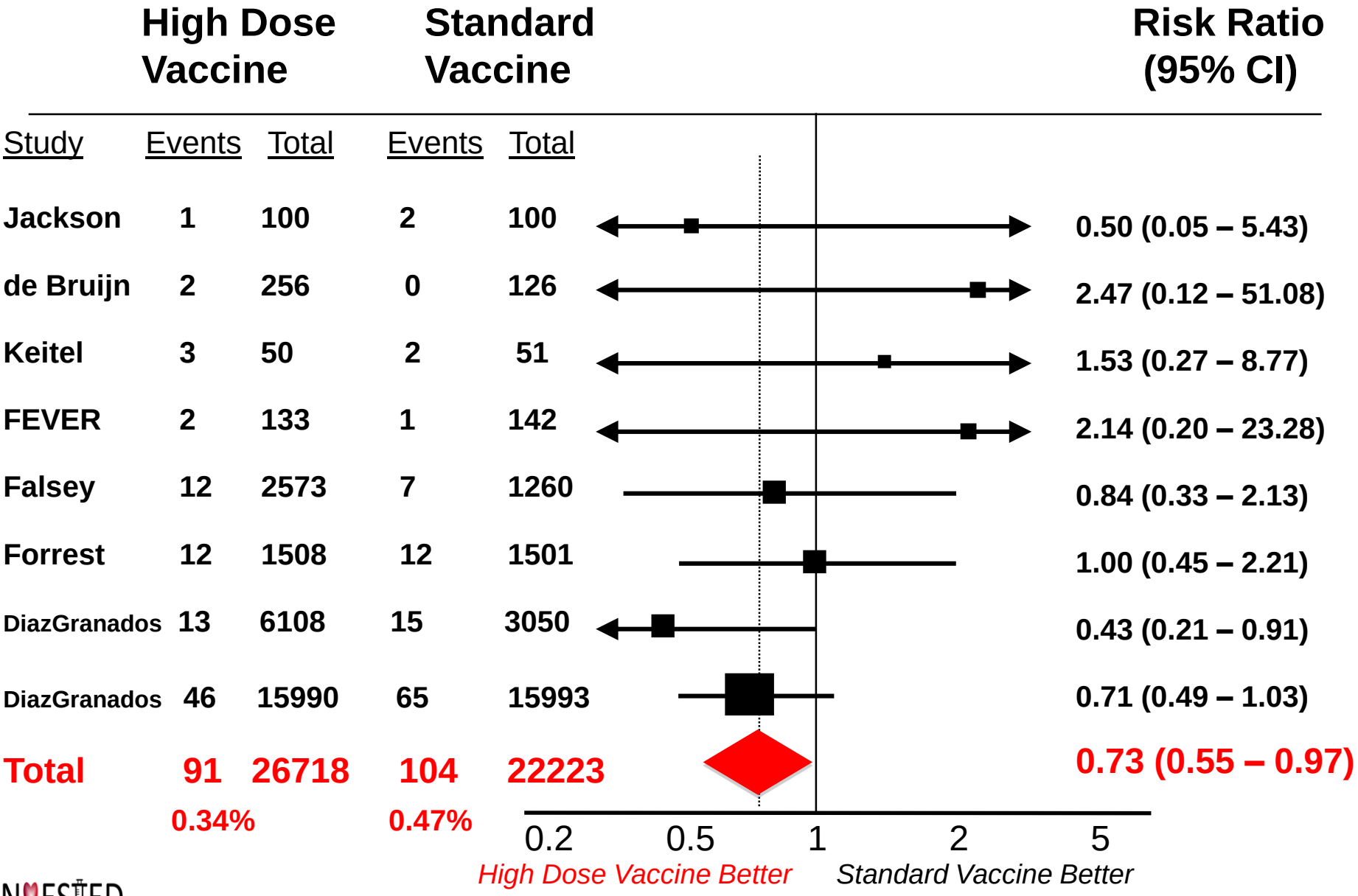
More Intensive Influenza Vaccine May Reduce CV Events



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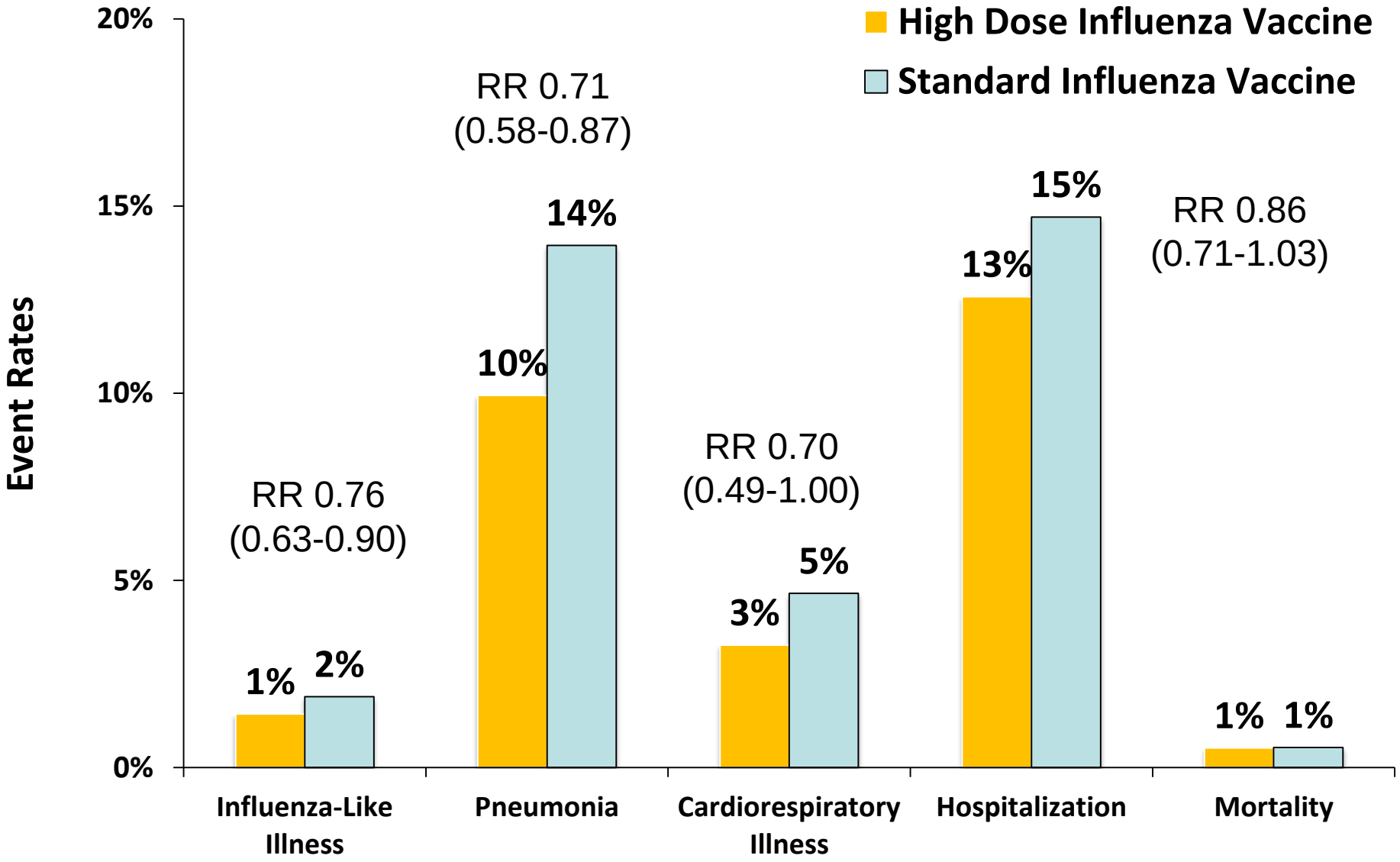
Test for Heterogeneity I^2=0%
Overall P-Value = 0.03

HD Vaccine Reduces Influenza and Cardiopulmonary Events



DiazGranados CA, et al. and Talbot HK NEJM 2014;371:635-45.

Safety Profile of Influenza Vaccine Very Good

Adverse Effect	High Dose (n=15,990)	Standard Dose (n=15,993)
Injection site pain	35.6%	24.3%
Injection site erythema	14.9%	10.8%
Myalgia	21.4%	18.3%
Malaise	18.0%	14.0%
Headache	16.8%	14.4%
Fever	3.6%	2.3%

SAE of special interest (<0.05%):

- **Bells palsy**
- **Acute disseminated encephalomyelitis**
- **Guillain-Barré Syndrome**
- **Stevens Johnson Syndrome**

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DiazGranados CA, et al. and Talbot HK NEJM 2014;371:635-45.

Summary of Rationale

- Influenza is a known trigger for cardiovascular events
- Patient with heart failure exhibit reduced immune responses to influenza vaccination which can be overcome with a higher dose of influenza vaccine
- In several analyses, high dose vaccine was associated with reduction in CV events
- High dose vaccine is currently approved for healthy older adults only; ACIP does not preferentially recommend one vaccine formulation over another
- The results of INVESTED have the potential to inform health care policy regarding optimal influenza vaccination for individuals with high risk cardiovascular disease

A Pragmatic Trial

- Large, “simple”, adequately powered, double-blind comparative effectiveness multicenter trial of vaccine strategy

Features

- Easy, annual administration: *“one shot deal”*
- 100% adherence
- Intervention well established / low risk
- Low cost intervention
- Pragmatic non-intrusive follow-up plan
- Three year strategy to allow realistic seasonal variation in influenza virulence and protection

Potential Benefits

- To impact a major population attributable CV risk
- Inform health policy regarding influenza vaccine strategy in high risk individuals
- Demonstrate link between flu vaccine response and major cardiopulmonary outcomes in high-risk CV patients

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Specific Aims

1. To test the hypothesis that high dose (4x) trivalent influenza vaccine will reduce the composite of death or cardiopulmonary hospitalizations compared with standard dose quadrivalent influenza vaccine in high-risk cardiovascular patients

2. To test the hypothesis that antibody titers to influenza vaccine antigens are associated with death or cardiopulmonary events

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INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated Heart Failure in Patients with CVD (INVESTED)

Post-MI or HF Hospitalization

N = 9300

RANDOMIZED 1:1 DOUBLE BLIND ANNUAL VACCINE STRATEGY

All other CV Rx per treating MD

High Dose Trivalent Influenza Vaccine

Standard Dose Quadrivalent Influenza Vaccine

Duration
3 Influenza Seasons + Vanguard Season

Followed up to 4 times a year with annual re-vaccination to assigned strategy

Primary EP
Death or Cardiopulmonary Hospitalization

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Primary Outcome

- Time to first occurrence of all-cause death or cardiopulmonary hospitalization within each influenza season

Examples (non-exclusive):

- non-fatal myocardial infarction	- arrhythmia
- non-fatal stroke	- unplanned revascularizations
- non-fatal cardiac arrest	- pulmonary embolism
- unstable angina	- respiratory tract infections
- incident or acute heart failure	- pulmonary disease exacerbations

Analysis of Efficacy Endpoints

- Analysis population: modified ITT
  - Subject's clock for each influenza season reset 2 weeks after influenza vaccination
  - Primary endpoint counted until July 31 of each season
  - Each subject can contribute primary endpoint events in more than one influenza season (considered independent)

Choice of Primary Outcome

- While the primary hypothesis was cardiovascular, we included endpoints that were likely to be modified by the experimental therapy
- Pulmonary endpoints can be difficult to distinguish from cardiovascular (HF) endpoints
- Combining the two makes adjudication simpler

Why not re-randomize?

- Considered randomizing each season vs. randomizing to strategy
- Randomization to strategy raises concern about differential drop-out
- Randomization each season would miss potential ”carry-over” effects

Secondary Outcomes/Analyses

- Primary endpoint over entire study (ITT)
  - While the primary endpoint is “per year” we are also interested in testing this “strategy” over multiple years
- Recurrent primary endpoint events
  - Consider effect of vaccine on first and recurrent cardiopulmonary hospitalizations
- Primary endpoints only in season
  - To assess the effect during influenza season
- Individual components of the primary endpoint
- Other secondary endpoints representing composites of key CV and respiratory events

Eligibility Criteria

INCLUSION

- Age 18 years or older
- Hospitalization for a myocardial infarction within the past 1 year

  OR

  Hospitalization for heart failure with past 2 years

  AND

- At least ONE additional risk factor:
  - age ≥ 65
  - LVEF < 40%
  - diabetes mellitus
  - obesity (BMI>30)
  - renal impairment (eGFR < 60)
  - history of ischemic stroke
  - history of peripheral artery disease
  - Current smoking

EXCLUSION

- Adverse reaction, intolerance, or allergy to influenza vaccination, or severe allergy to egg protein
- Influenza vaccination during enrolling season
- Any infection requiring antibiotics within 14 days of influenza vaccination
- Known fever over 100 degrees Fahrenheit or 38 degrees Celsius within 7 days of influenza vaccination
- Currently pregnant or breastfeeding
- Use of any investigational drugs, biologics, or devices within 30 days prior to randomization
- Non-cardiac conditions that confer a life expectancy < 9 mo

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Why these inclusion criteria?

- History of MI in 1 year or HF Hospitalization within 2 years to ensure a high risk population
- One additional risk factor to further increase event rate
- A lower risk/broader population would have required a much larger sample size

Sample Size/Power Analysis

- Target effect size: 18% reduction or hazard ratio (HR) 0.82
- Event rates: 9% in 1st season; 8% in 2nd; 7% in 3rd
- 30% : 70%=death : CP hospitalization
- 30% not being vaccinated in a subsequent season
- Primary endpoint events: 279, 448 and 549 in 1st, 2nd, 3rd
- A total of 1,276 events over three seasons
- Power=0.94 to detect HR=0.82 at a two-sided α=0.05
- Two interim analysis using O'Brien-Fleming

Event Ascertainment and Assessment

- Combination of traditional and more “modern” methods:

- Local study coordinators will perform assessment of hospitalizations by phone at the end of influenza season and mid-summer, and in person at subsequent year baseline visit
  - Discharge summaries for hospitalizations will be acquired for event categorization

- Sites with ability to utilize electronic resources will supplement other methods with EHR based ascertainment

- Central, blinded clinical events committee (Akshay Desai, MD, Chair) will ”adjudicate” based on CRFs, narratives and some source documentation

Why not EHR ascertainment only?

- Discussions with networks suggested that EHR approaches to event ascertainment would be incomplete and subject to substantial “leakage”

- Many sites currently don’t have the capability to perform EHR ascertainment

- Only the VA system had a comprehensive enough EHR to perform EHR-based ascertainment

Clinical Events Committee will Categorize Events

- Events will be centrally *categorized* as "cardiopulmonary" or not by an independent/blinded review committee based on hospital discharge summaries

- Categorization will be based on best available evidence rather than strict "adjudication" criteria
  - For example, a discharge summary with adequate documentation of myocardial infarction will not require cardiac marker data, and a heart failure hospitalization won't require evidence of "diuretic therapy"

- This approach will be less specific but more sensitive and will be far less costly and resource intensive than standard adjudication

- Events will be further categorized (into specific cardio-pulmonary events) based on available evidence

Recruitment Strategies

Early recruitment beginning several months prior to flu season (Recruitment timeline ~ 6 months)

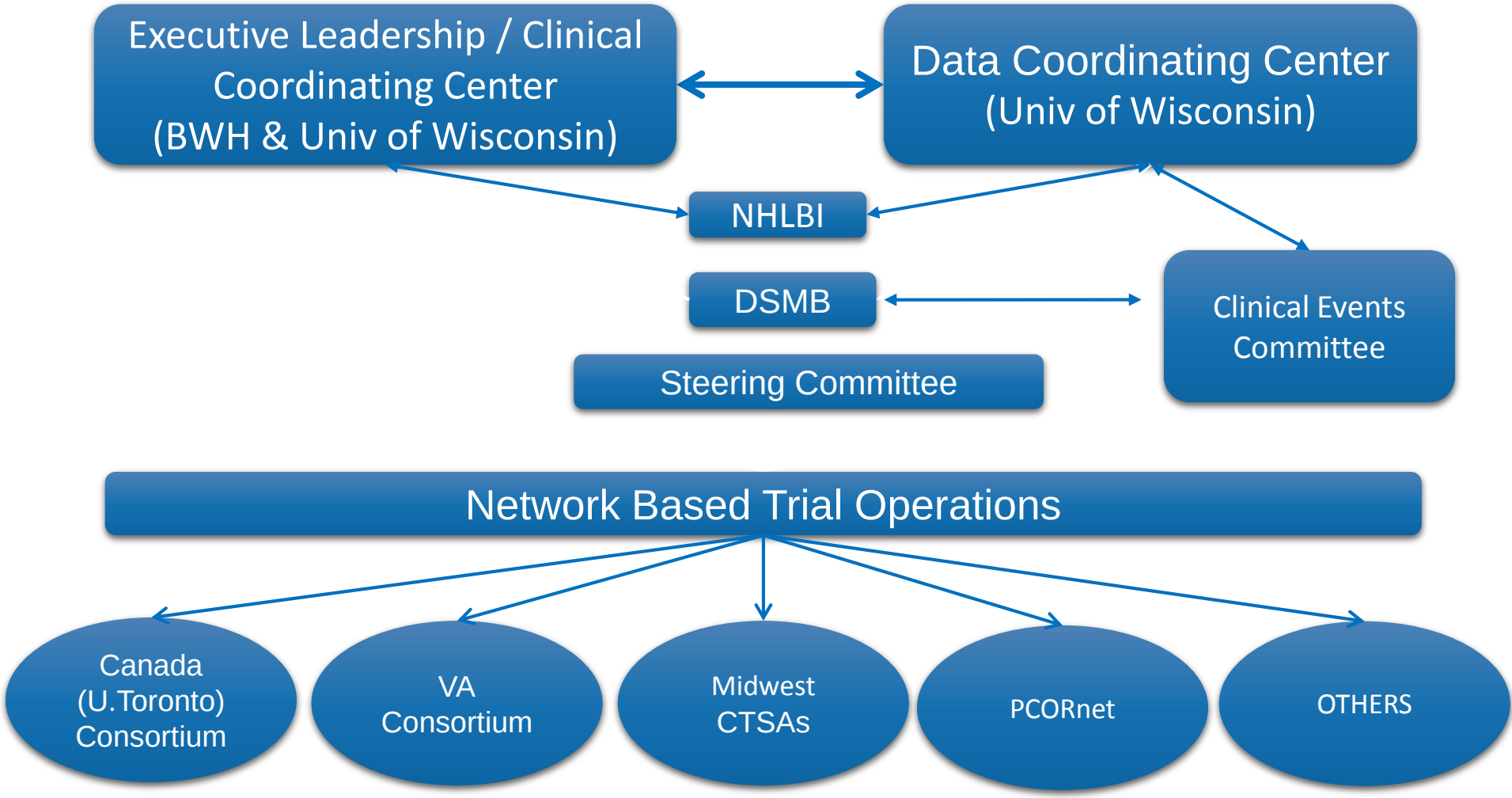
Recruitment materials: flyers, brochures, invitation letters (templates can be provided), email blasts
EHR queries using ICD-9/ICD-10 codes, to assess feasibility and create screening lists for pre-identifying subjects
Outpatient primary care or cardiology clinics (can also send invitation letter by individual providers)
Inpatient hospitalization for acute heart failure or AMI
Rehab facilities
Vaccination clinics

Data Capture

- Electronic data capture (Openclinica™) for all demographic data, adverse events, and suspected endpoints

- Endpoints committee will interface with DCC through data capture system

Overall INVESTED Trial Organization and Networks



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SMART IRB

- NIH policy: sites participating in multi-center NIH-funded studies involving human subjects research will use a single Institutional Review Board (sIRB)
  - In effect for grants received on or after May 25, 2017
- SMART IRB (formerly IRBrely) developed from a CTSA IRB reliance project funded by NCATS
- IRB Master Reliance agreement developed for INVESTED, with UW-Madison serving as the IRB of record
- Out of 17 sites (from Midwest consortium of CTSAs and PCORnet) initially approached, 16 agreed to cede review
- Currently 3 sites approved, 2 were added this week, 2 being submitted next week

What is “Pragmatic” about this trial?

- Testing a strategy of high-dose vs. low-dose influenza vaccine - formulations might change
- Inclusion criteria are straightforward and include a large number of potential subjects
- There are several viable recruitment strategies – in hospital, in clinic, EHR identification of appropriate subjects
- The intervention is “a one-shot deal” – no concern about “adherence”
- The endpoint is “relatively” simple and can be ascertained in multiple ways, including EHR-based approaches, and will require “minimal” adjudication

Why active comparator not placebo?

- While observational and randomized data suggest that influenza vaccine would reduce CV events, flu vaccination is recommended for these high risk patients despite the fact that many don't get it

Why Blinded and not Open-Label?

- Perception about what therapy might be "better" could bias participants resulting in differential dropout

Why compare High-Dose Trivalent Vaccine to Standard-Dose Quadrivalent Vaccine?

- Comparing high-dose trivalent to standard dose trivalent vaccine is scientifically the “purest” approach
- We opted to compare experimental therapy with currently best “standard of care” therapy
- Quadrivalent vaccine is rapidly becoming “standard of care”
- Best approach to maintain adequate “equipoise”

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INVESTED Trial Leadership

Scott D. Solomon, MD Professor of Medicine Harvard Medical School (CCC Co-PI)	Orly Vardeny, PharmD, MS Assoc Prof of Pharmacy and Medicine University of Wisconsin (CCC Co-PI)	KyungMann Kim, PhD Professor of Biostatistics and Medical Informatics University of Wisconsin (DCC-PI)
Jacob A. Udell, MD, MPH Assistant Professor of Medicine University of Toronto Canadian Co-PI	Michael Farkouh, MD, MSc Professor of Medicine University of Toronto Canadian Co-PI	J. Michael Gaziano, MD, MPH Professor of Medicine Harvard Medical School VA network co-PI
Keipp Talbot, MD, MPH Assistant Professor of Medicine Vanderbilt University	Allison McGeer, MD, MSc Professor of Laboratory Medicine, Pathobiology, and Public Health Sciences University of Toronto	Adrian Hernandez, MD, MHS Professor of Medicine Duke University PCORnet network lead
Jacob Joseph, MD Associate Professor of Medicine Harvard Medical School VA network co-PI	NIH Project Team: Lawton Cooper, MD, MPH Peter Kaufmann, PhD Yang Song, PhD	Protocol Review Committee Ileana Piña (Chair) Robert Atmar Ying Chen Nicole Deming Barry Make

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