Benefits of Influenza Vaccination in Patients with Cardiovascular Disease

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ABSTRACT

Influenza remains a significant global health problem. The risks of complications and death from influenza are greater in comorbid groups, such as those suffering from cardiovascular diseases. The true economic and social costs of influenza are far greater in these groups compared to healthy ones, as these groups are vulnerable to complications and even death. Cardiovascular disease is the leading cause of death, both globally and in Indonesia. The relationship between cardiovascular events and seasonal influenza has been established. The objective is to outline the impacts of influenza and the benefits of the influenza vaccine in groups with cardiovascular disease. Influenza vaccination is one of the prevention methods that has proven effective in preventing influenza infection and reducing the risk of major cardiovascular events. In addition to being effective, influenza vaccination is also safe and well-tolerated by adults and the elderly.

Keywords*: influenza, vaccine, cardiovascular diseases.*

INTRODUCTION

Influenza remains a significant global health problem. 1 billion people experience influenza infection each year, with 3-5 million people experiencing severe infection and 290,000-650,000 dying from the infection. [1] The risks of complications and death from influenza are greater in comorbid groups, such as those suffering from cardiovascular diseases. That being said, the impacts of influenza are still under-recognized. The public generally perceives influenza as just a common respiratory infection that resolves within a few days with mild symptoms. However, the true economic and social costs of influenza are far greater than this perception. The impacts are particularly felt among older patients and patients with comorbidities, such as heart disease, diabetes, asthma, stroke, COPD, and other chronic diseases.[2] Influenza infection in the older population, especially the older adults with comorbidities, has an increased risk of hospitalization of 3-7 times.[3] This population is also vulnerable to serious complications and even death. One of the most effective ways to prevent influenza complications is through vaccination. This review focuses on discussing the benefits of influenza vaccination in comorbid groups, particularly patients with heart disease.

INFLUENZA VIRUS

Influenza viruses are single-stranded, helical RNA viruses from the Orthomyxoviridae family. There are four types of influenza virus: A, B, C, and D. Influenza A causes moderate to severe disease and affects all age groups. In addition to causing disease in humans, influenza A also causes disease in animals, such as pigs and birds. Influenza B generally causes milder disease than type A and primarily affects children. It is also more stable than influenza A, with less antigenic drift and relatively stable immunity. Influenza B only infects humans. Meanwhile, the influenza C and D viruses are rarely reported as causing disease in humans, possibly because most cases are subclinical. They have also never been associated with disease epidemics.[4,5] Antigenic changes in hemagglutinin and neuraminidase in influenza A occur periodically. An antigenic shift is a major change that occurs in one or both of influenza A's surface antigens (H and/or N), resulting in a new viral subtype. This is caused by genetic recombination (exchange of gene segments) between influenza A viruses. Antigenic shift can cause a global pandemic if the new virus is transmitted efficiently from human to human. On the other hand, antigenic drift is a minor change in the surface antigen that can happen in all types of influenza viruses (less common in influenza C and D) and is caused by a point mutation in a gene segment, resulting in amino acid substitution. Antigenic drift produces a new subtype that is partially different from the previous subtype, and, depending on the mutation, this new subtype may still be partially recognized by the host immune system.[4,5] Influenza is easily transmitted through airborne aerosol and droplets, resulting from direct contact with an infectious person. Transmission occurs 1-2 days before symptoms appear, which last for 5-7 days. There is no carrier state. After transmission from the respiratory tract, the virus attaches to and penetrates the respiratory epithelial cells in the trachea and bronchi. Here, viral replication occurs, leading to the destruction of host cells. The virus persists in respiratory secretion for 5-10 days.[5]

The incubation period is generally 2 days, but can vary between 1 and 4 days. The severity of influenza depends on the virulence of the virus and previous immunological experience with the variant. In general, only about 50% of infected individuals will develop classic influenza symptoms. Classic influenza symptoms are characterized by sudden high fever (38-40°C), non-productive cough, sore throat, headache, and muscle pain, especially in the back muscles. Additional symptoms may include rhinorrhea, dizziness, substernal chest pain, and ocular symptoms (such as eye pain and sensitivity to light). Many people wrongly assume that any cough, runny nose, or fever is influenza. In fact, sudden fever of 38°C and cough lasting up to 10 days is more likely to be an influenza-like illness (ILI) because only about 20% of cases with these symptoms are caused by influenza viruses. Other causes include respiratory syncytial virus (RSV), rhinovirus, parainfluenza, and adenovirus.[4,5]

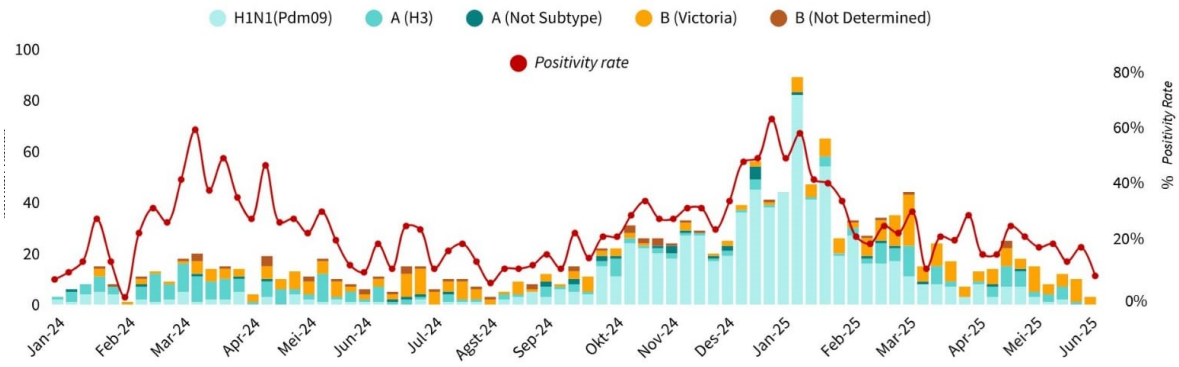

Figure 1. Indonesian surveillance for Influenza-Like Illness (ILI) and Severe Acute Respiratory Infections (SARI) found that influenza viruses, both A and B, spread throughout the year. Positive rates varied from month to month, reaching up to 80% in the samples. This finding confirms that influenza remains a significant health problem, especially in Indonesia.[35]

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INFLUENZA VACCINE

Composition

New influenza vaccines are produced annually due to the rapid antigenic changes that influenza viruses undergo. The vaccine antigens for the influenza virus types circulating in February for the next influenza season in the Northern Hemisphere are determined by the WHO. A similar process follows for the Southern Hemisphere, which begins in October. For the 2024-2025 Northern Hemisphere influenza season, the egg-based influenza vaccine contained hemagglutinins (HA) derived from: 1) Influenza A/Victoria/4897/2022 (H1N1) pdm09-like viruses; 2) Influenza A/Thailand/8/2022 (H3N2)-like viruses; and 3) Influenza B/Austria/1359417/2021-like viruses (B/Victoria lineage). For the 2024-25 Northern Hemisphere influenza season, cell culture-based inactivated and recombinant influenza vaccines contained HA derived from: 1) Influenza A/Wisconsin/67/2022 (H1N1) pdm09-like viruses; 2) A/Massachusetts/18/2022 (H3N2-like viruses); and 3) Influenza B/Austria/1359417/2021-like viruses (B/Victoria lineage).[6]

Vaccine types

WHO issues recommendations in February and September each year regarding the types of viruses to be included in vaccines for the Northern and Southern Hemispheres. In Indonesia, vaccination is carried out throughout the year using the influenza vaccine available at the time. Meanwhile, for travelers, vaccines are adjusted according to the destination. The types of influenza vaccines are divided into live attenuated influenza vaccines (LAIV), inactivated influenza vaccines (IIV), and recombinant influenza vaccines (RIV), and their use is adjusted by age group. Influenza vaccines can be further categorized into two types based on the type of strain contained: 1) Trivalent inactivated influenza vaccine (IIV3) which protects against two influenza A subtypes (A/H1N1 and A/H3N2) and one influenza B subtype (B/Victoria or B/Yamagata), and 2) Quadrivalent Inactivated Influenza Vaccine (IIV4) which protects against two influenza A subtypes (A/H1N1 and A/H3N2) and two influenza B subtypes (B/Victoria and B/Yamagata). The quadrivalent influenza vaccine provides greater protection compared to the trivalent influenza vaccine, because it covers two influenza B subtypes (B/Victoria and B/Yamagata) that co-circulate in the community.[6]

Trivalent and Quadrivalent Vaccines

The trivalent influenza vaccine is a synthetic vaccine containing three activated influenza viruses: two different influenza A subtypes and one influenza B subtype. The trivalent influenza vaccine is formulated annually based on the influenza subtypes projected to be dominant in the upcoming flu season. The quadrivalent influenza vaccine includes four different influenza virus types. This vaccine contains two different influenza A subtypes and two different influenza B subtypes. The primary advantage of the quadrivalent influenza vaccine is its ability to protect against a wider range of circulating influenza viruses. By including two influenza B subtypes, the vaccine can provide broader protection against the variety of viruses that may emerge during the flu season.[6]

RISK OF INFLUENZA IN THE CARDIOVASCULAR DISEASES POPULATION

Total prevalent cases of cardiovascular diseases principally ischemic heart disease and stroke nearly doubled from 271 million in 1990 to 523 million in 2019, while the number of cardiovascular deaths steadily increased from 12.1 million in 1990 to 18.6 million in 2019.[2] The relationship between cardiovascular events and seasonal influenza was established by observing the timing of increases in cardiovascular events, which were observed to occur concurrently or immediately after an influenza epidemic. The increase in cardiovascular mortality during

winter coincides with the peak of circulation of influenza viruses, and this association appears to be more prevalent in older adults.[29]

A study conducted by Gash et al. found that the incidence ratio (IR) of myocardial infarction within 1-3 days after influenza infection increased 9.8-fold (95% CI 2.37-40.5), while the IR of other viral infections, such as human metapneumovirus, rhinovirus, and respiratory syncytial virus, increased 2.81-fold (95% CI 0.39-20.3). The IR of stroke after influenza infection within 1-3 days reached 7.82 times (95% CI 1.07-56.9), and 4.86 times for other viral infections (95% CI 0.67-35.4).[7] Another study found increased risk of acute myocardial infarction and stroke within 1 week after influenza infection, increasing 6-10-fold for myocardial infarction and 3-8-fold for stroke within several weeks after influenza infection.[8,9]

In a study of 1.9 million hospitalized patients with acute myocardial infarction, patients with myocardial infarction and influenza had worse outcomes compared to those with myocardial infarction alone in terms of mortality during hospitalization and development of respiratory failure and acute kidney injury.[10] Another study found that influenza infection was associated with 4% of hospitalized patients with myocardial infarction aged >75 years. In the United States, the annual influenza-related mortality rate is estimated at 3.82 (95% CI 3.21-4.44) per 100,000 in the cardiovascular disease population.[11] Another study reported a strong association between influenza infection and increased atherothrombotic events in subjects aged ≥50 years in Spain. The risk of acute cardiovascular events doubled within 14 days after mild influenza infection in patients with fewer comorbidities but more than quadrupled after severe infection in more vulnerable patients with greater comorbidities. In these patients, the risk continued to double in the 2 months after infection.[25]

A study conducted by Aimee et al. found that older influenza patients with comorbidities, such as congestive heart disease and coronary artery disease, had a 3-7 times higher risk of hospitalization within 30 days after influenza infection compared to patients without influenza, with a ratio of 34.6% vs. 7.9% for congestive heart disease and 22.8% vs. 3.8% for coronary artery disease.[3] Another study conducted in Canada among the congenital heart disease population found a higher risk of cardiovascular complications, such as heart failure and myocardial infarction, within 9 months of hospitalization for influenza.[27] A meta-analysis study by Barnes et al. found a significant association between influenza infection and acute myocardial infarction. In this study, influenza infection and influenza-like illness were associated with an increased risk of acute myocardial infarction with an OR of 2.01 (95%CI 1.47-2.76).[28]

Several mechanisms have been proposed to explain the link between influenza infection and cardiovascular events. First, through plaque destabilization (*directly vascular*), influenza virus replication occurs in the arteries and can have a direct inflammatory effect on atherosclerotic plaque, leading to plaque accumulation and instability, ultimately increasing the risk of myocardial infarction, myocardial injury, and cardiac dysfunction. The second mechanism is through myocardial inflammation/infection (*direct myocardial*). Animal models have shown that the influenza virus can enter myocardial tissue, replicate, and cause myocardial inflammation and cardiac dysfunction. Finally, through systemic response, influenza infection can cause hypoxemia, hypercoagulability, increased myocardial oxygen demand, coronary vasoconstriction, and hypotension. In this mechanism, when influenza infection occurs, several inflammatory pathways are activated, leading to a systemic reaction. This can lead to myocardial hypoxia, which can then lead to type 1 and 2 myocardial infarction and exacerbation of heart failure.[12]

BENEFITS OF INFLUENZA VACCINATION IN PATIENTS WITH CARDIOVASCULAR DISEASE

A retrospective cohort study from Denmark concluded that influenza vaccination reduces the risk of death from cardiac or other causes, especially if the vaccine is given to patients with newly diagnosed heart failure.[13] MacIntyre

et al. observed that influenza vaccination has benefits equivalent to antihypertensive treatment or the cessation of smoking. This indicates that influenza vaccination plays an important role in the management and prevention of cardiovascular disease.[14] Another study in the UK found that influenza vaccination has a positive effect on heart failure and reduces the risk of hospitalization as a result of heart disease (95% CI: 0.71-0.76).[15] A meta-analysis of five randomized trials concluded that there was a reduction in cardiovascular disease events in vaccinated subjects compared with controls (RR 0.64, 95% CI: 0.48-0.86).[16]

Loeb et al. conducted a study involving 5,129 participants, and in this study, the influenza vaccine reduced hospitalization rates by 16% and the rate of community-acquired pneumonia by 42% in patients with heart failure. During the peak influenza season observed, all-cause mortality and deaths from cardiovascular events and pneumonia were also significantly reduced in the vaccine group compared to the placebo group.[17] Frobert et al. found that patients with myocardial infarction who received the influenza vaccine immediately after the infarction experienced reduced risk of death, recurrent myocardial infarction, and stent thrombosis, as well as reduced risk of cardiovascular death and all-cause death within 12 months compared to the placebo group. The incidence of all cause death was 2.9% compared to 4.5% for the placebo group with a hazard ratio of (HR) 0.59 (95% CI 0.39-0.89, p=0.010), death due to cardiovascular events was 2.7% vs 4.5% with a HR of 0.59 (95% CI 0.39-0.90 p=0.014) and the incidence of myocardial infarction was 2.0% vs 2.4% with a HR of 0.86 (CI 95% 0.50-1.46, p=0.57).[18]

A meta-analysis study conducted by Omidi et al found that a reduction in major cardiovascular events was seen in vaccinated subjects, compared to placebo subjects, with a relative risk (RR) of 0.70 (95% CI 0.55-0.91). Stratified analysis found reduced risk of myocardial infarction in vaccinated patients (RR 0.74, 95% CI 0.56-0.98) as well as death due to cardiovascular diseases (RR 0.67; 95% CI 0.45-0.98).[19] Behrouzi et al. conducted another meta-analysis involving 9,001 participants from six randomized controlled trials (RCTs). They found a correlation between influenza vaccination and the risk of major cardiovascular events (death from cardiovascular events, hospitalization due to myocardial infarction, unstable angina, stroke, heart failure, and urgent coronary revascularization) in the form of a 34% reduction in risk over a 12-month follow-up period. Individuals with recent acute coronary syndromes experienced even greater risk reduction of up to 45%.[20]

Other meta-analysis studies by Gupta et al and Modin et al concluded that influenza vaccine can reduce mortality in patients with heart disease with an odd ratio (OR) of 0.74 (95% CI 0.64-0.86) and a hazard ratio (HR) of 0.72 (95% CI 0.54-0.95) for mortality due to all causes and also for death from cardiovascular events with OR 0.73 (95% CI 0.59-0.92) and HR 0.63 (95% CI: 0.42-0.95).[21,22]

Davidson et al. conducted a study involving over 193,000 subjects, finding that the risk of acute cardiovascular events was reduced 15–28 days after vaccination with an incidence ratio (IR) of 0.72 (95% CI: 0.70–0.74), and this remained reduced until 91–120 days post-vaccination with an IR of 0.83 (95% CI 0.81–0.88). This reduction in the risk of cardiovascular events was seen after vaccination in all age groups.[26] Similarly, a meta-analysis study conducted by Barnes et al. found a significant reduction in the risk of acute myocardial infarction with OR 0.71 (95% CI 0.56-0.91), which is equivalent to an estimated vaccine effectiveness of 29% (95% CI 9-44%) against acute myocardial infarction.[28]

SAFETY PROFILE AND CONSIDERATIONS IN INFLUENZA VACCINATION

In addition to being effective, influenza vaccination is also safe and well-tolerated by adults and older adults. Generally, the side effects that may occur are mild and include mild local reactions like pain at the injection site, swelling, or redness. Systemic side effects are also typically mild and may include myalgia and low-grade fever. If these side effects occur, they can usually be managed with the administration of paracetamol. However, cardiovascular patients with the following conditions should not receive

influenza vaccination: 1) individuals with a life-threatening allergy to any component of the influenza vaccine (whether egg protein or other components) and, 2) individuals who have experienced a severe allergic reaction to one dose of an influenza vaccine should not receive that specific vaccine again and may be unable to receive other influenza vaccines.[23] Individuals who use immunosuppressants are generally considered safe to receive inactivated vaccines, including influenza; however, their immune response to the vaccine may be reduced.[24] The choice of vaccine should be made under strict medical supervision, and vaccine administration should be monitored by healthcare providers capable of recognizing and managing severe allergic reactions.

SITUATION AND IMPLEMENTATION IN INDONESIA

In a 2019 study on the occurrence of Influenza Like Illness (ILI) & Severe Acute Respiratory Infection (SARI) in East Jakarta, Indonesia, influenza contributed significantly to these illnesses with a 31% contribution to ILI and a 15% contribution to SARI[31]. Research in 2011 estimated that there are approximately 4 million flu cases in Indonesia every year, resulting in nearly 200,000 hospitalizations.[32] Meanwhile, the prevalence of cardiovascular diseases in Indonesia in 2023 reached 0.85% of the total population, or 877,531 people.[33] At present, there is no data on influenza vaccination coverage among the population with cardiovascular disease in Indonesia. Influenza vaccination has been included in the recommendations of the Indonesian Society of Internal Medicine Adult Immunization Task Force, and annual administration is recommended, especially to groups with comorbidities, such as cardiovascular disease. Regardless of this recommendation, influenza vaccination is not included in the national immunization program for this group.[34] Research on the knowledge of cardiovascular patients and doctors about the benefits of influenza vaccination in Indonesia is needed to obtain a complete picture of the situation and develop plans for future influenza vaccination programs.

CONCLUSION

Cardiovascular disease remains a major global health problem. Influenza infection can increase the risk of cardiovascular disease, and vaccination is one prevention method that has proven effective in the prevention of influenza infection and the reduction of risk of major cardiovascular events, especially myocardial infarction, worsening heart failure, and cardiovascular-related mortality.

CONFLICT OF INTERESTS

The authors have no competing interests.

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