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## Acute myocardial infarction triggered by influenza: Role of vaccine in its prevention

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## Acute myocardial infarction triggered by influenza: Role of vaccine in its prevention

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# Acute myocardial infarction triggered by influenza: Role of vaccine in its prevention

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## Abstract

Influenza is a major cause of hospitalization in all age groups. Cardiovascular complications due to influenza are important causes of morbidity and mortality in the US, especially in the elderly population (aged more than 65 years). Acute Myocardial Infarction (AMI) is the most serious among the cardiovascular causes of mortality following the attack of influenza, mainly in patients with various co-morbidities like pre-existing coronary artery disease (CAD), diabetes mellitus (DM), hypertension (HTN) and heart failure (HF). We have reviewed the association between influenza virus infection and AMI and extrapolated the beneficial effects of influenza vaccine in preventing AMI and its grave consequences.

**Key words:** Acute myocardial infarction, influenza, influenza vaccine

## Introduction

Influenza complications are important causes of morbidity and mortality in many parts of the world, especially in the elderly population (aged > 65 years). This seems to be on an increasing trend with the increase in life expectancy in the aging population<sup>1</sup>. Acute Myocardial Infarction (AMI) is the leading cardiovascular complication of influenza virus infection more importantly in the elderly and the high-risk individuals<sup>2-4</sup>. According to the data from CDC-Influenza Hospitalization Surveillance

Network, there were 30,453 laboratory-confirmed influenza-related hospitalizations between October 2017 and April 2018. The majority (58%) of influenza-associated hospitalizations were in the elderly age group<sup>5</sup>. Younger patients (age < 65 years) were at risk of influenza-related complications only in the setting of high-risk factors such as immune-compromised states, coronary artery disease (CAD), heart failure (HF) exacerbations, hypertension (HTN) and diabetes mellitus (DM)<sup>6</sup>. The purpose of this article is to provide an updated review on the potential of influenza virus infection as a trigger for AMI and the role of vaccination in the prevention of AMI associated hospitalization and mortality and also to highlight the key areas where further research is warranted.

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## Materials and methods

### Data extraction

We searched Medline and Embase using relevant Medical Subject Headings (MeSH) termed influenza or influenza virus or flu or flu vaccine and myocardial infarction or acute myocardial infarction or STEMI/ACS or heart attack literature published within the last five years with additional filters of human studies and customized articles. The titles and abstracts of all results were reviewed and studies

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were selected for full-text analysis according to their eligibility criteria.

### Eligibility criteria

We included human studies on AMI and influenza or influenza vaccination in adults (age more than or equal to 18 years) for full-text analysis. We excluded review articles and case reports.

### Outcomes of interest

The primary outcome was AMI triggered by influenza, including AMI hospitalizations and mortalities. The role of vaccination in the prevention of the above concomitances was examined in the secondary outcome analysis.

### Quality assessment and data extraction

Authors NBs and SS independently performed the study selection, data extraction and quality assessment.

### Study characteristics

The search using the appropriate MeSH terms yielded 1405 articles out of which 112 were relevant and fulfilled our eligibility criteria. From these, we excluded 99 articles and included only 13 for the discussion according to the homogeneity of these studies with ours (Flow chart depicted below). We

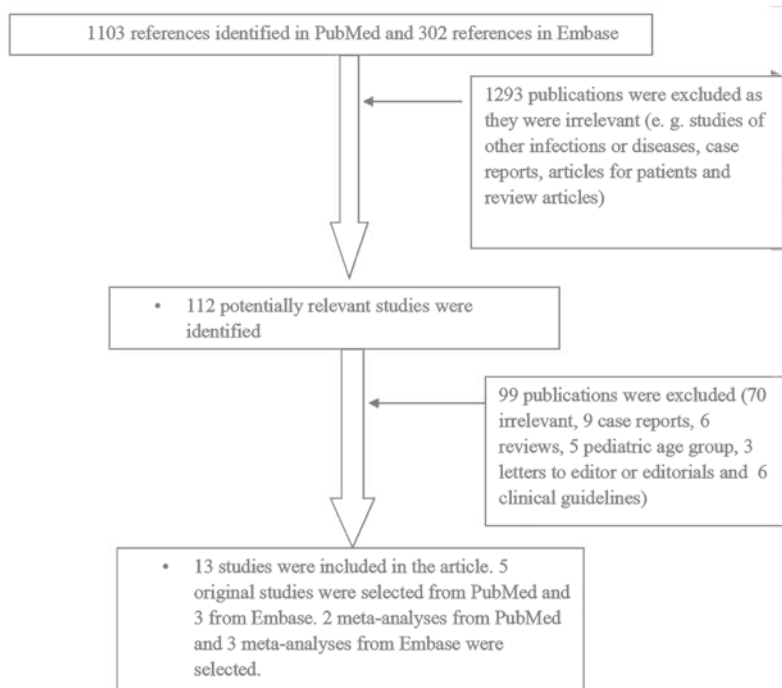
included data from CDC and other important studies for the references. We also included high-quality meta-analysis for the discussion regarding the role of influenza vaccination in the prevention of AMI associated hospitalization and death.

### Discussion

#### *Prevalence of influenza triggered AMI*

Influenza is a trigger for AMI and ischemic heart disease (IHD) particularly in the elderly population<sup>4, 7-9</sup>. Warren-Gash *et al*<sup>10</sup>. performed a multicentre prospective time series study in England, Wales and Hong Kong and found that influenza was associated with increased AMI related hospitalization and death, suggesting this infection as an independent risk factor for AMI<sup>10</sup>. This is further supported by an observational study by Song *et al*. who too reported that elderly patients suffering from influenza and having other comorbidities such as DM, HF, pre-existing CAD and HTN had higher in-hospital cardiac mortality (fatal cardiac arrest and ventricular arrhythmias) as compared to patients without these risk factors<sup>11</sup>.

A similar association between infection due to influenza virus and AMI was documented by Pearce *et al*.<sup>8</sup> and Kwong *et al*.<sup>4</sup>. Kwong *et al*. further



substantiated that the influenza virus was a stronger risk factor for the development of AMI than any other virus causing acute respiratory tract infection<sup>4</sup>. A time series study by Nguyen et al. found that there was a significant increase in all cause cardiovascular mortality and AMI mortality during the influenza outbreak<sup>12</sup>.

Guan and colleagues in the recent past stated that cases of AMI were more likely to have positive IgG antibodies to influenza virus A and B as compared to controls; an observation which supported the hypothesis that previous influenza virus infection had a role to play in the development of atherosclerosis, eventually triggering the occurrence of AMI<sup>13</sup>.

#### *Pathogenesis of post-influenza AMI*

The precise mechanism for the development of AMI following influenza virus infection is unclear. However, Naghavi et al. proposed that the virus promoted atherosclerotic plaque formation by inducing inflammation, smooth muscle cell proliferation and fibrin deposition. Histological analysis from the aortic sections of apolipoprotein E-deficient mice injected with influenza A virus

showed marked proliferation of intimal epithelial cells along with smooth muscle cells of tunica media, which were filled with macrophages and T lymphocytes, quite suggestive of atherosclerosis<sup>14</sup>.

Notwithstanding the above, the exact link between the formation of atherosclerotic plaque and influenza infection has not been clearly delineated. MacIntyre et al. recently proposed that influenza potentiated the release of inflammatory cytokines which could give rise to a prothrombotic state<sup>15</sup>. Further, influenza might have a direct effect on the heart, producing local inflammatory changes, as evidenced by histopathological and molecular studies on influenza-infected mice<sup>16</sup>. Thus, a series of studies conducted in the recent past, at various centres supported the above-mentioned hypothesis and these data have been presented vide Table 1.

Further studies are, however, needed to shed light on this fascinating aspect of the pathogenesis of AMI happening as a sequel of infection due to influenza virus.

**Table 1: Summary of reports depicting the role of influenza as a trigger for AMI**

Study	Study design	Outcome	Exposure	Result (95% CI)
Kwong et al. [4] 2018	Self-controlled case-series design	AMI	Influenza A Influenza B	IR= 10.11 (4.37-23.38) IR= 5.17 (3.02-8.84)
Warren-Gash et al. 2012 [17]	Self-controlled case-series design	AMI	Influenza-like illness (ILI) General acute respiratory infection (ARI)	IR= 7.31 ( 2.72-19.64) p=0.26 IR= 4.19 ( 3.18-5.53)
Schwartz et al. [18]	Time series and multivariate regression model	Mortality due to AMI	Influenza	p< 0.001 p<0.002
Warren-Gash et al. 2011 [10]	Time series	AMI associated mortality AMI associated hospitalizations	Seasonal influenza Seasonal influenza	3.1%-3.4% of 410, 204 MI-associated deaths (P < .001) 0.7%-1.2% of ≥1.2 million MI-associated hospitalizations (P < .001)
Foster et al. [3] 2013	Time series	AMI	Seasonal influenza and 2009 pandemic influenza	AMI AR not significant for person's age less than 65 years AMI AR of 0.5% for those persons over 65 years of age, AMI AR of 0.85% for those persons over 80 years
Guan et al. [13] 2008	Case-control studies comparing presence of antibodies to influenza A and B among patients with AMI (Cases) vs those without AMI (Controls)	Presence of IgG antibodies of influenza	AMI	Compared to controls presence of IgG to : Influenza-A in cases: Odds ratio (OR), 3.3; (95%CI), 1.5 to 7.4 Influenza-B in cases: Odds ratio (OR), 17.2; (95%CI), 7.7 to 38.0

IR: Incidence Ratio CAD: Coronary Artery Disease  
AR: Attributable Risk

*Can influenza vaccination prevent AMI and its complications?*

The proposed solution to prevent the AMI hospitalizations and mortality following an attack of influenza is prompt administration of influenza vaccine. Huang et al. conducted a cohort study and showed a significant reduction in the risk of ischemic heart disease in elderly patients receiving influenza vaccine<sup>19</sup>. A systematic review by Clar et al. also showed that AMI was significantly reduced after influenza vaccination<sup>20</sup>. In a prospective randomized open-ended study by Phrommintikul et al., influenza vaccination was shown to decrease major cardiovascular hospitalizations due to AMI. However, no significant difference was found in the incidence of cardiovascular deaths among vaccine recipient and non-recipient groups<sup>21</sup>. This is further supported in a meta-analysis by Udell et al., who reported that 42 of 3238 high risk patients (1.3%) died of cardiovascular cause within one year of being treated with influenza vaccine compared with 55 of 3231 high risk patients (1.7%) treated with placebo (RR, 0.81 [95% CI, 0.36-1.83];  $P = .61$ ;  $I^2 = 68\%$ ). As the difference is statistically non-significant, further studies are warranted to prove the benefit of influenza vaccine in the prevention of cardiovascular mortality, especially in high-risk patients with previous acute coronary syndrome<sup>22</sup>. However, vaccine, by preventing influenza and its associated hospitalizations, in a way could prevent the possibility of AMI triggered by the mechanisms discussed above and also might prevent the associated AMI related mortality.

In the light of the aforementioned ambiguity on the effect of administration of influenza vaccine on the prevention of AMI and its clinical outcome, it could, thus, be advocated that further randomized control trials would be needed to provide strong evidences supporting the beneficial role of vaccination against influenza in the prevention of cardiovascular mortality. Consistent with the above, a major multicentre prospective randomized control trial entitled, 'Influenza Vaccination after Myocardial Infarction (IAMI Trial) NCT02831608',

based on the Swedish Angiography and Angioplasty Registry (SCAAR) platform is ongoing to give us the insight on in-hospital influenza vaccination and cardiovascular outcomes in patients with AMI<sup>23</sup>.

### Conclusions

Many studies in the past put forth the view that influenza virus infection was a trigger for AMI<sup>24</sup>. Though the role of influenza virus in the initiation of AMI was proven by a number of investigations and the risk for AMI was found to be higher with infection due to influenza virus as compared to those due to other respiratory viruses<sup>4</sup>, yet data exhibiting concrete evidences in favour of the causal role of the influenza virus in giving rise to AMI are still lacking. Influenza vaccination could play a protective role in the occurrence of influenza-associated hospitalization and mortality due to AMI. Hence, vaccination should be encouraged to prevent cardiovascular complications and mortality especially among high-risk and elderly patients<sup>20-25</sup>.

### References

1. Thompson WW, Shay DK, Weintraub E, et al. Influenza-associated hospitalizations in the united states. *JAMA*. 2004;292(11):1333-40.
2. Ludwig A, Lucero-Obusan C, Schirmer P, Winston C, Holodniy M. Acute cardiac injury events  $\leq 30$  days after laboratory-confirmed influenza virus infection among U.S. veterans, 2010-2012. *BMC cardiovascular disorders*. 2015;15:109.
3. Foster ED, Cavanaugh JE, Haynes WG, et al. Acute Myocardial Infarctions, Strokes and Influenza: Seasonal and Pandemic Effects. *Epidemiology and infection*. 2013;141(4):735-44.
4. Kwong JC, Schwartz KL, Campitelli MA, et al. Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection. *The New England journal of medicine*. 2018;378(4):345-53.
5. CDC. Summary of the 2017-2018 Influenza Season CDC: CDC; 2018 [updated november 2, 2018. Available from: <https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm>
6. Mauskopf J, Klesse M, Lee S, Herrera-Taracena G. The burden of influenza complications in different high-risk groups: a targeted literature

- review. *Journal of Medical Economics*. 2013;16(2):264-77.
7. Warren-Gash C, Smeeth L, Hayward AC. Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review. *The Lancet Infectious Diseases*. 2009;9(10):601-10.
  8. Pearce DC, McCaw JM, McVernon J, Mathews JD. Influenza as a trigger for cardiovascular disease: An investigation of serotype, subtype and geographic location. *Environmental research*. 2017;156:688-96.
  9. Lichenstein R, Magder LS, King RE, King JC, Jr. The relationship between influenza outbreaks and acute ischemic heart disease in Maryland residents over a 7-year period. *The Journal of infectious diseases*. 2012;206(6):821-7.
  10. Warren-Gash C, Bhaskaran K, Hayward A, et al. Circulating influenza virus, climatic factors, and acute myocardial infarction: a time series study in England and Wales and Hong Kong. *The Journal of infectious diseases*. 2011;203(12):1710-8.
  11. Song BG, Wi YM, Lee YJ, Hong CK, Chun WJ, Oh JH. Clinical features in adult patients with in-hospital cardiovascular events with confirmed 2009 Influenza A (H1N1) virus infection: comparison with those without in-hospital cardiovascular events. *Journal of the Chinese Medical Association : JCMSA*. 2012;75(9):435-41.
  12. Nguyen JL, Yang W, Ito K, Matte TD, Shaman J, Kinney PL. Seasonal influenza infections and cardiovascular disease mortality. *JAMA cardiology*. 2016;1(3):274-81.
  13. Guan XR, Li X, Xin XM, et al. Influenza virus infection and risk of acute myocardial infarction. *Inflammation*. 2008;31(4):266-72.
  14. Naghavi M, Wyde P, Litovsky S, et al. Influenza infection exerts prominent inflammatory and thrombotic effects on the atherosclerotic plaques of apolipoprotein E-deficient mice. *Circulation*. 2003;107(5):762-8.
  15. MacIntyre CR, Mahimbo A, Moa AM, Barnes M. Influenza vaccine as a coronary intervention for prevention of myocardial infarction. *Heart*. 2016;102(24):1953.
  16. Fislová T, Gocník M, Sládková T, et al. Multiorgan distribution of human influenza A virus strains observed in a mouse model. *Archives of Virology*. 2009;154(3):409-19.
  17. Warren-Gash C, Hayward AC, Hemingway H, et al. Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study. *The Journal of infectious diseases*. 2012;206(11):1652-9.
  18. Schwartz BG, Qualls C, Kloner RA, Laskey WK. Relation of Total and Cardiovascular Death Rates to Climate System, Temperature, Barometric Pressure, and Respiratory Infection. *The American journal of cardiology*. 2015;116(8):1290-7.
  19. Huang CL, Nguyen PA, Kuo PL, Iqbal U, Hsu YH, Jian WS. Influenza vaccination and reduction in risk of ischemic heart disease among chronic obstructive pulmonary elderly. *Computer methods and programs in biomedicine*. 2013;111(2):507-11.
  20. Clar C, Oseni Z, Flowers N, Keshtkar-Jahromi M, Rees K. Influenza vaccines for preventing cardiovascular disease. *The Cochrane database of systematic reviews*. 2015(5):Cd005050.
  21. Phrommintikul A, Kuanprasert S, Wongcharoen W, Kanjanavanit R, Chaiwarith R, Sukonthasarn A. Influenza vaccination reduces cardiovascular events in patients with acute coronary syndrome. *European heart journal*. 2011;32(14):1730-5.
  22. Udell JA, Zawi R, Bhatt DL, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: A meta-analysis. *JAMA - Journal of the American Medical Association*. 2013;310(16):1711-20.
  23. Frobert O, Gotberg M, Angeras O, Jonasson L, Erlinge D, Engstrom T, et al. Design and rationale for the Influenza vaccination After Myocardial Infarction (IAMI) trial. A registry-based randomized clinical trial. *American heart journal*. 2017;189:94-102.
  24. Estabragh ZR, Mamas MA. The cardiovascular manifestations of influenza: a systematic review. *International journal of cardiology*. 2013;167(6):2397-403.
  25. Caldeira D, Costa J, Vaz-Carneiro A. Analysis of the cochrane review: Influenza vaccines for preventing cardiovascular disease. *Cochrane database syst rev*. 2015;5:Cd005050. *Acta Medica Portuguesa*. 2015;28(4):424-6.