BWH BRIGHAM AND WOMEN'S HOSPITAL

HARVARD MEDICAL SCHOOL

THE UNIVERSITY of WISCONSIN MADISON

UNIVERSITY OF TORONTO

INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated heart failure

NIH National Heart, Lung, and Blood Institute

VA U.S. Department of Veterans Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA

NIH National Heart, Lung, and Blood Institute

pcornet The National Patient-Centered Clinical Research Network

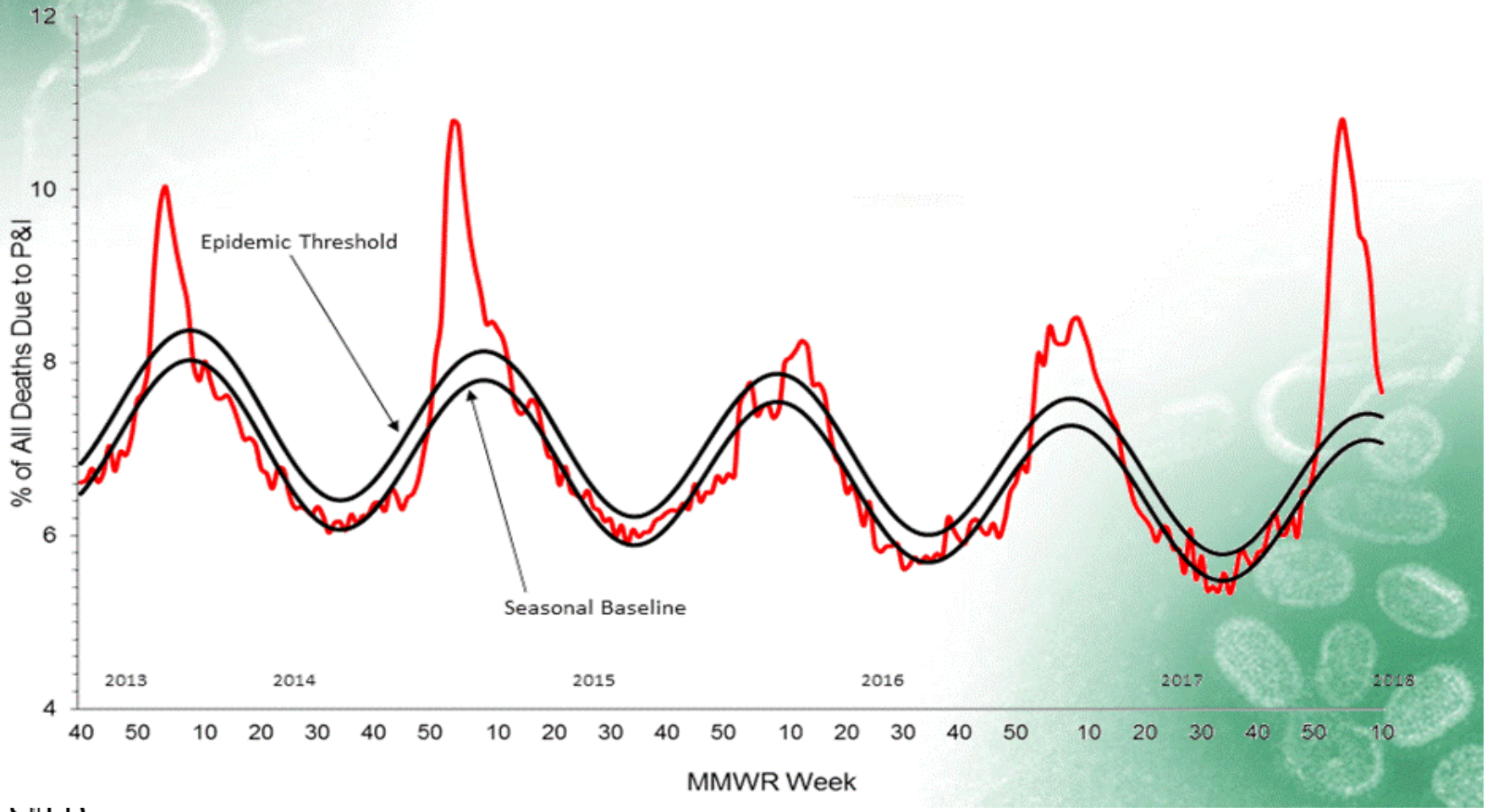
FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division

CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

Pneumonia and Influenza Mortality from the National Center for Health Statistics Mortality Surveillance System

Data through the week ending March 10, 2018, as of March 29, 2018



INVESTED

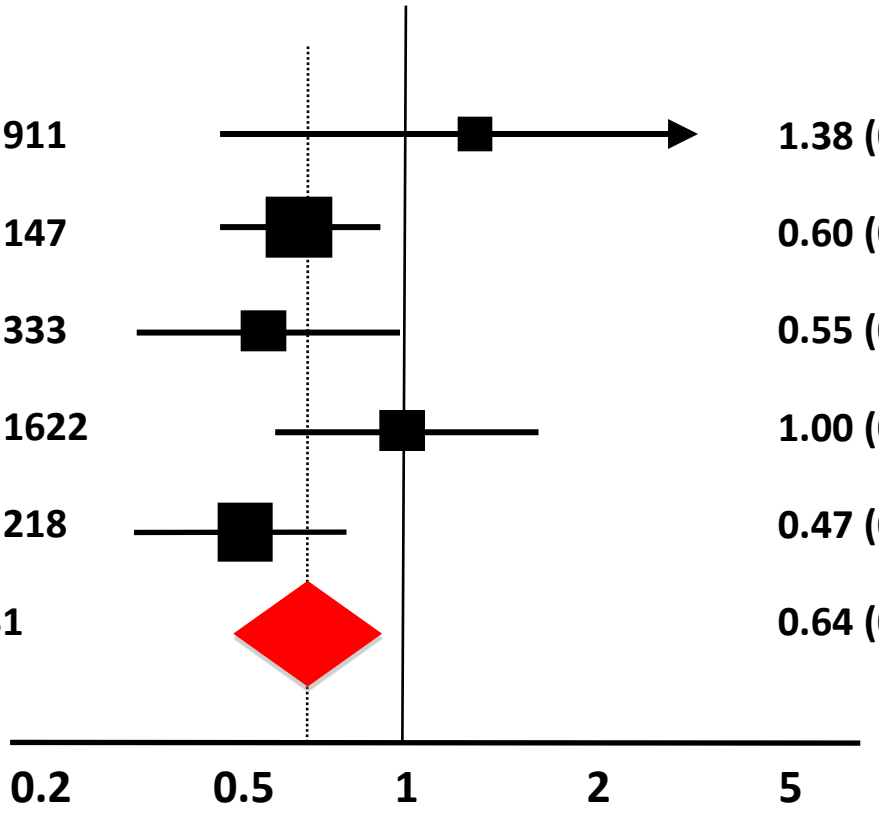
Impact of Influenza

- Approximately 36,000 influenza-associated deaths during each influenza season in the United States
- 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 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

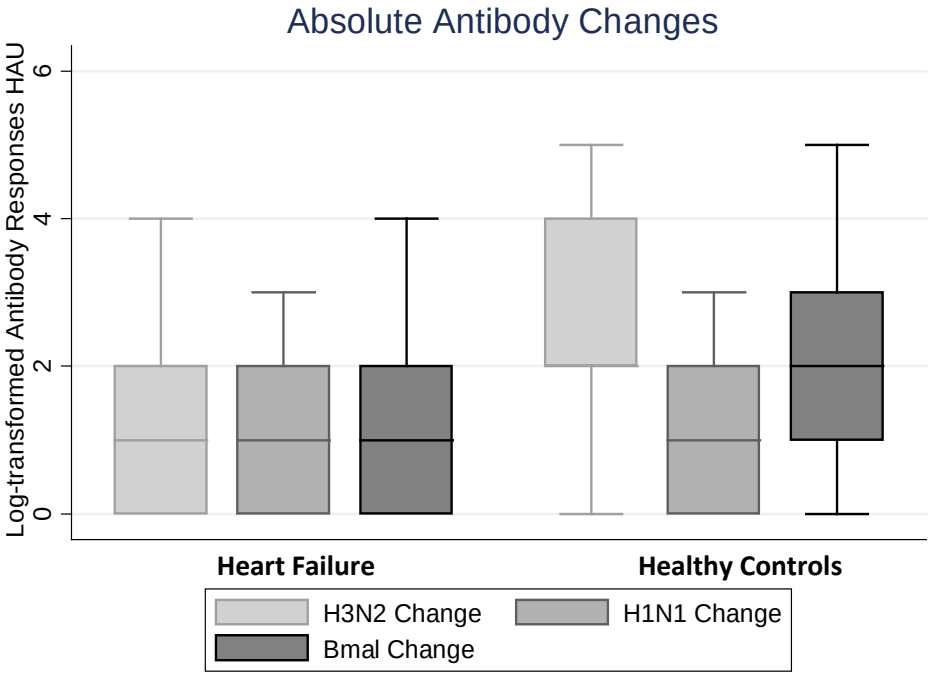
Test for Heterogeneity I^2=28%
Overall P-Value = 0.003

INVESTED

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

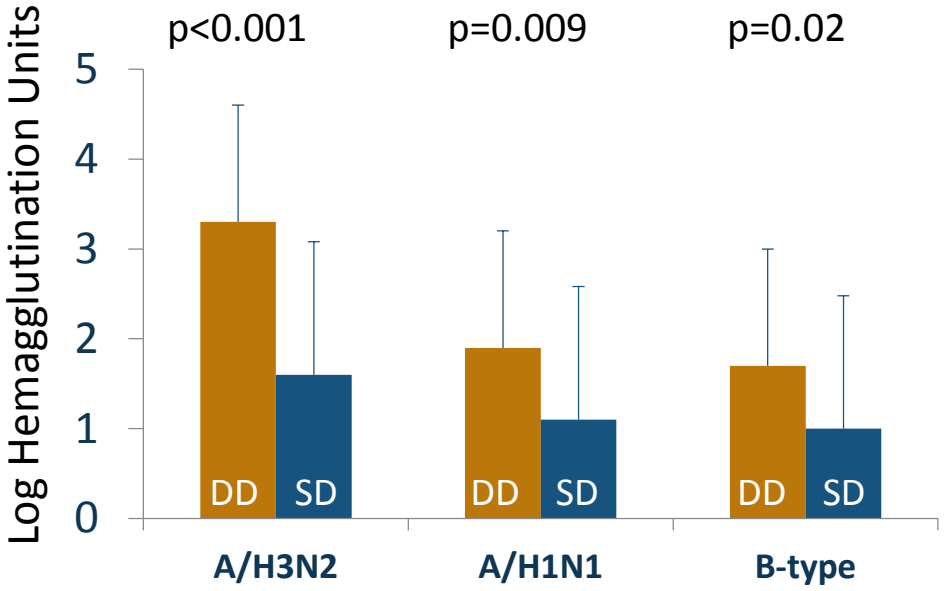
Patients with Heart Failure Exhibit *Reduced Immune Response* to Vaccine that can be *Overcome with a Higher Dose* of Vaccine

Reduced Ab Response in HF Patients



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

Increased Ab Titers with High Dose Vaccine



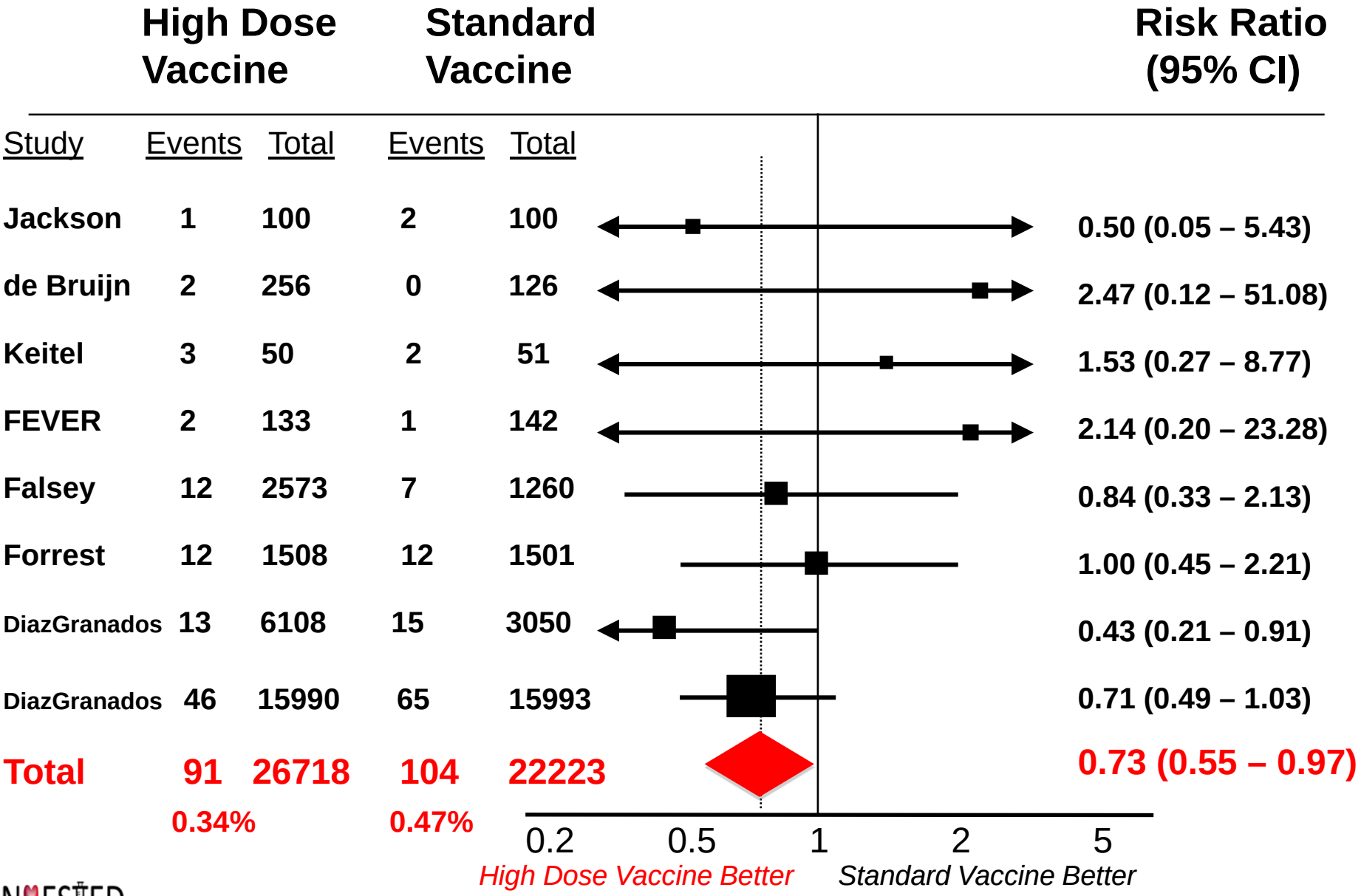
Pilot double-blind RCT of double dose (DD) vs. standard dose (SD) influenza vaccine

* Adjusted for baseline antibody titers

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

INVESTED

More Intensive Influenza Vaccine May Reduce CV Events



INVESTED

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

INfluenza Vaccine to Effectively Stop CardioThoracic Events and Decompensated heart failure (INVESTED)

INVESTED Study Design

NIH National Heart, Lung, and Blood Institute

Post-MI or HF Hospitalization

*with 1 additional CV risk factor
- Age ≥ 65
- LVEF <40%
- DM
- BMI>30
- eGFR<60
- Hx ischemic stroke
- Hx PAD
- Current smoking

N = 9300

RANDOMIZED 1:1 DOUBLE BLIND ANNUAL VACCINE STRATEGY

High Dose Trivalent Influenza Vaccine

Standard Dose Quadrivalent Influenza Vaccine

All other CV Rx per treating MD

Followed up to 4 times a year
Annual Vaccination
to assigned strategy

Duration
3 Influenza Seasons
+ Vanguard Season

Primary EP
Death or Cardiopulmonary Hospitalization

Visit and Ascertainment Schedule

Measurement	Screening[a]	Baseline	1 week call	2-4 week visit[c]	Spring	Summer call	Repeat for years 2 & 3
	Can be combined						
Informed Consent	X						
Randomization		X					
History[b]		X					
Current Meds		X					X
Blood Draws[c]		X		X			
Vaccine Administration		X				X	X
Tolerability Assessment			X	X			
Endpoint Assessment[d]			X	X	X	X	X
SAE reporting			X	X	X		X
Scheduling Yr 2&3					X		

a. Screening and Baseline may be completed at one visit
b. History includes previous vaccinations, study inclusion/exclusion criteria
c. In a subset of participating in the immune/biomarker substudy
d. Event assessments performed by study personnel at local sites

INVESTED

Blinding

- Double-blinded
- Blinding accomplished through over-labelling of study syringes
- To the extent possible, the study team member delivering vaccine should be different than the person who performs event ascertainment phone calls

Considerations for Blinding

- Differences in tolerability between vaccine formulations

- Perceived differences in efficacy between vaccines
  - Participant
  - Investigator/study team
  - Might bias affect hospitalization component of primary outcome?