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A Randomized Controlled Trial of Influenza Vaccine to Prevent Adverse Vascular Events (IVVE)

Mark Loeb MD

Professor, McMaster University

@MLRGreseach

McMaster University

Population Health Research Institute

HEALTH THROUGH KNOWLEDGE

Background

- Influenza increases the risk of CV events and deaths
- A lower rate of CV events related to ischemia and death has been reported with influenza vaccination
- 80% of CV disease burden occurs in LMICs where use of influenza vaccine is extremely low

Trial Design

- A pragmatic, double-blind, randomized trial comparing inactivated influenza vaccine to placebo, to prevent CV outcomes in ten countries in Asia, the Middle East, and Africa over three influenza seasons
- Use of a placebo was in keeping with WHO criteria for vaccine trials in LMICs, participants allowed to use influenza vaccine outside of the trial

Eligibility

- Patients aged ≥ 18 years with a clinical diagnosis of heart failure and NYHA functional class II, III and IV

- Excluded:
- - Anaphylactic reaction to a previous dose of TIV
- - Known IgE-mediated hypersensitivity to eggs
- - GBS within 8 wks of previous influenza vaccine
- - Anaphylactic reaction to neomycin
- -Influenza vaccine in 2 of 3 previous years
- - Severe valvular disease where repair or replacement considered

Study Vaccines

- 0.5 ml IM dose of inactivated influenza vaccine (VAXIGRIP vaccine, TIV or QIV if available)
- Placebo (0.5 ml saline)

- Administered annually for 3 influenza seasons

Co-Primary Outcomes

- First Primary Outcome: composite of CV death, non-fatal MI, and non-fatal stroke

- Second Primary: First Co-Primary and heart failure hospitalizations

Secondary Outcomes

- Components of Primary
  - Non-fatal MI
  - Non-fatal Stroke
  - CV deaths
- All hospitalizations
- Pneumonia
- All deaths

Sample size

- 5,000 participants, 80% power to detect reduction in primary composite from 17% in the control group to 14% in the vaccine group

Primary Analysis

- Events (irrespective of influenza circulation) were analysed by ITT for the first and second primary composite outcomes
- Step-down fall-back approach, first primary composite (time to first event) at two-sided alpha 0.04, if not significant, second primary (recurrent events) tested at 0.01

Secondary Analysis

- Time to event for secondary outcomes
- Recurrent hospitalizations for heart failure and recurrent all-cause hospitalizations
- Analysis of events that occurred during peak influenza circulation and outside of them

Baseline Characteristics

	Influenza vaccine (n=2560)	Placebo (n=2569)
Age (yrs)	57.4±15.1	57.0±15.6
Heart rate	80.3±15.1	80.3±14.9
Systolic BP	125.8±23.3	125.6±24.1
Female	1333 (52.1)	1305 (50.8)
Region		
China	348 (13.6)	346 (13.5)
India	583 (22.8)	588 (22.9)
Africa	1023 (39.9)	1028 (40.0)
Philippines	359 (14.0)	359 (14.0)
Middle East	247(9.6)	248 (9.7)

Heart Failure

	Influenza vaccine (n=2560)	Placebo (n=2569)
NYHA Class		
II	1773 (69.3)	1790 (69.7)
III	683 (26.7)	657 (25.6)
IV	104 (4.1)	122 (4.7)
LV Function		
Preserved (>50%)	560 (21.9)	597 (23.2)
Mild (LVEF 40-49%)	441 (17.2)	422 (16.4)
Mod (LVEF 31-39%)	621 (24.3)	629 (24.5)
Severe (LVEF ≤30%)	821 (32.1)	800 (31.1)

Co-Morbidity

	Influenza vaccine (n=2560)	Placebo (n=2569)
Prior stroke	202 (7.9)	207 (8.1)
Prior MI	546 (21.3)	514 (20.0)
COPD	136 (5.3)	121 (4.7)
Hypertension	1661 (64.9)	1668 (64.9)
CKD	176 (6.9)	167 (6.5)
Diabetes	570 (22.3)	590 (23.0)
Hyperlipidemia	419 (16.4)	427 (16.6)
Atrial fibrillation	248 (9.4)	282 (10.4)

Medications

	Influenza vaccine (n=2560)	Placebo (n=2569)
Beta blocker	1545 (60.4)	1550 (60.3)
ACE inhibitor or ARB	1853 (72.3)	1835 (71.4)
Aldosterone inhibitor	1232 (48.1)	1207 (47.0)
Other Diuretics	1702 (66.5)	1681 (65.4)
Long-acting nitrate	370 (14.5)	388 (15.1)
Digoxin	597 (23.3)	588 (22.9)
Aspirin or thienopyridines	1543 (60.2)	1534 (59.7)
Vitamin K antagonists	263 (10.3)	242 (9.4)
Direct oral anticoagulants	35 (1.4)	38 (1.5)

First Events by Study Group

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95% CI)	P value
First primary	380 (14.8)	410 (16.0)	0.93 (0.81-1.07)	0.30
Second primary	520 (20.3)	568 (22.1)	0.91 (0.81-1.03)	0.13
All deaths	427 (16.7)	473 (18.4)	0.90 (0.79-1.03)	0.13
CV death	334 (13.0)	374 (14.6)	0.89 (0.77-1.04)	0.13
Non-CV death	93 (3.6)	99 (3.9)	0.94 (0.71-1.25)	0.68
Non-fatal MI	21 (0.8)	23 (0.9)	0.91 (0.50-1.65)	0.76
Non-fatal Stroke	47 (1.8)	43 (1.7)	1.10 (0.73-1.66)	0.66

First Events by Study Group

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95% CI)	P value
All Hosp	388 (15.2)	455 (17.1)	0.84 (0.74-0.97)	0.01
HF Hosp	245 (9.6)	277 (10.8)	0.88 (0.74-1.05)	0.15
Pneumonia	61 (2.4)	104 (4.0)	0.58 (0.42-0.80)	0.0006

Recurrent Events by Study Group

	Influenza vaccine (N=2560)	Placebo (N=2569)	Influenza vaccine vs. Placebo	
	No. of events (%)	No. of events (%)	HR (95%CI)	P
Second primary	754 (29.4)	819 (31.9)	0.92 (0.83-1.02)	0.08
All Hosp	557 (21.8)	671(26.1)	0.83 (0.74-0.93)	0.001
HF Hosp	346 (13.5)	377 (14.7)	0.92 (0.79-1.06)	0.26

First Events during Peak Influenza Season and Non-Peak Period

	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	HR (95% CI)	Influenza vaccine	Placebo	HR (95% CI)
First Primary	193 (7.7)	227 (9.4)	0.82 (0.68-0.99)	187 (7.5)	173 (6.9)	1.08 (0.88-1.33)
Second Primary	270 (10.8)	307(12.2)	0.88 (0.74-1.03)	254 (10.3)	263 (10.6)	0.96 (0.81-1.14)

First Events during Peak Influenza Season and Non-Peak Period

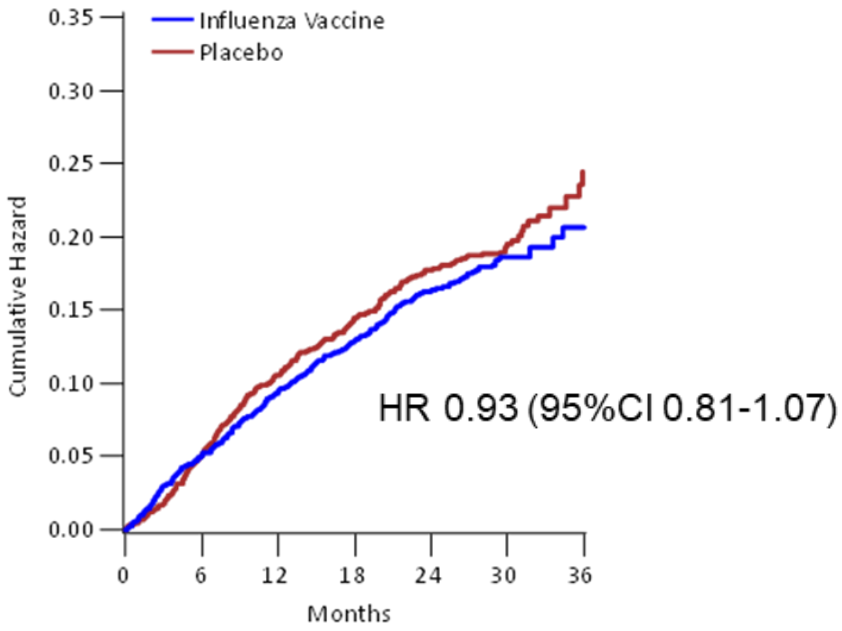
	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	HR (95% CI)	Influenza vaccine	Placebo	HR (95% CI)
All death	212 (8.4)	269 (10.6)	0.79 (0.66-0.95)	215 (8.6)	204 (8.1)	1.05 (0.87-1.28)
CV death	170 (6.7)	221 (8.7)	0.77 (0.63-0.94)	164 (6.6)	153 (6.1)	1.07 (0.86-1.34)
Non CV death	42 (1.7)	48 (1.9)	0.88 (0.58-1.34)	51 (2.0)	52 (2.0)	1.00 (0.68-1.48)
Non-fatal MI	9 (0.4)	13 (0.5)	0.69 (0.29-1.61)	12 (0.5)	10 (0.4)	1.20 (0.52-2.77)
Non-fatal stroke	23 (0.9)	24 (0.9)	0.98 (0.55-1.74)	24 (1.0)	19 (0.8)	1.26 (0.69-2.31)

First Events during Peak Influenza Season and Non-Peak Period

	Peak Influenza			Outside of Peak Season		
	Influenza vaccine	Placebo	HR (95% CI)	Influenza vaccine	Placebo	HR (95% CI)
All Hosp	195 (7.8)	230 (9.2)	0.84 (0.69-1.01)	193 (7.9)	225 (9.1)	0.84 (0.70-1.03)
HF Hosp	128 (5.1)	124 (4.9)	1.03 (0.80-1.31)	117 (4.7)	153 (6.1)	0.76 (0.60-0.97)
Pneumonia	28 (1.1)	54 (2.1)	0.51 (0.32-0.81)	33 (1.3)	50 (2.0)	0.65 (0.42-1.01)

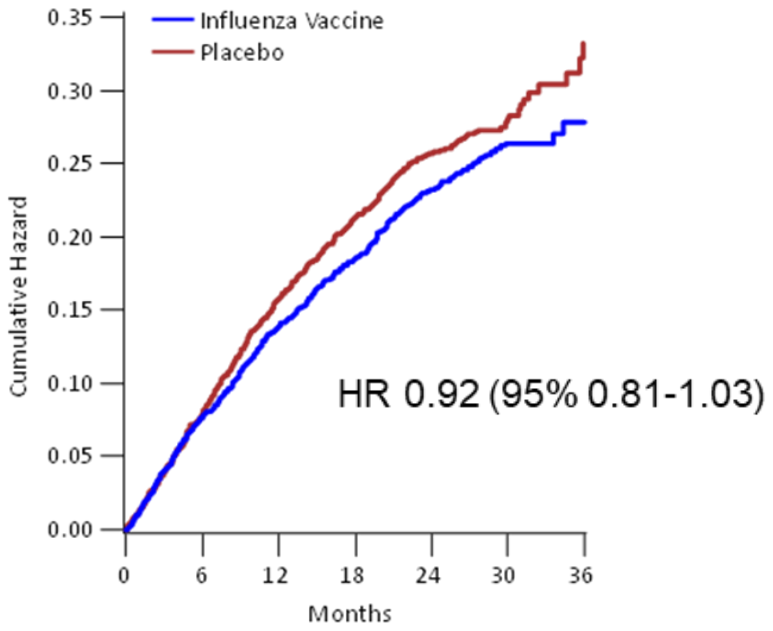
Kaplan Meier rates of the Primary Outcomes for First Events

A. *Primary Composite 1:* CV death, non-fatal myocardial infarction, or non-fatal stroke



No. at risk							
Infl. Vacc.	2560	2320	2112	1791	1551	490	98
Placebo	2569	2338	2099	1774	1547	489	115

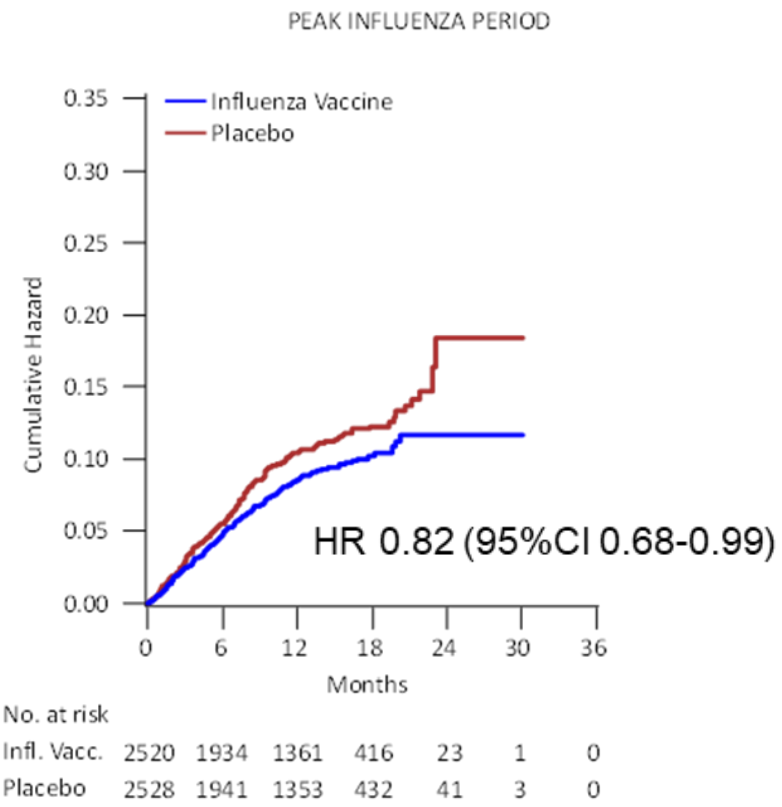
B. *Primary Composite 2*: CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure

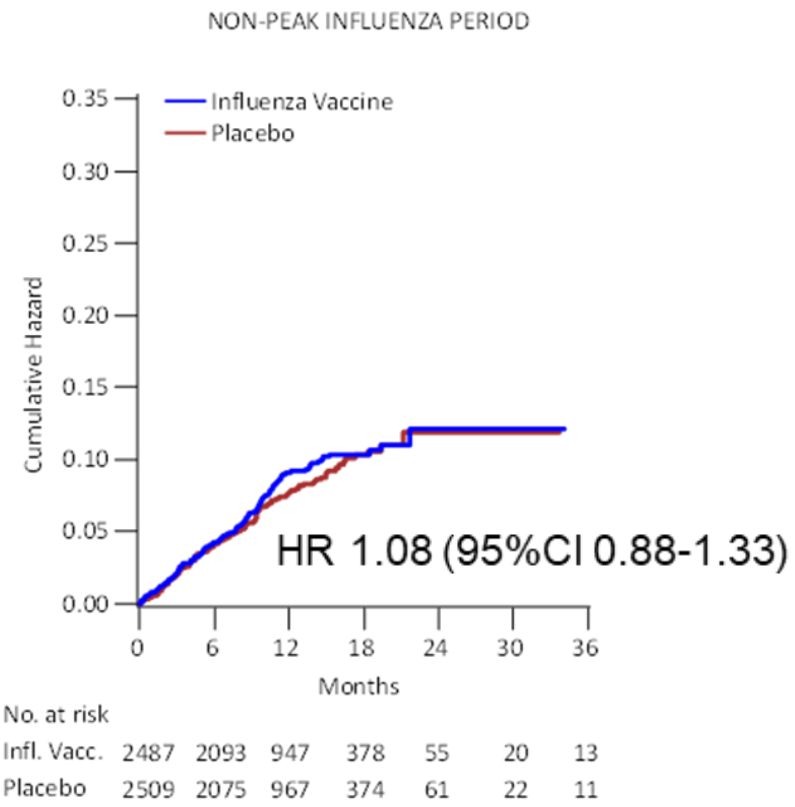


No. at risk							
Infl. Vacc.	2560	2252	2019	1697	1454	445	89
Placebo	2569	2274	1996	1660	1439	426	99

Kaplan Meier rates of the First Primary Outcome during Peak Influenza Period and Non-Peak Period

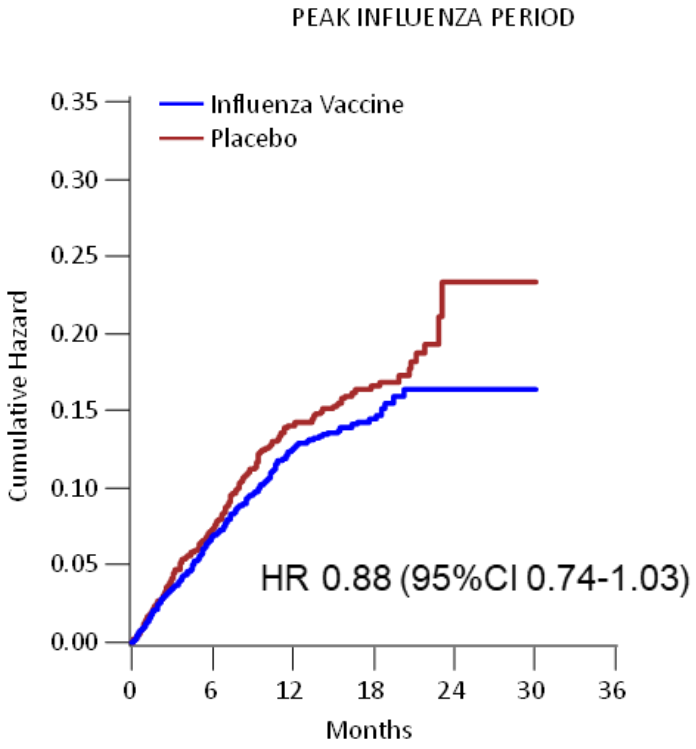
A. *Primary Composite 1:* CV death, non-fatal myocardial infarction, or non-fatal stroke

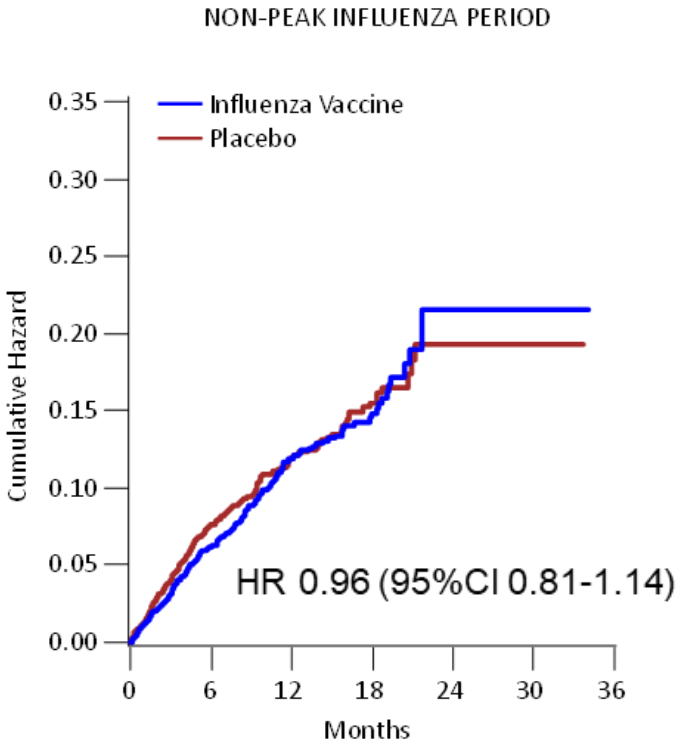




Kaplan Meier rates of the Second Primary Outcome during Peak Influenza Period and Non-Peak Period

B. *Primary Composite 2:* CV death, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for heart failure





Summary

- No significant difference in the primary outcomes between participants assigned to influenza vaccine versus placebo
- Secondary outcomes of pneumonia and hospitalization were reduced in the influenza vaccine group
- During periods of peak influenza circulation, there was a significant reduction in first primary outcome, deaths, and pneumonia in influenza vaccine group compared to placebo

Department for International Development
UKRI Medical Research Council
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SANOFI PASTEUR

IVVE Investigators

Mark Loeb MD, Ambuj Roy MD, Hisham Dokainish MD, Antonio Dans MD, Lia M Palileo- Villanueva MD, Kamilu Karaye MD, Jun Zhu MD, Yan Liang MD, Fastone Goma MD, Albertino Damasceno MD, Khalid F Alhabib MD, Gerald Yonga MD, Charles Mondo MD, Wael Almahameed MD, Arif Al Mulla MD, Vitheya Thanabalan, Purnima Rao-Melacini MSc, Alex Grinvalds, Tara McCready PhD, Olga Shestakovska MSc, Shrikant I. Bangdiwala PhD, Salim Yusuf FRSC, D Phil, for the IVVE investigators