



Influenza and Cardiovascular Disease

How does World Health Organization (WHO) define Cardiovascular Diseases?

Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels and they include:

- coronary heart disease – disease of the blood vessels supplying the heart muscle;
- cerebrovascular disease – disease of the blood vessels supplying the brain;
- peripheral arterial disease – disease of blood vessels supplying the arms and legs;
- rheumatic heart disease – damage to the heart muscle and heart valves from rheumatic fever, caused by streptococcal bacteria;
- congenital heart disease – malformations of heart structure existing at birth;
- deep vein thrombosis and pulmonary embolism – blood clots in the leg veins, which can dislodge and move to the heart and lungs.¹

Burden of disease

CVD is the number one cause of death globally.¹ Influenza is one of the leading infectious diseases to cause death globally.

People with Cardiovascular Disease are at high risk of developing serious complications from the flu.

During 2009 (H1N1) pandemic, patients with more severe influenza including viral pneumonia were more likely to have underlying cardiac disease. Cardiac disease was also identified as a leading risk factor for ICU admission and death from influenza, with a RR of 8 for severe disease in India.²

Chronic illness, including immunosuppression, cardiovascular disease, chronic lung disease, neuromuscular disease, neurological disease, chronic renal disease, and metabolic diseases increased the risk of mortality from influenza.³

¹ WHO Cardiovascular Diseases Fact Sheet Last updated May 2017 Accessed 27th July 2017

² Fischer WA 2nd et al Global burden of influenza as a cause of cardiopulmonary morbidity and mortality Glob Heart 2014 Sep;9(3):325-36

³ Mertz D Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ. 2013 Aug 23;347:f5061.

Burden may be underestimated

The already substantial global mortality burden of influenza is likely underestimated due to unrecognized cardiopulmonary complications in influenza-infected individuals worldwide.

Given that confirmatory testing is often not performed, the total burden of influenza on annual cardiopulmonary (respiratory and cardiac) hospitalizations is likely even higher.

Influenza as a trigger for Acute Myocardial Infarction (AMI)

There is increasing evidence that influenza is associated with acute myocardial infarction (AMI)

Acute MI shows a seasonal variation, having its highest incidence in the winter months. Influenza activity has been suggested as a reason for this winter peak in the MI rate.⁴

Proposed mechanism of influenza virus triggering cardiovascular events

Influenza epidemics are associated with a significant increase in cardiovascular deaths.

This can occur by direct effect of the influenza virus on the myocardium or through the aggravation of existing cardiovascular disease. The virus may cause inflammation of the myocardium which may be asymptomatic or so severe that it causes cardiogenic shock and death.⁵

Influenza causes acute arterial-wall inflammation and may trigger plaque destabilization that leads to acute coronary syndrome.⁶

Influenza may cause an increase in:

- proinflammatory, prothrombotic cytokines
- endothelial dysfunction
- plasma viscosity
- tachycardia
- release of endogenous catecholamines
- psychological distress
- dehydration leading to hypotension and decreased oxygen in the blood which could cause cardiac arrest (2)

Who is most affected?

Influenza exerts an even greater toll in low income, resource-constrained environments where it is the cause of 5% to 27% of all severe acute respiratory infections. The likely reasons for the increased burden in this group are: higher rates of comorbidities, such as immunodeficiency virus, decreased access to healthcare infrastructure, including oxygen therapy or critical care support.⁷

⁴ Madjid M, Miller CC, Zarubaev VV, Marinich IG, Kiselev OI, Lobzin YV, Filippov AE, Casscells SW., 3rd Influenza epidemics and acute respiratory disease activity are associated with a surge in autopsy-confirmed coronary heart disease death: results from 8 years of autopsies in 34,892 subjects. *European heart journal*. 2007;28(10):1205–1210

⁵ Estabragh ZR, Mamas MA The cardiovascular manifestations of influenza: a systematic review *Int J Cardiol* 2013 Sep 10;167(6):2397-403

⁶ Madjid M et al Influenza and cardiovascular disease *Tex Heart Instit J* 2004; 31(1): 4–13.

⁷ Fischer WA 2nd et al Global burden of influenza as a cause of cardiopulmonary morbidity and mortality *Glob Heart* 2014 Sep;9(3):325-36

Benefits of influenza vaccine

Cardio-protective mechanism of influenza vaccine

The bradykinin 2 receptor (BKB2R) was identified as a principal host protein which could mediate molecular processes underlying the cardioprotective effect of influenza vaccines.⁸

Epidemiological studies have demonstrated an association between influenza epidemics and cardiovascular mortality and a decrease in cardiovascular mortality in high risk patients has been demonstrated following vaccination with influenza vaccine.⁹

Meta-analysis by Cochrane of eight RCTs with 12,029 participants

Overall, studies in people with heart disease suggest that flu vaccination may reduce death as a result of cardiovascular disease and may reduce combined cardiovascular disease events (such as heart attacks, strokes, necessity for bypass operations, etc.). However, these studies were small and had some risk of bias, so larger studies of better quality are needed to confirm the results.¹⁰

Who benefits most from influenza vaccination?

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.¹¹ A large, adequately powered, multicenter trial is warranted to address these findings and assess individual cardiovascular end points.

Potential benefits of influenza vaccination preventing cardiovascular events and death in people with type 2 diabetes

A large, 7-year cohort study from the United Kingdom found that type 2 diabetes patients who were vaccinated had a 30% lower risk of hospitalization for stroke, a 22% lower risk for heart failure, and a 15% lower risk for pneumonia or flu, compared with their unvaccinated counterparts. Also, the vaccinated patients had a 24% lower risk of death from any cause during the flu season. Influenza vaccination was associated with lower rates of admission to hospital for acute MI, but this association was not statistically significant.¹²

Observational studies have shown the protective effectiveness of influenza vaccine against AMI is between 19% and 45%.

Data from the United Kingdom General Practice Database showed that influenza vaccination was associated with a **19%** reduction in acute myocardial infarction.¹³ A systematic review of 16 case-control studies found that influenza vaccination was associated with a reduction in AMI with an estimated **29%** effectiveness

⁸ Veljkovic V. et al. Influenza vaccine as prevention for cardiovascular diseases: Possible molecular mechanism. *Vaccine*. 2014 Jul 19. pii: S0264-410X (14)00933-5

⁹ Mamas MA et al Cardiovascular manifestations associated with influenza virus infection *Int J Cardiol* 2008 Nov 28;130(3):304-9.

¹⁰ Clar C et al *Cochrane Database Syst Review* 2015 May 5;(5):CD005050

¹¹ Udell JA et al Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. *JAMA* 2013 Oct 23;310(16):1711-20.

¹² Vamos EP, Pape UJ et al Effectiveness of influenza vaccine in preventing admission to hospital and death in people with type 2 diabetes *CMAJ*. 2016 Oct 4;188(14):E342-E351

¹³ Siritwadana AN et al Influenza vaccination, pneumococcal vaccination and risk of acute myocardial infarction: matched case-control study *CMAJ October 19, 2010 vol. 182 no. 15*

against AMI. This was on a par with or better than accepted AMI preventive measures, with the estimates of the efficacy of statins for secondary prevention of 36%, antihypertensives of 15%–18% and smoking cessation interventions of 26%.¹⁴

A case-control study from a tertiary referral hospital in Sydney, Australia with 559 participants with inpatients with AMI or controls were outpatients without AMI. Influenza vaccination was significantly protective with a vaccine effectiveness of **45%** against AMI.¹⁵

Less favourable results

Data was obtained from two cohort studies, OPTIC registry, AMISTAD study and PERFORM trial in patients who had experienced a recent ischaemic stroke or TIA. The findings were that there was no reduction in cardiovascular events as a result of influenza vaccination.¹⁶

Barriers to obtaining data that is unbiased

Observational studies are subject to methodological biases, with case–control studies being prone to biases from participant selection and measurement of exposure. Observational studies are the only ethical study type to measure the association between influenza infection and AMI, with the majority of published studies being of case–control design.

Although initial analyses suggest that influenza vaccination was associated with reduced risk of major adverse vascular events during influenza seasons when the influenza vaccine matched the circulating virus, sensitivity analyses revealed that risk of bias remained. A randomized trial is needed to definitively address this question.¹⁷

Currently published RCTs are limited to recurrent events in high-risk patients, have heterogeneous outcome measures and are performed in low-income and middle-income countries without established influenza vaccination recommendations. Well-conducted and powered studies are needed.

Area of further investigation

Optimal effectiveness from influenza vaccination relies upon intact immune responses, which may be compromised in those with cardiovascular conditions. In a small (28 patients) single-centre, double-blind, pilot RCT, antibody responses in patients with ischemic and non-ischemic HF were augmented using a higher dose of influenza vaccine.¹⁸ This is a strategy which may offer hope in the future for older adults and those with chronic underlying conditions.

¹⁴ Barnes M et al Acute myocardial infarction and influenza: a meta-analysis of case-control studies *Heart* 2015 Nov;101(21):1738–47.

¹⁵ Macintyre CR Ischaemic heart disease, influenza and influenza vaccination: a prospective case control study. *Heart*. 2013 Dec;99(24):1843–8.

¹⁶ Lavallée PC et al Influenza vaccination and cardiovascular risk in patients with recent TIA and stroke. *Neurology*. 2014 May 27;82(21):1905–13.

¹⁷ Johnstone J et al Influenza vaccination and major adverse vascular events in high-risk patients. *Circulation*. 2012 Jul 17;126(3):278–86.

¹⁸ Udell JA Does influenza vaccination influence cardiovascular complications? *Expert Rev Cardiovasc Ther*. 2015 Jun;13(6):593–6.

Recommendation by World Health Organization (WHO)

WHO recommends annual influenza for people with specific chronic medical conditions including those with Cardiovascular Disease.

