The importance of influenza vaccination in cardiovascular patients

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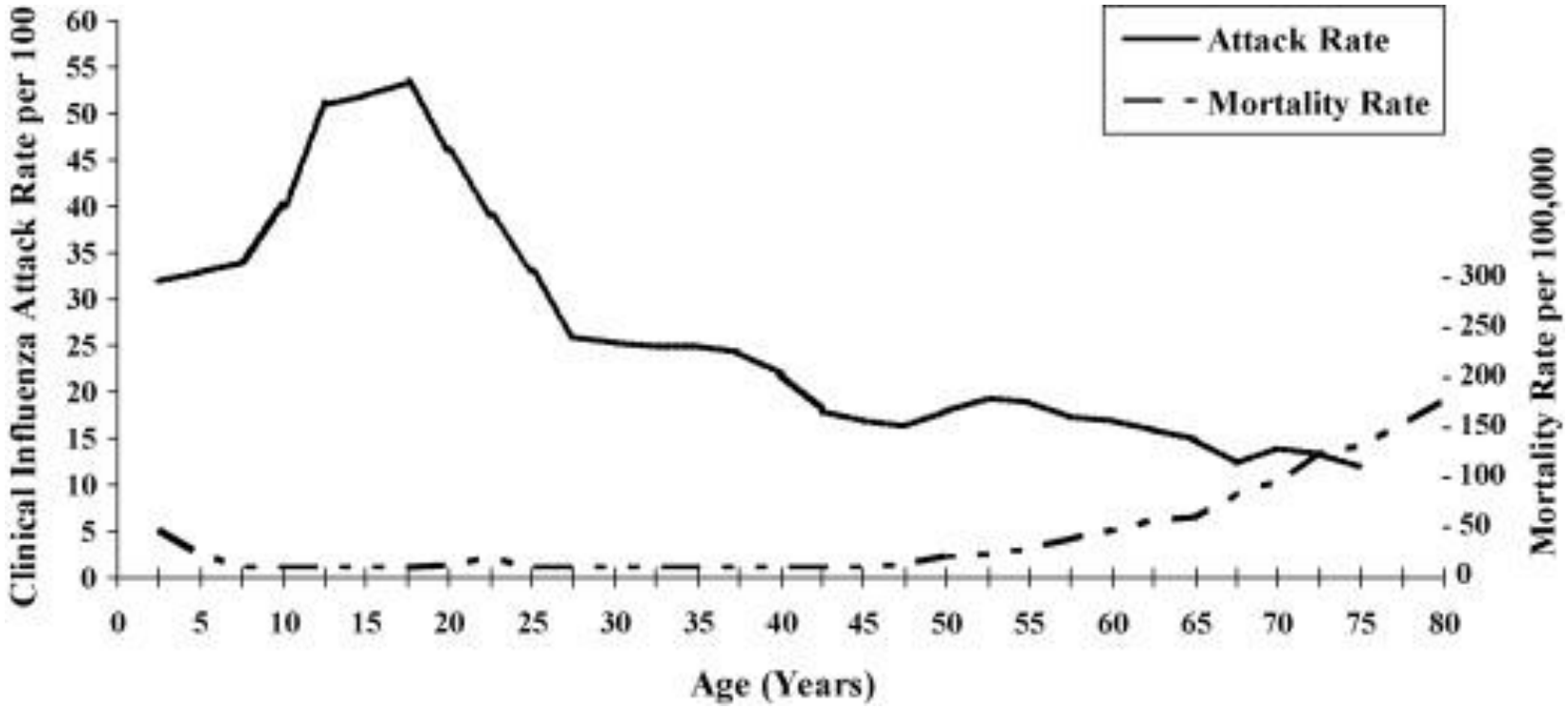
Epidemiology and Burden

- Seasonal influenza infects **millions annually**; a substantial fraction have underlying cardiovascular disease (CVD).
- Heart disease is one of the most common comorbidities in flu hospitalizations (**about 50% of adults hospitalized for flu**).In high-risk groups (elderly, chronic CVD), flu-associated morbidity and mortality are markedly increased[1].
- Epidemiological studies consistently link **peaks of influenza activity with surges in cardiovascular events.** For example, flu seasons coincide with higher rates of myocardial infarction (MI) and stroke [2] . A self-controlled case series found MI risk is about 6-fold higher in the week after laboratory-confirmed influenza infection [1]. Similarly, respiratory infections (proxy for influenza) have been associated with transiently elevated odds of acute coronary and cerebrovascular events [2].

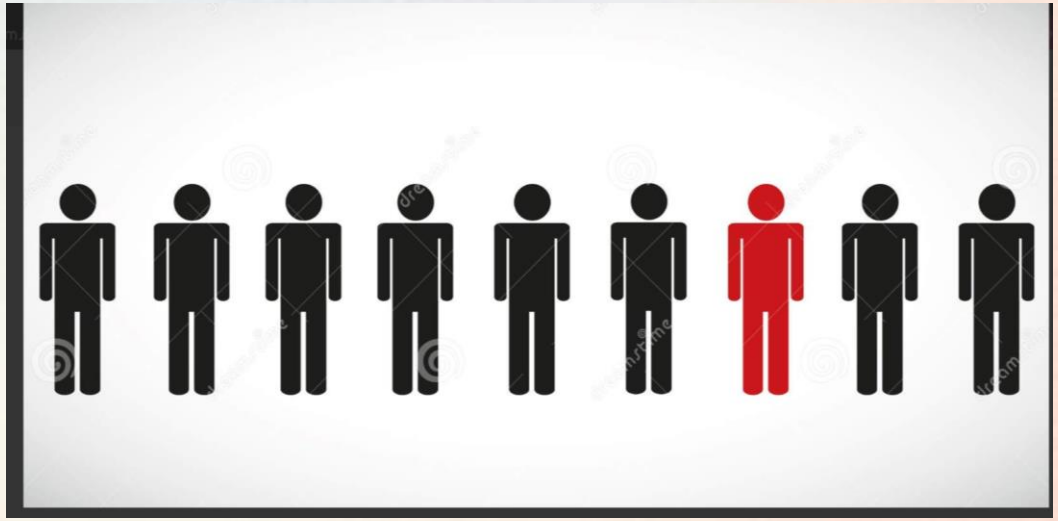
Mortality versus Attack Rate



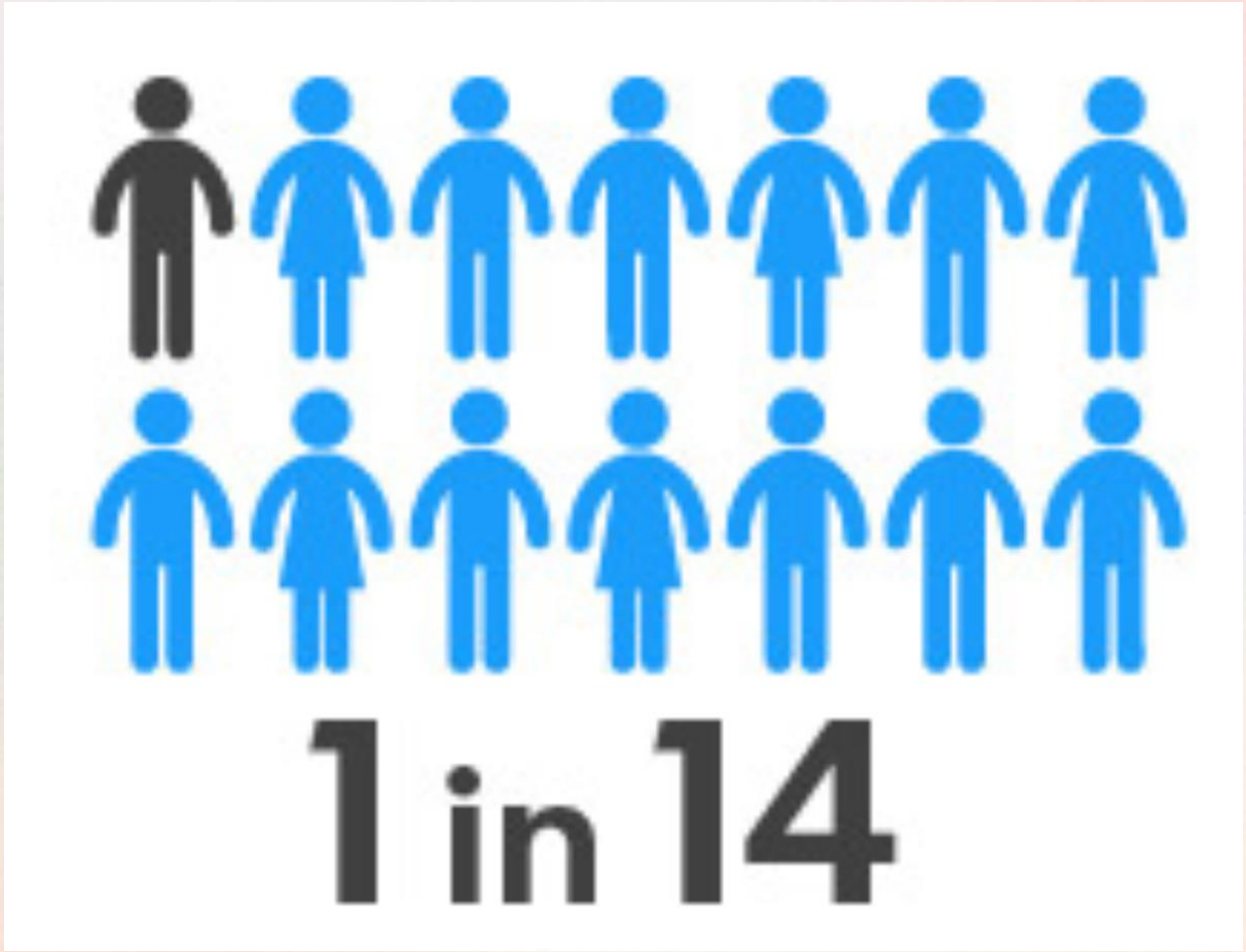
- Among hospitalized influenza patients, acute cardiac complications are common.
- One CDC analysis of >80,000 adults with flu over 8 seasons found about **12% developed an acute cardiac event** (acute HF or ischemic heart disease) during admission; of these, 30% required ICU care and 7% died in-hospital . Even mild outpatient influenza has been linked to a about 2-fold higher short-term risk of acute cardiovascular events in older adults [1].

Need ICU care

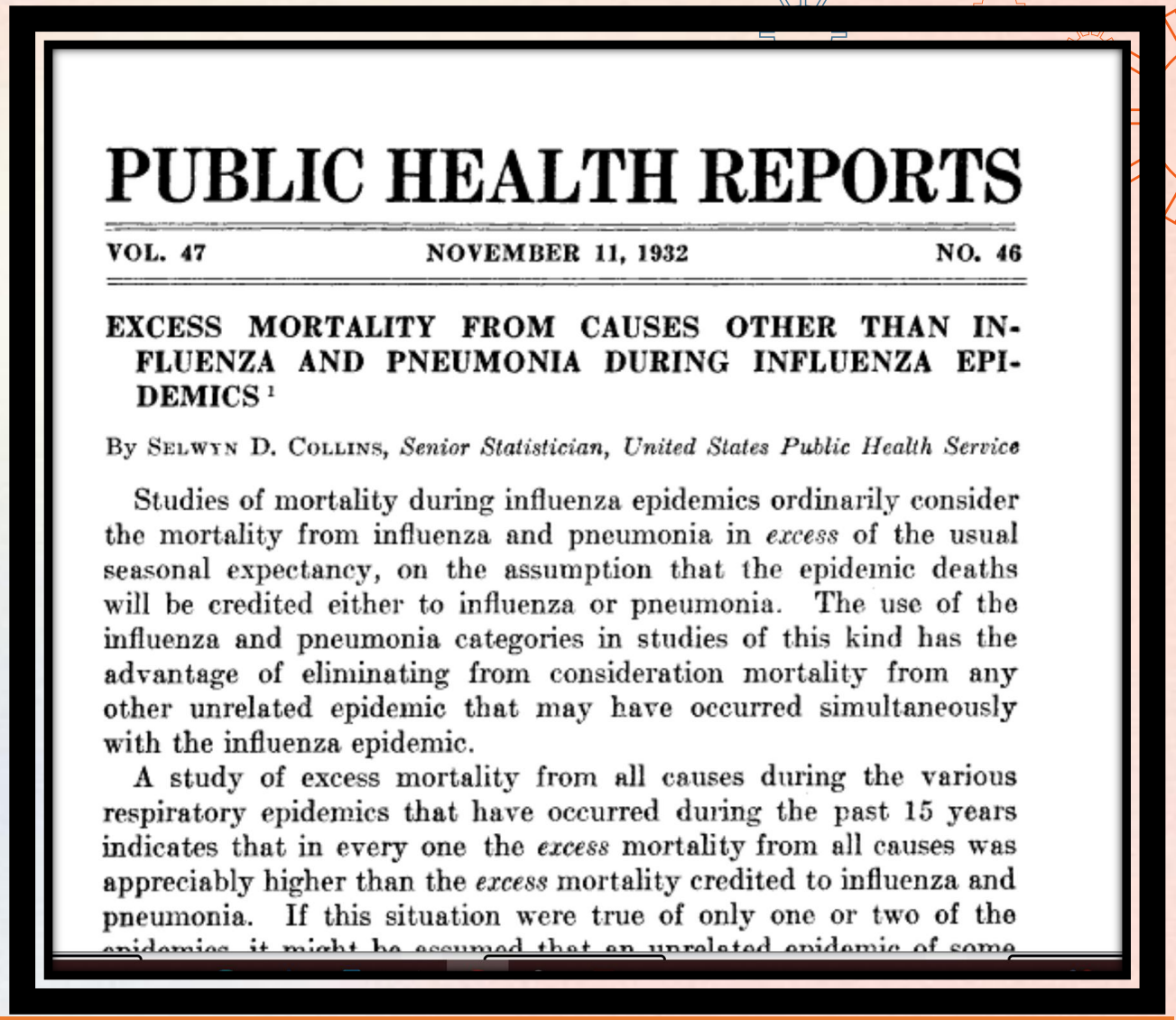
Acute cardiac Event



Death



- Excess mortality from cardiovascular disease during influenza epidemics was **first recognized early in the 20th century**, but the specific association of influenza and other infections with myocardial infarction was not characterized until decades later.



PUBLIC HEALTH REPORTS

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EXCESS MORTALITY FROM CAUSES OTHER THAN INFLUENZA AND PNEUMONIA DURING INFLUENZA EPIDEMICS [1]

By SELWYN D. COLLINS, *Senior Statistician, United States Public Health Service*

Studies of mortality during influenza epidemics ordinarily consider the mortality from influenza and pneumonia in *excess* of the usual seasonal expectancy, on the assumption that the epidemic deaths will be credited either to influenza or pneumonia. The use of the influenza and pneumonia categories in studies of this kind has the advantage of eliminating from consideration mortality from any other unrelated epidemic that may have occurred simultaneously with the influenza epidemic.

A study of excess mortality from all causes during the various respiratory epidemics that have occurred during the past 15 years indicates that in every one the *excess* mortality from all causes was appreciably higher than the *excess* mortality credited to influenza and pneumonia. If this situation were true of only one or two of the

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

Jeffrey C. Kwong, M.D., Kevin L. Schwartz, M.D., Michael A. Campitelli, M.P.H., Hannah Chung, M.P.H., Natasha S. Crowcroft, M.D., Timothy Karnauchow, Ph.D., Kevin Katz, M.D., Dennis T. Ko, M.D., Allison J. McGeer, M.D., Dayre McNally, M.D., Ph.D., David C. Richardson, M.D., Laura C. Rosella, Ph.D., M.H.Sc., Andrew Simor, M.D., Marek Smieja, M.D., Ph.D., George Zahariadis, M.D., and Jonathan B. Gubbay, M.B., B.S., M.Med.Sc.

Flu infection may raise risk of heart attack, particularly in first 7 days

ICES

Study confirms importance of flu vaccination for people at risk of heart disease.

Researchers looked at nearly 20,000 Ontario adult cases of lab-confirmed influenza (2009-2014) and then identified 332 patients who were hospitalized for a heart attack within one year of flu diagnosis.

For this population, the risk of heart attack was

6 times higher

within the first week of a flu diagnosis.

Factors that may be associated with more risk:

- being age 65 and older
- infection with influenza B
- no previous heart attack

The researchers say that people at risk of heart disease should take care to prevent flu through measures including handwashing and vaccination, and should not delay medical evaluation for heart symptoms, particularly in the first week of an acute respiratory infection.

Kwong JC et al. *NEJM*. 2018.

Institute for Clinical Evaluative Sciences
ices.on.ca

Public Health Ontario | Santé publique Ontario

- **Short-Term Risk of MI after Influenza**
  The risk of myocardial infarction rises sharply in the first days after influenza infection. Studies show a **6–10 fold increase in MI incidence within the first week** after diagnosis, especially in older adults and patients with pre-existing coronary artery disease. This is mainly due to acute inflammation, plaque destabilization, and hypercoagulability.
- **Long-Term Risk of MI after Influenza**
  Beyond the acute period, the excess risk diminishes but may persist for several weeks. Prolonged systemic inflammation, endothelial dysfunction, and residual hypercoagulability can extend vulnerability up to **1–2 months** after infection. However, in the long term (beyond this period), influenza does not independently increase MI risk unless recurrent infections or chronic inflammation are present.

How Influenza Triggers Type 1 Myocardial Infarction

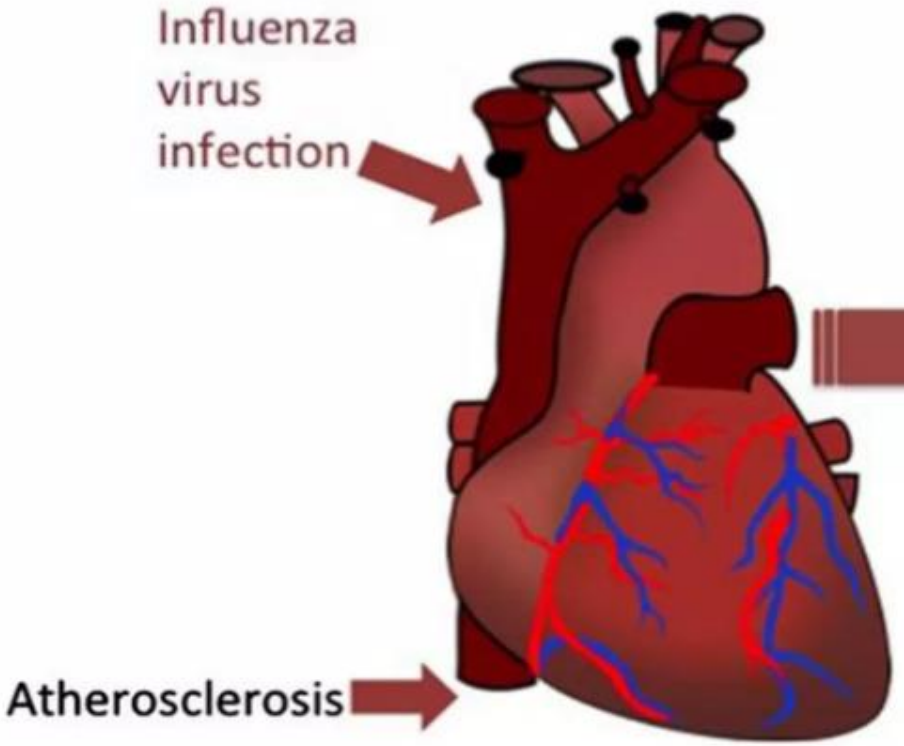
Influenza infection provokes a strong systemic inflammatory response. Circulating cytokines activate inflammatory cells inside atherosclerotic plaques, increasing enzymatic activity and oxidative stress. This weakens the fibrous cap, destabilizes the plaque, and promotes rupture. Once the plaque ruptures, acute coronary thrombosis develops, leading to type 1 myocardial infarction.

How Influenza Triggers Type 2 Myocardial Infarction

Influenza increases systemic inflammation and fever, raising metabolic demand. This leads to higher heart rate, reduced diastolic filling time, and impaired coronary perfusion. In patients with coronary stenosis, hypoxemia from pneumonia, or septic shock, oxygen delivery to the myocardium falls further. The mismatch between oxygen supply and demand causes *demand ischemia*, resulting in type 2 myocardial infarction.

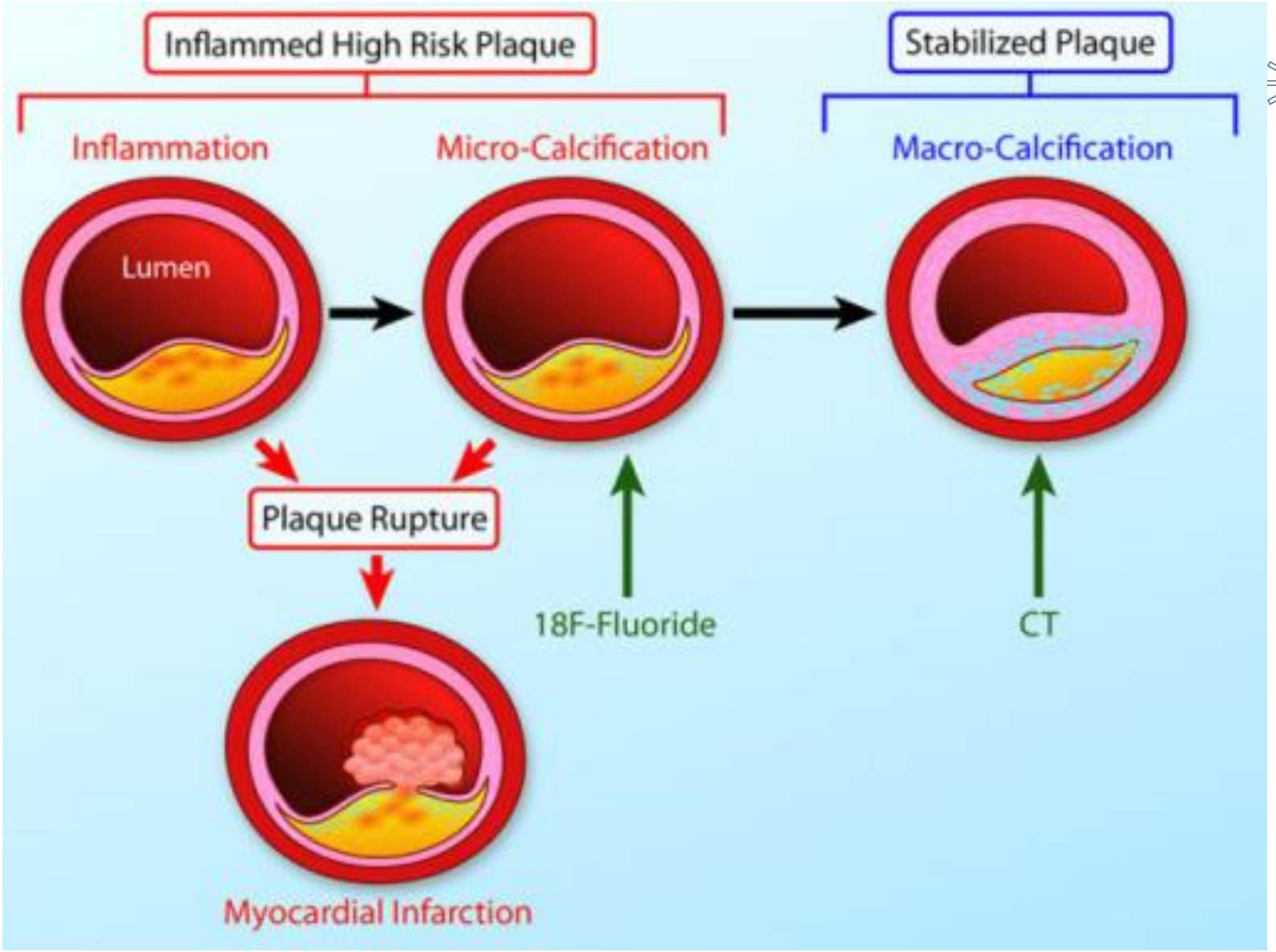
Direct Myocardial Injury from Infection

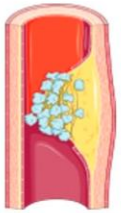
Animal and human studies show that infections like pneumococcal bacteremia or influenza can directly damage heart muscle, independent of coronary arteries. These lesions involve myocyte loss and myocardial disruption, leading to elevated troponin, arrhythmias, and worsening heart failure. In severe infections, cytokine storm further impairs mitochondrial oxygen use, contributing to acute cardiac dysfunction even in patients without pre-existing coronary disease.



- Tachycardia
- Hypoxia
- Acute inflammation
- Cytokine release
- Vasoconstriction
- Effect on receptors
- Coronary plaque disruption
- Thrombogenesis

Acute myocardial infarction


Inflammed High Risk Plaque
Stabilized Plaque
Inflammation
Micro-Calcification
Macro-Calcification
Lumen
Plaque Rupture
18F-Fluoride
CT
Myocardial Infarction



Activation of coagulation:

- platelets activation
- elevated levels of thrombogenic factors
- release of tissue factor

oxLDL

Dysfunction of endothelium:

- pro-inflammatory properties
- pro-aggregation properties
- adhesion and chemotactic factors
- impaired vasodilation

Vascular smooth muscle cells:

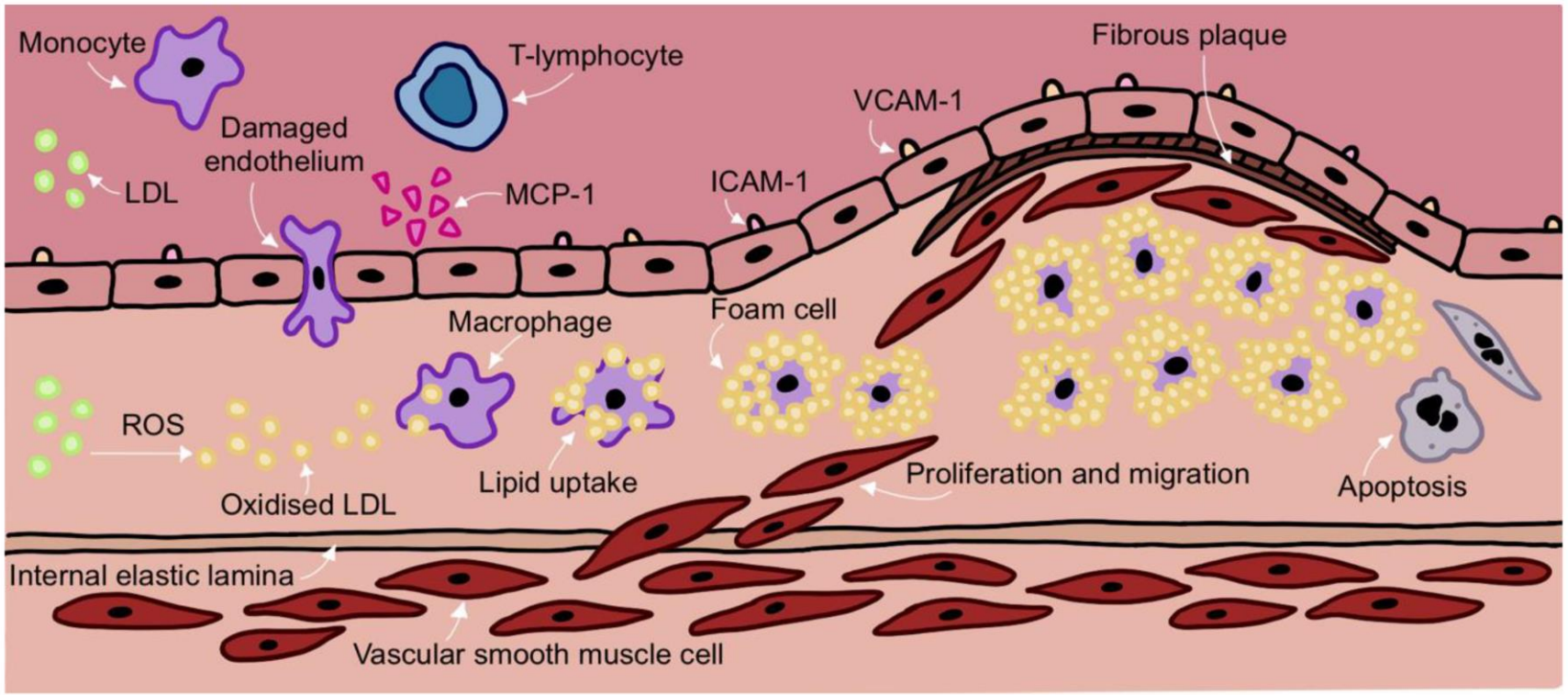
- migration and proliferation
- collagen synthesis
- apoptosis

Immune cells:

- chemotaxis, adhesion, lymphocyte T and monocytes diapedesis
- oxLDL uptake by macrophages
- lipid core enlargement

Oxidative Stress

- ***Oxidative stress***, which causes lipid peroxidation and maintains inflammation, is the basis of processes leading to the formation and destabilization of atherosclerotic



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Impact of Inflammation Related to Influenza Infection

Influenza infection causes inflammation that can remain weeks after infection

Inflammation increases hospitalization risk, especially in vulnerable populations

Vascular inflammation can worsen chronic conditions & raise risk for myocardial infarction, stroke

Possible Causative Role of Influenza Infection in Cardiovascular Diseases

Exacerbation of existing CVD

Systemic inflammation leading to disruption of atherosclerotic plaques

Myocardial infarction

Cerebrovascular accident

Influenza infection may also lead to disruption of homeostasis

Direct effect

Viral myocardial infection leading myocarditis or myopericarditis

Chronic heart failure

Pathophysiological Links (Inflammation & Plaque Instability)

- Influenza triggers a **systemic inflammatory response** (cytokine release, acute phase reactants) that can destabilize atherosclerotic plaques. Viral infection induces pro-inflammatory cytokines (e.g. TNF-α, IFN-γ) and endothelial activation, promoting thrombosis and plaque rupture .Experimental studies show **influenza viruses can replicate in atherosclerotic plaques and increase local inflammation** and lipid accumulation, rendering plaques more rupture-prone[1].

- At the same time, vaccination has been shown to have opposite immunomodulatory effects (shifting cytokine milieu toward plaque stability), suggesting a direct link between infection/vaccination and atherosclerotic inflammation .In general, any severe infection (influenza or otherwise) may trigger “Type 1” MI through plaque destabilization or “Type 2” MI via supply-demand mismatch, but influenza’s intense inflammatory cascade is a strong driver of this process [1].

- Influenza also induces endothelial dysfunction, pro-coagulant changes (e.g. platelet activation, hypercoagulability) and adrenergic surge. Hypoxemia from flu pneumonia, combined with fever and tachycardia, increases myocardial oxygen demand . Systemic hypotension and vascular constriction can occur in severe flu, further compromising coronary perfusion. The net effect can be myocardial ischemia or injury even without classic plaque rupture [1] .

Pathophysiological Effects on Myocardium

- Direct viral myocarditis is possible but uncommon in influenza. Animal models and autopsy reports have shown influenza virus can infect cardiomyocytes, triggering local inflammation, fibrosis, and apoptosis . However, in humans the predominant mechanism of myocardial injury during flu appears to be systemic (hypoxia, hypotension, demand) rather than massive direct infection [1] .

- Myocardial injury (troponin elevation) is frequently observed in severe influenza. In cohort studies, hospitalized flu patients often have evidence of cardiac injury without overt coronary occlusion . Such injury may manifest clinically as reduced ejection fraction or arrhythmias, and appears multifactorial (cytokine-mediated cardio-depression plus myocardial demand-supply mismatch) [1] .

- Patients with pre-existing heart failure (HF) have especially limited reserve. Influenza-driven pulmonary compromise and metabolic stress often precipitate acute decompensated HF. A large U.S. database study (8.2 million HF admissions) found that HF patients with concurrent influenza had higher in-hospital mortality (6.2% vs 5.4%; OR 1.15) and much higher rates of respiratory failure (36.9% vs 23.1%; OR 1.95) than HF admissions without flu . These data underscore how flu can worsen HF outcomes through pulmonary and hemodynamic strain [2].

Cardiovascular Complications of Influenza

- **Myocardial Infarction:** Influenza strongly correlates with acute coronary events. As noted, flu infection can transiently multiply MI risk (e.g. 6-fold in one study) [1]. Multiple time-series and self-controlled studies (Kwong et al., Warren-Gash et al., etc.) have documented significant associations between laboratory-confirmed influenza or high community influenza activity and subsequent MI and stroke . The proposed mechanisms include plaque rupture and thrombosis as above [2].

- **Stroke:** Influenza is also linked to an increased risk of acute ischemic stroke, particularly in the short-term following infection. Stroke and MI share similar pathophysiology (atherothrombosis precipitated by systemic inflammation), and many epidemiologic reports list stroke alongside MI as a complication of flu[2] .

Cardiovascular Complications of Influenza

- **Heart Failure Exacerbation:** Influenza is a well-recognized trigger of HF exacerbation. Seasonal peaks of influenza activity correlate with surges in HF hospitalizations. The stress of infection (hypoxemia, fluid shifts, catecholamines) often leads to acute decompensation. The aforementioned JACC Heart Failure study found that HF patients with influenza had longer hospital stays and worse outcomes, highlighting influenza as an avoidable contributor to HF morbidity[1].
- **Arrhythmias and Other Cardiac Issues:** Influenza-related systemic illness can precipitate arrhythmias (e.g. new or worsening atrial fibrillation, ventricular arrhythmias) due to fever, hypoxia, and inflammation, although large-scale data on arrhythmia incidence are limited. Cases of influenza-associated myocarditis and pericarditis have been reported (more often in fatal cases), suggesting possible direct cardiac inflammatory complications . Clinically, any acute cardiac ischemia or injury can also secondarily cause arrhythmias [2].

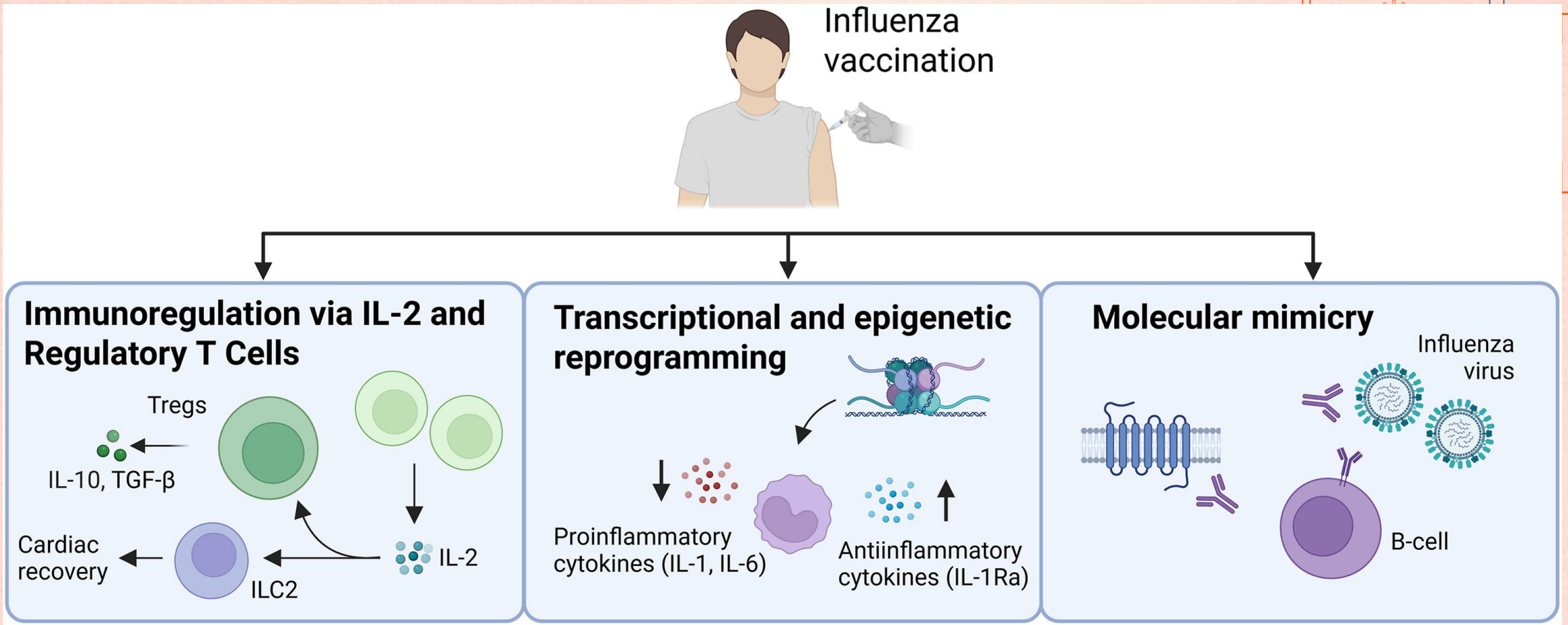
High-Risk Populations and Risk Stratification

- **Pre-existing Cardiovascular Disease:** Patients with established CVD are both more susceptible to influenza complications and more likely to have cardiac events precipitated by flu. For example, among adults hospitalized with influenza, roughly half have heart disease, making them particularly vulnerable . Studies consistently show that individuals with coronary artery disease, prior MI, or chronic HF face especially high morbidity and mortality when infected with influenza. Vulnerable subgroups include older adults (≥65 yrs) with atherosclerotic disease or reduced ejection fraction, as well as those with multivessel CAD or recent ACS [1].

- **Congenital and Structural Heart Disease:** Even younger patients with congenital heart disease (CHD) face elevated risk. A recent Canadian cohort of adults with CHD (age 40–65) showed those hospitalized for influenza had over twice the hazard of subsequent cardiovascular events (HF, MI, arrhythmias, etc.) in the following 9 months compared to matched controls (HR 2.48). This highlights that any form of structural heart disease magnifies influenza's CV impact [2].

Outcomes of Influenza in CVD Patients

- **Acute Morbidity and Mortality:** In high-risk CVD cohorts, influenza significantly worsens outcomes. The Panhwar et al. (JACC: Heart Failure 2019) study quantified this in HF patients: HF admissions with influenza had higher in-hospital mortality (6.2% vs 5.4%; OR 1.15) and more complications (respiratory failure, AKI) than HF admissions without flu . Overall, influenza infection is associated with greater short-term mortality in CVD patients, on the order of 10–20% relative increase depending on the population[1].
- **Longer-Term Risk:** There is evidence that influenza can have lasting cardiovascular consequences. For example, patients hospitalized with flu have a higher cumulative incidence of MI, HF, arrhythmias or stroke over the ensuing year(s) compared to controls . The inflammatory and prothrombotic insults from an episode of severe influenza may accelerate atherosclerosis or cardiac decline over time. As one summary notes, even after surviving acute infection, the hazard of CVD may remain elevated for months to years post-influenza[2].
- **Population Impact:** Modeling studies and national data emphasize that a substantial proportion of seasonal CV events may be attributable to influenza. During periods of low flu activity (e.g. due to social distancing), several countries saw reductions in cardiovascular mortality, suggesting influenza contributes meaningfully to population CVD burden. Thus, influenza's toll extends beyond respiratory illness to a measurable increase in population-level cardiovascular complications[2].


Influenza vaccination
Immunoregulation via IL-2 and Regulatory T Cells
Tregs
IL-10, TGF-β
Cardiac recovery
ILC2
IL-2
Transcriptional and epigenetic reprogramming
Proinflammatory cytokines (IL-1, IL-6)
Antiinflammatory cytokines (IL-1Ra)
Molecular mimicry
Influenza virus
B-cell

Influenza Vaccination: Rationale for Cardiovascular Protection

- **Immunization as Indirect CV Prevention:** By preventing influenza infection, vaccines indirectly protect the cardiovascular system. Less infection means less inflammation, hypoxemia, and adrenergic stress. Vaccination also reduces influenza-related pneumonia and sepsis, major precipitants of cardiovascular decompensation. Clinical studies support this: vaccinated patients have fewer hospitalizations and deaths overall in flu season.
- **Direct Evidence in CVD Patients:** Multiple clinical trials and meta-analyses have tested whether flu vaccination reduces cardiovascular events in patients with established CVD. These studies generally compare vaccinated vs unvaccinated (or placebo) groups among cardiac patients, tracking outcomes like MI, death, or HF hospitalizations. While not all individual trials are definitive, the collective evidence suggests a protective cardiovascular effect of vaccination.
- **Immunological Effects:** Beyond preventing infection, influenza vaccines modulate immune response. Data show vaccination can lower levels of pro-atherogenic cytokines and raise anti-inflammatory markers, potentially stabilizing plaques . Thus, vaccination may confer additional benefit by dampening chronic inflammation in atherosclerotic disease.

Clinical Trial and Meta-Analysis Evidence

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Overview of randomized studies of influenza vaccination in ischemic heart disease.

Study name	Population	Number of participants	Intervention	Comparator	Primary outcome	Key results
FLUVACS Gurfinkel, EP, 2004	Recent MI patients	301	Influenza vaccine	No vaccine (control)	Cardiovascular death and combined cardiovascular events at 6 months	Influenza vaccination significantly reduced cardiovascular death and combined cardiovascular events at 6 months in patients with recent MI.
FLUCAD Ciszewski A, 2008	Stable coronary artery disease	658	Influenza vaccine	Placebo	Major adverse cardiovascular events at 12 months	Influenza vaccination reduced major adverse cardiovascular events in patients with stable coronary artery disease over 12 months.
Phrommintikul A, 2011	Acute coronary syndrome, hospitalized	439	Influenza vaccine	No vaccine (control)	Cardiovascular hospitalizations and major CV events at 12 months	Vaccination lowered major cardiovascular events in patients hospitalized with acute coronary syndrome; reduction in cardiovascular hospitalizations at 12 months.
INVESTED Vardeny O, 2021	High-risk patients with prior MI or heart failure	5260	High-dose influenza vaccine	Standard-dose influenza vaccine	All-cause death or cardiopulmonary hospitalization	High-dose versus standard-dose influenza vaccine showed no significant difference in rates of all-cause death or cardiopulmonary hospitalization in high-risk cardiovascular patients.
IAMI Frobert O, 2021	Hospitalized patients with recent MI	2571	In-hospital influenza vaccine	Placebo	All-cause death, MI, or stent thrombosis at 12 months	Influenza vaccination during hospitalization for MI reduced all-cause death, MI, or stent thrombosis at 12 months; it also reduced all-cause and cardiovascular mortality.
IVVE Loeb M, 2022	Heart failure, 30 % ischemic etiology	5129	Influenza vaccine	Placebo	CV death, nonfatal MI/stroke; total CV events incl. HF hospitalizations	No significant effect on primary outcomes of cardiovascular death, MI, or stroke. All-cause hospitalisations and pneumonia were significantly reduced in the vaccine group
VIP-ACS Fonseca HAR, 2022	Patients hospitalized with acute coronary syndrome	1801	In-hospital double-dose influenza vaccine	Outpatient standard-dose influenza vaccine (30 days post-discharge)	Hierarchical composite of death, MI, stroke, UA, HF hospitalization, revascularization, and respiratory hospitalization	Double-dose versus standard-dose influenza vaccine showed no significant difference between groups.

Association between influenza vaccination and prognosis in patients with ischemic heart disease: A systematic review and meta-analysis of randomized controlled trials

2025

Xiao Liu et al

Background

There is substantial epidemiological evidence demonstrating that influenza contributes to cardiovascular events in patients who already have cardiovascular diseases. However, the efficacy of influenza vaccination on the prognosis of patients with ischemic heart disease (IHD) is unclear.

Methods

We conducted a systematic search for eligible **randomized controlled trials (RCTs) in PubMed, Cochrane, and Embase** on September 13, 2024, to investigate the effects of the influenza vaccine on the prognosis of patients with IHD. The effect sizes were combined using random-effects models, and Trial Sequential Analysis (TSA) was used to assess the reliability and validity of the results.

Results

Five RCTs with a total of 5659 patients (median age ranging from 57.1 to 66 years, 67.8% male) with IHD were included. The use of influenza vaccine reduced the risk of **MACE** (risk ratio [RR] = 0.67, 95% confidence interval [CI] 0.52–0.87, number-needed-to-treat [NNT] of 37, high certainty), **cardiovascular death** (RR = 0.55, 95% CI 0.35–0.87, moderate certainty**), all-cause mortality** (RR = 0.58, 95% CI 0.40–0.84, high certainty) and myocardial infarction (MI) (RR = 0.66, 95% CI 0.46–0.93, high certainty) in patients with IHD compared with control. The analysis revealed no significant benefit regarding hospitalization for heart failure (HF) (RR = 0.91, 95% CI 0.21–3.99, moderate certainty) and revascularization (RR = 0.59, 95% CI 0.10–3.45, moderate certainty). **The NNT to avoid 1 event was 37 for major adverse cardiovascular events**, 56 for cardiovascular death, 67 for MI, and 41 for all-cause death. TSA showed that the benefit of influenza vaccine in reducing MACE was conclusive, no more trials were necessary.

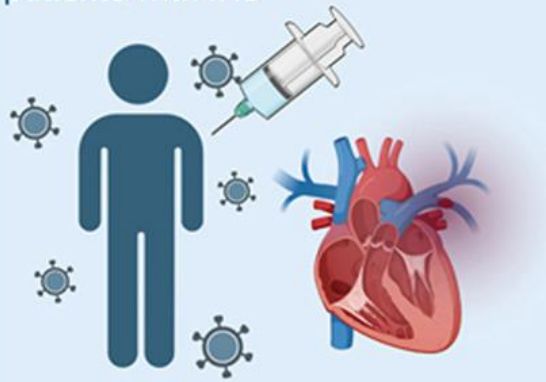
Conclusion

This study suggests high level of evidence that the use of influenza vaccine reduce the risk of major adverse cardiovascular events in patients with IHD.

Association between influenza vaccination and prognosis in patients with ischemic heart disease: a systematic review and meta-analysis

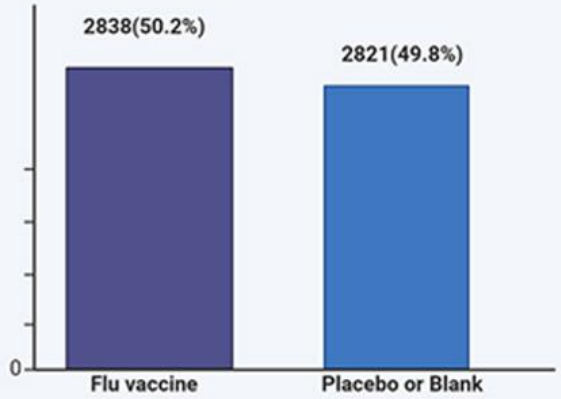
CLINICAL QUESTION

To evaluate the effect of influenza vaccination on the prognosis of patients with IHD



STUDY SELECTION AND RESULT

- Five RCTs from PubMed, Embase and Cochrane
- 5,659 patients with IHD received either the flu vaccine, placebo or no treatment



MACE	RR 0.767(0.52-0.87)	High quality*
Cardiovascular death	RR 0.55(0.35-0.87)	Moderate quality
All-cause death	RR 0.58(0.40-0.84)	High quality*
Myocardial infarction	RR 0.66(0.46-0.93)	High quality*
Hostpitalization for HF	RR 0.91(0.21-3.99)	Moderate quality
Revascularization	RR 0.59(0.10-3.45)	Moderate quality

CONCLUSION

The use of influenza vaccine may reduce the incidence of MACE, cardiovascular disease mortality, all-cause mortality, and myocardial infarction in patients with IHD

Abbreviation: IHD: Ischemic heart disease; RCT: Randomized controlled trail; MACE:Major adverse cardiovascular event; RR: Relative risk; HF:Heart failure

*:Represents the level of evidence for GRADE evaluation

Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis

2013

Jacob A Udell et al.

- **Objectives:** To determine if influenza vaccination is associated with prevention of cardiovascular events.

- Results: **Five published and 1 unpublished randomized clinical trials** of 6735 patients (mean age, 67 years; 51.3% women; 36.2% with a cardiac history; mean follow-up time, 7.9 months) were included. Influenza vaccine was associated with a lower risk of composite cardiovascular events (2.9% vs 4.7%; RR, 0.64 [95% CI, 0.48-0.86], P = .003) in published trials. A treatment interaction was detected between patients with (RR, 0.45 [95% CI, 0.32-0.63]) and without (RR, 0.94 [95% CI, 0.55-1.61]) recent ACS (P for interaction = .02). Results were similar with the addition of unpublished data.

- Conclusions and relevance: In a meta-analysis of RCTs, the use of influenza vaccine was associated with a lower risk of major adverse cardiovascular events. The greatest treatment effect was seen among the highest-risk patients with more active coronary disease. A large, adequately powered, multicenter trial is warranted to address these findings and assess individual cardiovascular end points.

Association of Influenza Vaccination With Cardiovascular Risk: A Meta-analysis

2022

Bahar Behrouzi et al.

- **Objective:** To evaluate, via an updated meta-analysis, if seasonal influenza vaccination is associated with a lower risk of fatal and nonfatal cardiovascular events and assess whether the newest cardiovascular outcome trial results are consistent with prior findings.
- **Results:** Six published RCTs comprising a total of 9001 patients were included (mean age, 65.5 years; 42.5% women; 52.3% with a cardiac history). Overall, influenza vaccine was associated with a lower risk of composite cardiovascular events (3.6% vs 5.4%; RR, 0.66; 95% CI, 0.53-0.83; P < .001). A treatment interaction was detected between patients with recent ACS (RR, 0.55; 95% CI, 0.41-0.75) and without recent ACS (RR, 1.00; 95% CI, 0.68-1.47) (P for interaction = .02). For cardiovascular mortality, a treatment interaction was also detected between patients with recent ACS (RR, 0.44; 95% CI, 0.23-0.85) and without recent ACS (RR, 1.45; 95% CI, 0.84-2.50) (P for interaction = .006), while 1.7% of vaccine recipients died of cardiovascular causes compared with 2.5% of placebo or control recipients (RR, 0.74; 95% CI, 0.42-1.30; P = .29).
- **Conclusions and relevance:** In this study, receipt of influenza vaccination was associated with a 34% lower risk of major adverse cardiovascular events, and individuals with recent ACS had a 45% lower risk. Given influenza poses a threat to population health during the COVID-19 pandemic, it is integral to counsel high-risk patients on the cardiovascular benefits of influenza vaccination.

Influenza Vaccine in Heart Failure: Cumulative Number of Vaccinations, Frequency, Timing, and Survival: A Danish Nationwide Cohort Study

2018

Daniel Modin **et al.**

Background:

Influenza infection is a serious event for patients with heart failure (HF). Little knowledge exists about the association between influenza vaccination and outcome in patients with HF. This study sought to determine whether influenza vaccination is associated with improved long-term survival in patients with newly diagnosed HF.

Methods:

We performed a **nationwide cohort study** including all patients who were >18 years of age and diagnosed with **HF in Denmark** in the period of January 1, 2003, to June 1, 2015 **(n=134 048).** We collected linked data using nationwide registries. Vaccination status, number, and frequency during follow-up were treated as time-varying covariates in time-dependent Cox regression.

Results:

Follow-up was 99.8% with a **median follow-up time of 3.7 years** (interquartile range, 1.7–6.8 years). The vaccination coverage of the study cohort ranged from 16% to 54% during the study period. In unadjusted analysis, receiving ≥1 vaccinations during follow-up was associated with a higher risk of death. **After adjustment for inclusion date, comorbidities, medications, household income, and education level, receiving ≥1 vaccinations was associated with an 18% reduced risk of death** (all-cause: hazard ratio, 0.82; 95% CI, 0.81–0.84; *P*<0.001; cardiovascular causes: hazard ratio, 0.82; 95% CI, 0.81–0.84; *P*<0.001). Annual vaccination, vaccination early in the year (September to October), and greater cumulative number of vaccinations were associated with larger reductions in the risk of death compared with intermittent vaccination.

Conclusions:

In patients with HF, influenza vaccination was associated with a **reduced risk of both all-cause and cardiovascular death after extensive adjustment for confounders**. Frequent vaccination and vaccination earlier in the year were associated with larger reductions in the risk of death compared with intermittent and late vaccination.

Effects of Influenza Vaccine on Mortality and Cardiovascular Outcomes in Patients With Cardiovascular Disease: A Systematic Review and Meta-Analysis

2021

Siva H Yedlapati et al.

- **Background:** Influenza infection causes considerable morbidity and mortality in patients with cardiovascular disease. We assessed the effects of the influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease.

- **Method and result:** We searched PubMed, Embase, and the Cochrane Library through January 2020 for randomized controlled trials and observational studies assessing the effects of influenza vaccine on mortality and cardiovascular outcomes in patients with cardiovascular disease. Estimates were reported as random effects risk ratios (RRs) with 95% CIs. Analyses were stratified by study design into randomized controlled trials and observational studies. A total of 16 studies (n=237 058), including 4 randomized controlled trials (n=1667) and 12 observational studies (n=235 391), were identified. Participants' mean age was 69.2±7.01 years, 36.6% were women, 65.1% had hypertension, 31.1% had diabetes mellitus, and 23.4% were smokers. At a median follow-up duration of 19.5 months, influenza vaccine was associated with a lower risk of all-cause mortality (RR, 0.75; 95% CI, 0.60–0.93 [P=0.01]), cardiovascular mortality (RR, 0.82; 95% CI, 0.80–0.84 [P

- **Conclusion:** Data from both randomized controlled trials and observational studies support the use of the influenza vaccine in adults with cardiovascular disease to reduce mortality and cardiovascular events, as currently supported by clinical guidelines. Clinicians and health systems should continue to promote the influenza vaccine as part of comprehensive secondary prevention.

Influenza Vaccination After Myocardial Infarction: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Trial

2021

Ole Fröbert et al.

Background:

Observational and small, randomized studies suggest that influenza vaccine may reduce future cardiovascular events in patients with cardiovascular disease.

Methods:

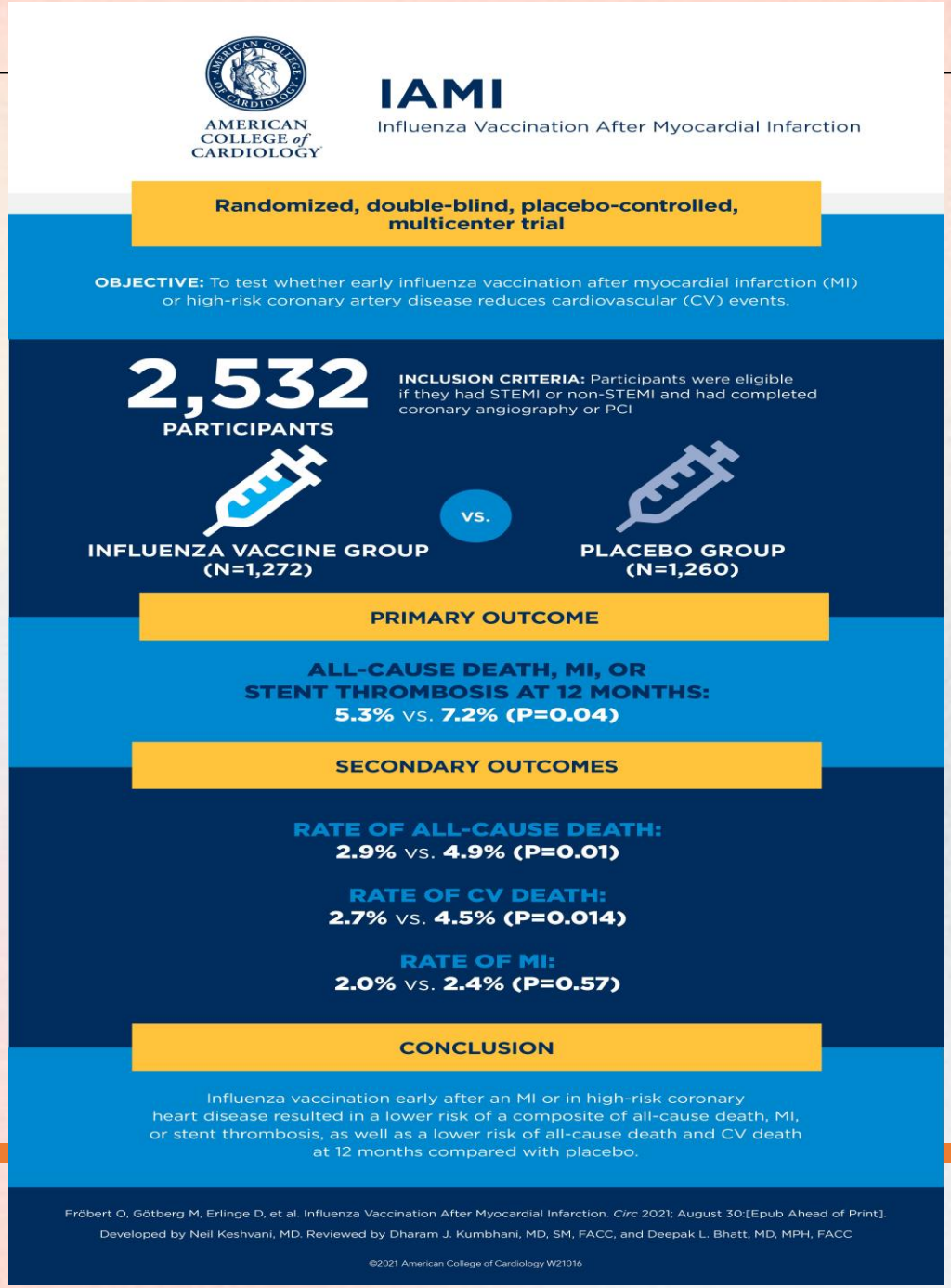
We conducted an investigator-initiated, randomized, double-blind trial to compare inactivated influenza vaccine with saline placebo administered shortly after myocardial infarction (MI; 99.7% of patients) or high-risk stable coronary heart disease (0.3%). The primary end point was the composite of all-cause death, MI, or stent thrombosis at 12 months. A hierarchical testing strategy was used for the key secondary end points: all-cause death, cardiovascular death, MI, and stent thrombosis.

Results:

Because of the COVID-19 pandemic, the data safety and monitoring board recommended to halt the trial before attaining the prespecified sample size. Between October 1, 2016, and March 1, 2020, 2571 participants were randomized at 30 centers across 8 countries. Participants assigned to influenza vaccine totaled 1290 and individuals assigned to placebo equaled 1281; of these, 2532 received the study treatment (1272 influenza vaccine and 1260 placebo) and were included in the modified intention to treat analysis. Over the 12-month follow-up, the primary outcome occurred in 67 participants (5.3%) assigned influenza vaccine and 91 participants (7.2%) assigned placebo (hazard ratio, 0.72 [95% CI, 0.52–0.99]; *P*=0.040). Rates of all-cause death were 2.9% and 4.9% (hazard ratio, 0.59 [95% CI, 0.39–0.89]; *P*=0.010), rates of cardiovascular death were 2.7% and 4.5%, (hazard ratio, 0.59 [95% CI, 0.39–0.90]; *P*=0.014), and rates of MI were 2.0% and 2.4% (hazard ratio, 0.86 [95% CI, 0.50–1.46]; *P*=0.57) in the influenza vaccine and placebo groups, respectively.

Conclusions:

Influenza vaccination early after an MI or in high-risk coronary heart disease resulted in a lower risk of a composite of all-cause death, MI, or stent thrombosis, and a lower risk of all-cause death and cardiovascular death, as well, at 12 months compared with placebo.



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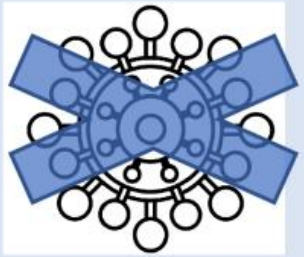
INFLUENZA VACCINATION AS SECONDARY PREVENTION AFTER MYOCARDIAL INFARCTION

Post MI patients



Vaccination to prevent influenza and future CV events

IAMI Trial

Major Adverse CV events

28%

CV Death
All Cause Death

41%

Post-MI checklist

Magnitude of reduction in recurrent CV events:

- Statins, beta-blockers, ACEI/ARBs by 17-30%

- Influenza vaccination - by 15-49%

Overcoming Barriers

- Reinforce existing guidelines
- Education to Patients
- Education to Clinicians
- Emphasize efficacy
- Endorse safety
- Build Trust
- Combat misinformation
- Implementation Strategies
- Post MI check lists

behestan darou

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A recent experience on the role of influenza vaccination on cardiovascular events

2023

María Inés Sosa-Liprandi et al.

- **primary endpoint:** The purpose of this review is to update the recent information regarding the role of influenza vaccination (IV) as a strategy to reduce cardiovascular (CV) events.

- **Result and conclusion:** During the last 2 years, new meta-analysis, guidelines, and two randomized controlled trials (RCTs) were published. The IAMI trial added information regarding the safety and efficacy of IV right after an acute myocardial infarction hospitalization. A significant reduction in the primary endpoint—including mortality—was observed. More recently, the influenza vaccine to prevent vascular events trial (IVVE) trial did not meet the primary CV endpoint in patients with heart failure (HF). However, a significant reduction was observed during the seasonal peaks of Influenza circulation. COVID-19 pandemic provoked recruitment difficulties in these trials, as well as an altered influenza seasonality and incidence. Further analysis of IVVE trial is needed to clarify the precise role of IV in patients with HF. A recent meta-analysis of RCTs and observational studies indicated that IV was safe and effective to reduce CV events, and it was included in the most updated guideline. Despite these benefits, and the recommendations for its prescription by scientific societies and health regulatory agencies, the vaccination rate remains below than expected globally. The correct understanding of implementation barriers, which involve doctors, patients, and their context, is essential when continuous improvement strategies are planned, in order to improve the IV rate in at-risk subjects.

DANFLU 2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

High-Dose Influenza Vaccine Effectiveness against Hospitalization in Older Adults

Authors: Niklas Dyrby Johansen, M.D., Ph.D. , Daniel Modin, M.D. , Matthew M. Loiacono, Ph.D., Rebecca C. Harris, M.Bioch., Ph.D., Marine Dufournet, Ph.D., Carsten Schade Larsen, M.D., D.M.Sc., Lykke Larsen, M.D., Ph.D., +30 , and Tor Biering-Sørensen, M.D., M.P.H., Ph.D. Author Info & Affiliations

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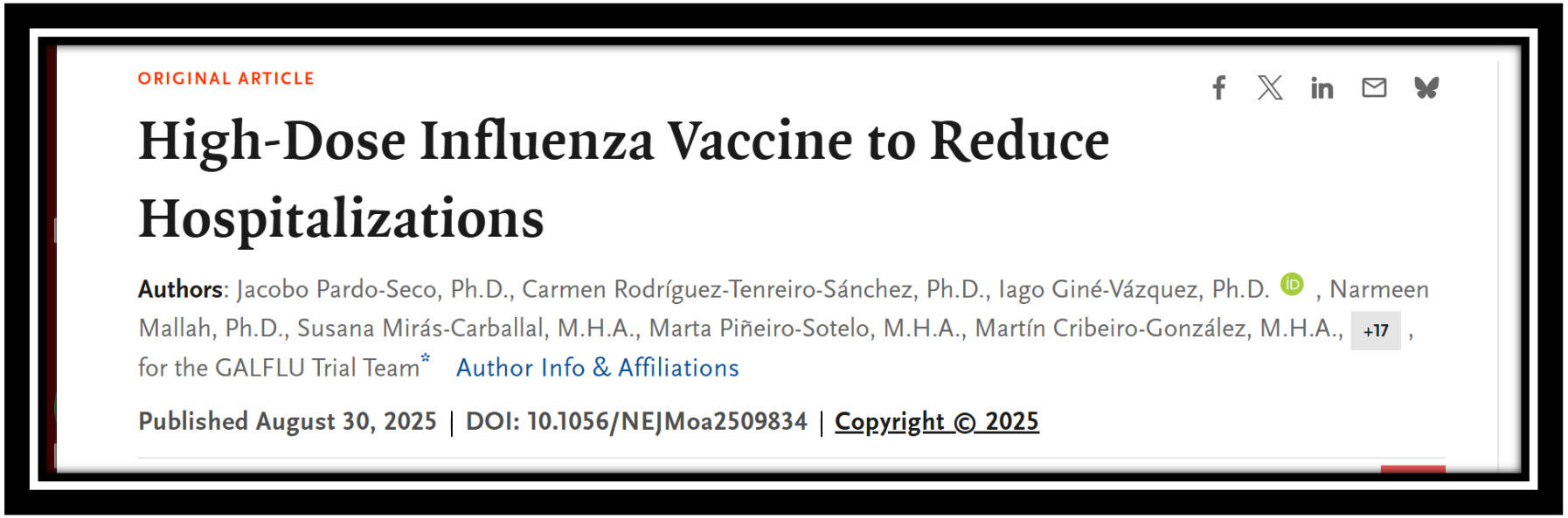
DANFLU 2

- In this trial, the high-dose vaccine did not result in a significantly lower incidence of hospitalization for influenza or pneumonia (the composite primary end point) among adults 65 of age or older than the standard-dose vaccine.
- Although no definitive conclusions can be drawn regarding the secondary end points, the results are consistent with possible benefits of the high-dose vaccine over the standard-dose vaccine for prevention of hospitalization for influenza and cardiorespiratory disease.

GUNFLU trial



ORIGINAL ARTICLE

High-Dose Influenza Vaccine to Reduce Hospitalizations

Authors: Jacobo Pardo-Seco, Ph.D., Carmen Rodríguez-Tenreiro-Sánchez, Ph.D., Iago Giné-Vázquez, Ph.D. , Narmeen Mallah, Ph.D., Susana Mirás-Carballal, M.H.A., Marta Piñeiro-Sotelo, M.H.A., Martín Cribeiro-González, M.H.A., +17 , for the GALFLU Trial Team* Author Info & Affiliations

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Secondary Analysis DANFLU-2

JAMA Cardiology | Original Investigation

High-Dose vs Standard-Dose Influenza Vaccine and Cardiovascular Outcomes in Older Adults

A Prespecified Secondary Analysis of the DANFLU-2 Randomized Clinical Trial

Niklas Dyrby Johansen, MD, PhD; Daniel Modin, MD; Matthew M. Loiacono, PhD; Rebecca C. Harris, MBioch, MSc, PhD; Marine Dufournet, PhD; Carsten Schade Larsen, MD, DMSc; Lykke Larsen, MD, PhD; Lothar Wiese, MD, PhD; Michael Dalager-Pedersen, MD, PhD; Brian L. Claggett, PhD; Kira Hyldekær Janstrup, PhD; Katja Vu Bartholdy, MD; Katrine Feldballe Bernholm, MD; Julie Inge-Marie Helene Borchsenius, MD; Filip Soeskov Davidovski, MD; Lise Witten Davodian, MD; Maria Dons, MD; Lisa Steen Duus, MD; Caroline Espersen, MD; Frederik Holme Fussing, MD; Anne Marie Reimer Jensen, MD; Nino Emanuel Landler, MD, PhD; Adam Cadovius Femerling Langhoff, MD; Mats Christian Højbjerg Lassen, MD; Anne Bjerg Nielsen, MD; Camilla Ikast Ottosen, MD; Morten Sengeløv, MD; Kristoffer Grundtvig Skaarup, MD; Manan Pareek, MD, PhD, MSc; Scott D. Solomon, MD; Martin J. Landray, PhD; Gunnar H. Gislason, MD, PhD; Lars Køber, MD, DMSc; Pradeesh Sivapalan, MD, PhD; Cyril Jean-Marie Martel, PhD; Jens Ulrik Stæhr[illegible]ng-Sørensen, MD, MSc, MPH, PhD

Influenza and cardiovascular disease

Secondary Analysis DANFLU-2

- This study found reduced incidence of cardiorespiratory hospitalization among those who received HD-IIV vs SD-IIV, driven by a ***lower incidence of CV hospitalizations***, and particularly ***heart failure hospitalizations***.
- The results suggest additional effectiveness with HD-IIV compared with SD-IIV against cardiovascular outcomes but should be interpreted as ***exploratory findings*** in the setting of a large randomized clinical trial with a ***neutral primary outcome***.

Guidelines and Recommendations

- **AHA/ACC Guidelines**: Professional societies explicitly endorse influenza vaccination in CVD patients. The 2006 AHA/ACC Secondary Prevention guidelines assigned a Class I, Level of Evidence B recommendation for annual influenza vaccine in patients with coronary or other atherosclerotic vascular disease. In other words, vaccination was strongly recommended as part of secondary prevention[1] .
- **CDC/ACIP Recommendations**: The CDC's Advisory Committee on Immunization Practices recommends annual influenza immunization for all individuals aged ≥6 months without contraindications, with particular priority for high-risk groups (including those with cardiovascular disease) . The rationale explicitly includes prevention of serious complications – and the CDC highlights heart disease patients as a key high-risk group. In February 2024, CDC stated that flu vaccination is "especially important for people at higher risk of developing serious flu complications, including people with heart disease" [2].

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VOL. 85, NO. 22, 2025

CLINICAL PRACTICE GUIDELINE

2025 ACC/AHA/ACEP/NAEMSP/SCAI Guideline for the Management of Patients With Acute Coronary Syndromes

A Report of the American College of Cardiology/American Heart Association
Joint Committee on Clinical Practice Guidelines

Developed in Collaboration With and Endorsed by the American College of Emergency Physicians,
National Association of EMS Physicians, and Society for Cardiovascular Angiography
and Interventions

Recommendation for Immunization
Referenced studies that support recommendation are summarized in the Evidence Table.

COR	LOE	RECOMMENDATION
1	A	1. In patients with ACS without a contraindication, annual influenza vaccination is recommended to reduce the risk of death and MACE.[1-4]

ESC
European Society of Cardiology

Vaccination as a new form of cardiovascular prevention: an ESC Clinical Consensus Statement

30 Jun 2025

Topic(s): *Risk Factors and Prevention;*

Key take-aways

- A newly published ESC Clinical Consensus Statement describes the pivotal role of vaccination in the prevention of cardiovascular events.
- Infections such as pneumonia, influenza and SARS-CoV-2, among others, exacerbate heart failure and increase the risk of major cardiovascular events. In addition to preventing infections, vaccination can reduce cardiovascular complications, particularly in at-risk patients with existing cardiovascular disease.
- The new document concludes that vaccination should be considered as a foundational pillar for cardiovascular prevention alongside other established measures.

- **Summary of Guideline Quotes:** According to an ACC perspective, “Influenza vaccination is a proven strategy to reduce influenza. complications, as well as prevent influenza-associated cardiovascular events” . The responsibility is seen as belonging to the entire cardiovascular care team to ensure patients receive annual flu vaccination. Similarly, the CDC emphasizes that “flu vaccination may help prevent [acute cardiac events in flu]” and that it “is recommended and especially important for people. with heart disease” [1,2] .

American Heart Association®

Flu

People with heart disease and those who have had a stroke are more likely to develop serious flu complications. A 2018 study found that the risk of having a heart attack was 6 times higher within a week of a confirmed flu infection. Get vaccinated in September/October, in advance of flu season.

Age recommendation

6 months and older, with rare exceptions

65+ should get the high-dose vaccine for extra protection.

American Heart Association.

Vaccines and CVD

What Research Shows About Vaccines and Viruses

Vaccinations can have an incredibly positive impact on heart health. It's important to know how vaccines against COVID-19, flu, RSV, shingles and pneumonia relate to risk factors for cardiovascular disease and stroke.

Without the relevant vaccinations:

- People may be at greater risk for cardiovascular disease (CVD) because of these viruses.
- CVD and stroke patients may face more severe complications from these viruses.

COVID-19

COVID-19 infection can raise the risk of myocarditis, a rare heart inflammation, and atrial fibrillation, a common heart rhythm disorder, both of which were observed in patients hospitalized with the virus.

Age recommendation

6 months and older, especially those 65+

Flu

People with heart disease and those who have had a stroke are more likely to develop serious flu complications. A 2018 study found that the risk of having a heart attack was 6 times higher within a week of a confirmed flu infection. Get vaccinated in September/October, in advance of flu season.

Age recommendation

6 months and older, with rare exceptions

65+ should get the high-dose vaccine for extra protection.

RSV (adults)

Respiratory syncytial virus can have serious implications for heart patients. Complications related to RSV, such as congestive heart failure and arrhythmias, account for 14% to 22% of hospitalizations for adults. Underlying CVD has also been linked to 45% to 63% of adult hospitalizations for RSV.

Age recommendation

75 and older

60–74 at increased risk of severe RSV*

*People with chronic heart or lung disease, certain other chronic medical conditions, and residents of nursing homes or other long-term care facilities

Shingles

People who've had shingles are nearly 30% more likely to experience a heart attack or stroke in the long term.

Age recommendation

50+

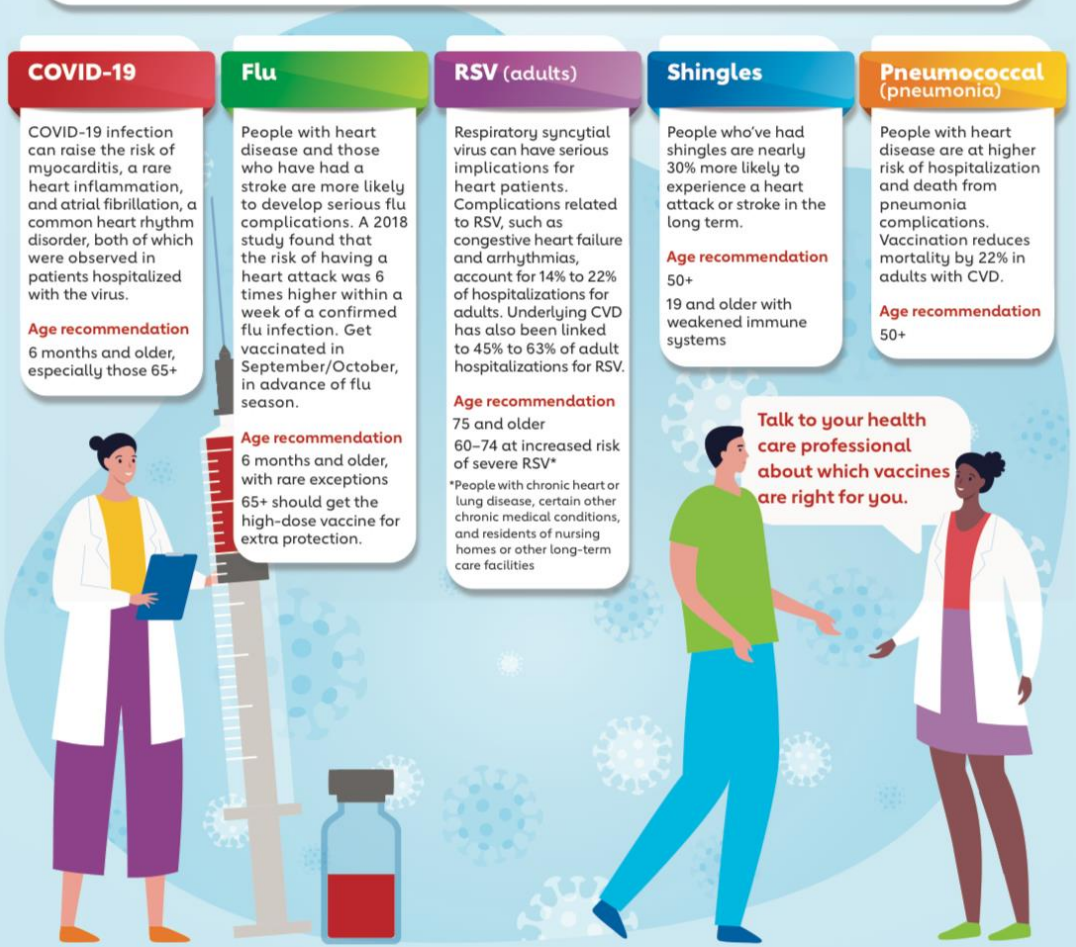
19 and older with weakened immune systems

Pneumococcal (pneumonia)

People with heart disease are at higher risk of hospitalization and death from pneumonia complications. Vaccination reduces mortality by 22% in adults with CVD.

Age recommendation

50+



Visit *heart.org/vaccines* for more information

Knowledge and implementation gaps

- Outside the influenza season, is it effective?
- Revaccination during cardiovascular events
- Higher dose versus standard dose
- Novel platforms, such as mRNA-based formulations

“Flu vaccination for patients with heart disease can be just as effective as quitting smoking.”

– Allen J. Taylor, MD
MedStar Washington Hospital Center
(representing American College of Cardiology)