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Review Article

The Role of Influenza Vaccination and its Impact on Cardiology

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Abstract

Influenza is a common, but serious illness, which has a burden of disease all over theworld. It is estimated that there are about 3 to 5 million severe case of the disease that may require hospital admission, and around 290,000 to 650,000 deaths in each seasonal outbreak. The whole population is at risk of becoming ill due to influenza. However, children and patients with chronic illnesses, such as those with cardiovascular diseases or multiple disorders, have ahigher risk of developing complications. The prevention of infection due to influenza through vaccination is well known in the childhood population, but also has an important role in the maintenance of health and prevention of mortality and morbidity in patients with cardiovas- cular disease. This is due to known cardioprotective mechanisms, mainly in the prevention ofacute myocardial infarction or heart failure. Nowadays, immunization must be included in thecomprehensive secondary prevention in these patients

Keywords: Influenza; Vaccination; Prevention; Acute myocardial infarction; Heart failure

Introduction

Influenza is an acute respiratory disease, caused by influenza viruses that infect the respiratory system. There are four types of influenza viruses: influenza A, B, C and D. Influenza viruses C and D are uncommon and the disease they generate in humans tends to be mild, contrary to what happens with influenza A and B viruses because their circulation is very frequent, they have a high burden of disease and are responsible for influenza pandemics or epidemics [1].

Influenza A viruses are classified into sub-types according to the antigenic properties of their two surface glycoproteins, hemagglutinin (HA) and neuraminidase (NA). So far, 16 hemagglutinins and 9 neuraminidases have been isolated in birds (H1-H16 y N1-N9) and additional RNA of two hemagglutinins and neuraminidases, identified in bats (H17 y H18, y N10 y N11). At present, the most commonly circulating influenza A viruses are AH1N1 and AH3N2. As for the influenza B viruses, they are not classified into sub-types but into antigenically distinct lineages, B/Victoria and B/Yamagata, which currently co-circulate in humans [2]. According to the above, the influenza viruses that cause disease and circulate in the world are AH1N1, AH3N2, B/Victoria and B/Yagamata, and their circulation would depend not only on the season, but also on the hemisphere where we are located. Northern hemisphere countries would have their influenza season from October to April or May. Southern hemisphere countries, on the other hand, would enter into their influenza season in the months of May or June, until October, But what happens in tropical countries such as Colombia? Influenza circulates throughout the year, with a higher proportion during the winter seasons, and causes illness during any month of the year.

According to the National Institute of Health's XIII acute respiratory infection event report for 2019, the respiratory viruses identified as responsible for unusually severe acute infection were both the influenza virus A (AH1N1 --- AH3N2) and influenza virus B; the latter having the highest percentage of identified viruses in all age groups, mainly in those aged 40-59 years, with the exception of children under 1 year of age, in whom the respiratory syncytial virus predominates [3].

Common cold or influenza?

It is important to differentiate the common cold from influenza. When reference is made to influenza, we are not talking about the flu or a common cold. Influenza is an illness that can be severe and associated with several complications.

When referring to the common cold or the flu, the main difference is the severity of the symptoms. In the common cold, symptoms are milder and usually do not lead to complications or incapacitation, and this clinical picture is usually caused by viruses different from those that cause influenza. Influenza, on the other hand, is characterized by having a sudden onset accompanied by fever, usually above 38 degrees Centigrade, the chills, dysphagia, headache, myalgias, arthralgias, hyporexia, fatigue and coughing. In children it is frequent that this condition also presents with nausea, vomiting and diarrhea. Influenza disease lasts much longer than a common cold, it can take weeks or even months and the symptoms are so severe that they force the patient to seek medical advice. Among the complications that can result from influenza infection are not only the worsening of chronic diseases, such as heart failure, diabetes or COPD, which will lead the person to require inpatient management, but also complications such as pneumonia, otitis, sinusitis, meningitis, myocarditis, acute myocardial infarction, seizures and Guillain-Barré syndrome. There are several signs and symptoms to consider in adult patients with cardiopathy and influenza, such as dyspnea, constant pain or pressure in the chest or abdomen, persistent dizziness, confusion,

difficulty to wake up, seizures, oliguria, myalgia, severe weakness or unsteadiness, fever or cough that improves but recurs or worsens, and a worsening of chronic conditions [4-6].

The contagion

Influenza is spread from person to person through droplets or aerosols that are produced when people with the disease cough, sneeze or talk. It is also possible to spread through fomites, when a person touches a surface or object contaminated with the influenza virus and puts his or her hand to his or her mouth, nose, or eyes, because influenza viruses can survive on different surfaces for up to 3 days.

The incubation period of influenza can be from 1 to 4 days, after which, the person enters a period of contagion that can last up to 10 days in an immunocompetent person and longer in an immunocompromised person, before he or she presents with symptoms. Once the person reaches this period, symptoms appear (symptomatic period), which can last up to 7 days in a healthy person, but in the case of a chronic patient, he/she would probably end up with a longer-lasting condition and would require inpatient management [7-9].

Who is hospitalized more due to influenza, and who should get vaccinated?

According to the CDC (Center for Disease Control and Prevention) weekly reports on hospitalizations associated with influenza, adults with comorbidities are those who are hospitalized first; in almost 50% of the cases it is adults with cardiovascular disease, followed by those with metabolic disorders (diabetes mellitus) and obesity, and in fourth place by patients with chronic lung diseases [10].

Given that influenza can cause severe illness and it can sometimes lead to death, different international organizations, such as the CDC and the World Health Organization (WHO), recommend annual vaccination against this virus in populations at higher risk of complications, admission into intensive care units, and death[11].

Risk groups

- Young children from 6 months to 5 years of age.
- Persons with chronic diseases or immunosuppression, including: cardiovascular diseases, other chronic diseases, such as morbid obesity, body mass index greater than or equal to 40 in adults, renal insufficiency, hemoglobinopathies and anemias, asplenia, chronic liver disease, severe neuromuscular diseases, immunosuppression, including that caused by HIV infection or medications, or in transplant recipients. Disorders and diseases leading to cognitive dysfunction: Down syndrome, dementia, and others.
- Pregnant women Travelers
- Elderly adults over 60 years of age
- Health care personnel because they present a higher risk of contagion and exposure.

The impact of influenza on cardiovascular events

Associations between influenza and cardiovascular events have been evident for many years. Regardless of the observational approach, it has been shown that a clinically significant association does exist. Collins found an excess in mortality from all causes during each influenza epidemic, primarily for heart disease in 35 large cities in the United States from 1918 to 1929 [12]. A 2011 observational study found a strong association between influenza and death from acute myocardial infarction in both the United Kingdom (RR 1.051, $p < 0.05$) and Hong Kong (RR 1.077, $p < 0.05$), with a 4.7- to 6.4-times higher AMI mortality rate during influenza outbreaks, indicating that 3-6% of AMI deaths were associated with influenza [13].

In a time series analysis of vital statistics records and emergency room visits occurring during the influenza seasons in New York City, for cardiovascular deaths occurring between 2006 and 2012, it obtained as a result that in adults 65 years and older there was an excess of cardiovascular mortality; additionally, it was shown how increased influenza circulation was associated with and a predictor of mortality due to cardiovascular disease in those aged over 65 years of age. The incidence of influenza during the previous 21 days was associated with an increase between 2.3% (CI 95%, 0.7 - 3.9%) and 6.3% (CI 95%, 3.7 - 8.9%) for mortality from cardiovascular disease and between 2.4% (CI 95%, 1.1 - 3.6%) and 6.9% (CI 95%, 4.0 - 9.9%) for mortality from ischemic heart disease among adults aged 65 years and older. The associations were most acute and stronger for mortality due to acute myocardial infarction during the previous 14 days and were associated with increases in mortality of between 5.8% (IC 95%, 2.5 - 9.1%) and 13.1% (IC 95%, 5,3 - 20,9%) [14].

In a self-controlled case series study, it was shown that those diagnosed with influenza have a 5,17 risk of having a myocardial infarction with influenza A and a 10,11 risk with influenza B in the first 7 days of the infection [15].

In a study conducted by Panhwar et al., it was found that influenza infection is associated with increased hospital morbidity and mortality in patients with heart failure. It was found in this study that patients with HF and concomitant infection with influenza presented a higher incidence of hospital mortality versus those without concomitant infection, 6,2% vs. 5,4%, respectively (OR: 1,15 CI95%: 1,03 - 1,30; p 0,02), acute respiratory failure 36.9 *vs.* 23.1%, respectively (OR: 1.95 CI95%: 1.83 - 2.07; $p < 0.001$), acute respiratory failure requiring mechanical ventilation 18.2% vs. 11.3%, respectively (OR: 1.75 CI95%: 1.62 - 1.89; $p < 0.001$), acute kidney injury 30.3 *vs.* 28.7%, respectively (OR: 1.08 CI95%: 1.02 - 1.15; p 0.01), and dialysis 2.4 *vs.* 1.8%, respectively (OR: 1.37 CI95%: 1.14 - 1.65; p 0.001) they were hospitalized for longer periods of time [16].

Kytömaa *et al.,* found that influenza activity was temporally associated with an increase in hospitalizations due to heart failure during four influenza seasons between 2010 and 2014. During this time, it was evident how a 5% monthly absolute increase in influenza activity was associated with a 24% increase in heart failure hospitalization rates (incidence rate, 1.24; CI 95%, 1.11 - 1.38; $p < 0.001$).This model suggests that, in a month with high influenza activity, approximately 19% of hospitalizations for heart failure (CI 95%, 10 - 28%) could be attributable to influenza disease [17].

The role of influenza infection in cardiovascular events

Proposed mechanisms

The immune response generated after a respiratory infection can lead to a variety of negative cardiovascular outcomes [18,19].

1. At the time influenza infection occurs, a pro-inflammatory cytokine cascade occurs which causes an increase in the expression of cell adhesion molecules to the endothelial surface, thus leading to leukocyte transmigration to the vascular intima, thereby causing vascular damage, leading to an increased risk of rupture in the atherosclerotic plaque and acute myocardial infarction. In turn, that activation of pro-inflammatory cytokines causes the activation of foamy cells within the atherosclerotic plaque, thus contributing to the rupture of the plaque and to infarction.
2. The rupture of plaque and the risk of AMI may also be related to hypercoagulability, secondary to influenza infection.
3. The production of TNF-α and interleukin-1-b during acute disease can lead to impaired myocyte contractility. Specifically,

the pro-inflammatory cytokine cascade affects the beta-adrenergic responsiveness of myocytes, by activation of an esfingomyelinase pathway and alterations in a nitric oxide pathway.

4. The sustained cytokine expression may lead to adverse myocardial remodeling due to excessive production of matrix metalloproteinases tissue inhibitors which have been associated with the increase of the myocardial collagen and left ventricular dilatation, and thus have contributed to worsening HF.
5. The increased oxygen demands secondary to a respiratory infection in a patient with cardiovascular disease and impaired inotropy increase the risk of myocardial ischemia due to hypoxia or the exacerbation of heart failure.

It is important to keep in mind that these patients are at risk of developing a concomitant bacterial infection, mainly due to pneumonia by *Staphylococcus pneumoniae* which is one of the most frequent complications of influenza infection and may increase the risk of coronary outcomes due to the prolongation of pro-inflammatory cytokine levels and procoagulant state.

Impact of the influenza vaccine on cardiovascular events

It is considered that vaccination against influenza can prevent the adverse impact of infection in the cardiac patient, since, by preventing infection, it avoids the main trigger for the generation of inflammation, hypervolemia, oxidative stress, arrhythmias, fibrosis and myocardial damage, which frequently lead to infarction or heart failure.

A retrospective cohort study including 29,763,704 patients showed that patients vaccinated against influenza had a lower prevalence of acute myocardial infarction compared to those who were not vaccinated (3.4% vs. 4.4%), with an adjusted OR for AMI of 0.91 (CI 95%: 0.87-0.96) in vaccinated patients compared to unvaccinated patients [20]. Another cohort study conducted by Modin et al. with 134,048 patients diagnosed with heart failure, found that receiving one or more vaccines was associated with an 18% reduced risk of death (all causes): HR 0.82; CI 95% 0.81 - 0.84; $p < 0.001$; cardiovascular causes: HR 0.82; CI 95%, 0.81 - 0.84; $p < 0.001$). Annual vaccination and higher cumulative number of vaccinations were associated with greater reductions in the risk of death compared to intermittent vaccination or non-vaccination [21]. A systematic review that included 42 studies in the analysis demonstrated the protective impact of vaccination against influenza on the reduction of acute myocardial infarction or death from a cardiovascular event with intervention, case-control, and cohort studies [22].

In a meta-analysis of case-control studies, it was evidenced that vaccination against influenza was associated with a protective effect for AMI with an OR: 0,71, CI 95% (1,47 - 2,76) [23]. In a review of the impact of influenza vaccination in patients with heart failure, a randomized controlled trial found a significant benefit in those vaccinated for all causes of death and hospitalization for acute coronary syndrome, heart failure, or infarction.

In another study included in this review, a 19% reduction in hospitalization for cardiovascular causes was demonstrated in vaccinated vs. unvaccinated patients, which demonstrated a significant prevention of hospitalization due to heart failure by preventing any respiratory condition. The "HF-Paradigm" study demonstrates a significant association between vaccination against influenza and all-cause mortality reduction in patients with a decreased fraction of ventricular ejection [18].

Several observational studies and clinical trials demonstrate that the influenza vaccine protects against acute myocardial infarction. The estimates of the efficacy of the influenza vaccine in preventing infarction range from 15 to 45%. This is a similar range of efficacy in comparison with accepted routine secondary coronary prevention such as a cessation of smoking (32 - 43%), use of statins (19 - 30%), and antihypertensive therapy (17 - 25%), so it is considered that vaccination against influenza should be part of the integral treatment in patients with cardiovascular disease [24].

Proposed possible cardioprotective mechanisms of vaccination

The influenza vaccine can protect against cardiovascular events via multifactorial mechanisms. Prevention of infections prevents disruptions in homeostasis and, on the other hand, the immune response to the vaccine may generate cardiovascular benefits.Two possible mechanisms have been proposed, a nonspecific effect associated with the elimination of infections that may destabilize chronic atherosclerotic inflammation of the arterial wall by sudden activation of an inflammatory cascade, inhibiting atherogenesis, vascular damage, alteration in contractility, and activating hemodynamic stabilization by activation of the bradykinin 2 receptor. The specific mechanism proposes an "antigenic mimic" between the influenza virus and atherosclerotic plaque antigens [18,25].

Why does one need to be vaccinated every year?

There are two main reasons why annual vaccination against influenza is recommended. The first is because the antibodies produced in response to the previous influenza vaccine decline over time, around 12 months after administration. And the second, due to the normal evolutionary process of the influenza virus, which includes a series of minor antigenic variations involving a difference in a small number of amino acids in the hemagglutinin and neuraminidase proteins is why the vaccine must be updated year after year as per the WHO, since the circulating influenza virus strains will be different from those of previous years. The virus circulates all year round in Colombia, but there are two peaks, between April and June, and between September and December. Therefore, it is recommended that people get vaccinated in the first half of the year to cover the two crucial times of the year [26].

Vaccination in patients with cardiovascular disease

Recommendation

Various health authorities, international bodies and medical societies recommend vaccination against influenza for patients with cardiovascular disease.

1. The World Health Organization (WHO): indicates annual vaccination against influenza for all persons who are part of the at-risk groups, including those with a particular risk of developing a serious illness leading to hospitalization or death [11].
   - Pregnant women, children under 5 years of age, adults over 60 years of age, immunosuppressed or chronically ill patients.
2. The United States Vaccine Advisory Committee (ACIP):
   - Recommends universal vaccination against influenza, indicated for the entire population on an annual basis starting at 6 months of life. Priority is given to those patients at risk [27].
3. European Society of Cardiology:
   - Recommends annual vaccination against pneumococcus and influenza in patients with symptomatic HF. It also indicates vaccination against influenza in all patients with coronary artery disease, including all patients who have survived a STEMI [28,29].
4. American College of Cardiology and the American Heart Association:
   - Recommend that patients with cardiovascular disease should receive annual influenza vaccination, due to an increased risk of complications from influenza [30].

The importance of influenza B co-circulation and the evolution of vaccines

The influenza A (H1N1), A (H3N2), and influenza B viruses are responsible for a significant burden of disease in humans during seasonal epidemics. In the past, it was believed that influenza B viruses caused milder disease than influenza A, but several studies have recently shown that influenza A and B infections are clinically indistinguishable and can cause severe complications in both children and adults. The influenza B viruses originally represented a homogeneous group, but since the late 1980s, they have evolved into two antigenically and genetically distinct lineages, defined by the reference strains B/Yamagata/16/88 (Yamagata lineage) and B/Victoria/2/87 (Victoria lineage). In the 1990s, Yamagata predominated worldwide, while the Victoria lineage was mainly restricted to East Asia. However, during the 2000/2001 and 2001/2002 seasons, viruses of the Victoria lineage re-emerged in North America and Europe and spread across the globe. Since then, the two B lineages have circulated worldwide, with variability in terms of geographic distribution and genomic evolution [31].As with the influenza virus, vaccines have evolved over the years, adjusting to the needs in terms of prevention and protection of the population. The monovalent and bivalent vaccines against influenza that once existed were replaced by trivalent vaccines, and today by tetravalent vaccines against influenza. What does this last change correspond to? Before 2002, there was a circulation of a lineage of influenza type B (Yamagata or Victoria) in each season of influenza regardless of the hemisphere (north, south, tropical) which changed from year to year, further to two sub-types of A (H1N1 and H3N2), so the recommended vaccine against influenza was the trivalent vaccine which contained the two sub-types of A and a lineage of B recommended for the composition of the vaccine by the WHO. However, since 2002 there has been evidence of co-circulation of the two B lineages during the same season. This was documented in Europe, Australia, the United States, and years later the co-circulation of the two influenza B lineages was also confirmed in Colombia [32,33].

A subtyping of influenza B was performed in Colombia in 2014, which allowed the confirmation of the co-circulation of the two lineages of B in the same season, with 63% of the circulation of B corresponding to B/Victoria and 37% to B/Yamagata in our country. Once again, in 2018, the subtyping for B showed that, despite the fact that AH1N1 circulated the most, there were cases of both B/Yamagata and B/Victoria. It is important to clarify that information on co-circulation is limited since the subtyping of B is not routinely performed in the country due to costs. Therefore, the report is mainly to identify influenza B and/or subtyping for one of the two lineages for the other years. The confirmation of cocirculation between lineages of influenza B allows the evidencing of a major problem; that of mismatching. This refers to what is present in the vaccine does not correspond to what is circulating, and this was observed for influenza type B with trivalent vaccines. Thus, even if the population is vaccinated, a percentage of the population will be at risk of influenza disease due to that lineage of influenza B which is not included in the trivalent vaccine [32,33].

Following this, the WHO in 2012 published a Position Paper recommending the change from trivalent (TIV) to tetravalent (QIV) influenza vaccine, and in 2013 the first tetravalent vaccines against influenza appeared, in accordance with the needs and recommendations of the WHO, thus including two sub-types of influenza A and the two lineages of influenza B (B/Victoria and B/Yamagata). The use of the tetravalent vaccine is currently recommended by different international organizations; it is not only recommended for at risk groups, such as pregnant women, children under 5 years of age, adults over 60 years of age, chronic diseases, travelers and health care personnel; but it is also recommended for all people from 6 months of age for annual vaccination [33]. In Colombia, the 2016 update document on the Guidelines for Adolescent and Adult Immunization by the Colombian Association of Infectious Diseases (ASCIN) regarding vaccination against influenza, establishes that the tetravalent vaccine should ideally be administered to avoid possible mismatches between vaccine strains and circulating wild-type strains [34].

Two vaccines against influenza are currently available in Colombia: the trivalent vaccines, used by the expanded program on immunization and indicated for a certain group of patients at risk, such as those with cardiovascular disease according to the 2020 guidelines, congenital, rheumatic, and ischemic heart disease, and the tetravalent vaccines [35].

Conclusion

Influenza is one of the leading causes of respiratory infection responsible for an increase in both morbidity and mortality among the chronic population worldwide, and there is increasing evidence of the association between influenza and negative cardiovascular outcomes, such as acute myocardial infarction and heart failure. Pathological mechanisms responsible for these events have been identified, such as the release of pro-inflammatory cytokines, increased sympathetic activity, hypoxia, disruption of atherosclerotic plaque, and hypercoagulability. Likewise, the cardioprotective mechanisms of vaccination by preventing infection and thus disruptions in homeostasis and cardiovascular benefits have been proposed. Different types of studies have evaluated the efficacy of vaccination against influenza in the chronic population with cardiovascular disease and they have demonstrated the impact of this intervention versus non-vaccination among this population. Therefore, it is considered that it should be included among the routinely employed coronary prevention activities which are accepted worldwide, along with cessation of smoking, antihypertensive therapy, and the use of statins. Despite the fact that several international bodies and scientific societies recommend annual vaccination in patients with cardiovascular disease, vaccination rates in risk groups continue to be suboptimal. A paradigm shift is needed in clinical practice, and in the management of these patients with regard to the prevention of immunopreventable diseases and their secondary complications. The recommendation of vaccination should be given by the treating physician, and it should be included as a tool in the prevention of cardiovascular diseases.

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Conflict of Interest

None

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