Consensus Guidelines for Influenza Vaccination in Patients with Diabetes

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ABSTRACT

Influenza is a prevalent health issue encountered in daily practice. Patients with diabetes mellitus face a higher risk of infections, including influenza, owing to the compromised immune system associated with diabetes. This susceptibility arises from the potential of diabetes mellitus to weaken the immune system. Moreover, elevated blood glucose levels can create a conducive environment for the growth of bacteria and viruses. This consensus is formulated by a multidisciplinary team to serve as practical guidance for the administration of influenza vaccinations to patients with diabetes mellitus in daily practice.

Keywords: *influenza, diabetes mellitus, vaccination*

INTRODUCTION

Influenza and Influenza-like Illness (ILI) are respiratory infections that are clinically challenging to distinguish because routine diagnosis is rarely performed. Influenza occurs throughout the year in Indonesia with spikes in certain months and every year, various strains of influenza viruses A (A/H1N1, A/H3N2) and B (B/Victoria and B/Yamagata) circulate simultaneously.[1] In a 2019 study related to the occurrence of ILI and Severe Acute Respiratory Infection (SARI) in East Jakarta, Indonesia, the contribution of Influenza showed significant figures (31% in ILI, 15% in SARI).[2] Research in 2011 estimated that there are approximately a total of 4 million flu cases in Indonesia every year, resulting in nearly 200,000 hospitalizations related to the flu.[3]

Diabetes mellitus (DM), both type 1 and type 2, remains a significant health issue in Indonesia. According to the 2018 Basic Health Research (Riskesdas) report, the prevalence of diabetes mellitus in Indonesia increased from 6.9% to 8.5%.[4] In 2021, the International Diabetes Federation (IDF) reported approximately 19.46 million adults with DM, ranking Indonesia as the 5th highest country in the world regarding the number of individuals affected by diabetes.[5] Diabetes mellitus (DM) can weaken the immune system, making it more challenging for the body to fend off infections. Moreover, elevated blood sugar levels create a favorable environment for the growth of bacteria and viruses, thus increasing the risk of infection. DM can also harm blood vessels and nerves, leading to impaired circulation and delayed healing times. Consequently, individuals with DM are at a higher risk of contracting infections, including influenza.[6]

The burden of influenza in the diabetic population, compared to influenza patients without diabetes, increases significantly.[7] It can be up to 6 times greater for the risk of hospitalization, 4 times higher for the risk of intensive care unit (ICU) admission[8], and 6 times higher for the risk of death.[9] Patients infected with influenza also exhibit significantly higher average Diabetes Complications Severity Index (DCSI) scores compared to the non-influenza group. This leads to an increase in overall healthcare costs for diabetic patients with influenza.[10] According to various reports, managing influenza can incur very high costs, including both direct costs related to outpatient and inpatient care and indirect costs associated with transportation, disease management, and mortality.

This consensus is formulated as a guideline for doctors to administer influenza vaccination to patients with diabetes mellitus (DM). Currently, influenza vaccination for patients with DM is already recommended in the Adult Immunization Schedule as per the Immunization Task Force of the Indonesian Society of Internal Medicine 2023, as well as in the Guidelines for the Management and Prevention of Type 2 Diabetes Mellitus in Adults in Indonesia published by the Indonesian Society of Endocrinology in 2021.

INFLUENZA VIRUS

Virus Types

There are four types of influenza viruses: influenza types A, B, C, and D. Influenza A and B are responsible for seasonal epidemics in populations (commonly referred to as seasonal flu) nearly every winter in the United States. Influenza A is known for causing flu pandemics. Influenza C typically causes mild symptoms and does not result in epidemics in humans. Influenza C primarily infects livestock, with transmission to other animals, but it is not known to transmit to humans. Influenza A viruses are further divided into subtypes based on two proteins on the virus's surface, namely hemagglutinin (H) and neuraminidase (N). There are 18 different hemagglutinin subtypes and 11 different neuraminidase subtypes (H1 to H18 and N1 to N11). There are over 130 known combinations of influenza A subtypes found in nature, primarily among wild birds. These combinations of influenza subtypes have the potential to re-emerge due to the exchange of genetic segments from the virus genes (reassortment). Reassortment can occur when two types of influenza viruses infect a host simultaneously and exchange genetic information. Subtypes of influenza A that regularly circulate among humans include H1N1 and H3N2. Influenza B is categorized into Victoria and Yamagata lineages. These subtypes can further break down into smaller genetic segments called "clades" and "subclades." Influenza types A and B play a role in seasonal flu every year. Influenza A (H3N2 or H1N1) undergoes genetic changes seasonally and can lead to less effective immune responses in humans. Influenza B can experience similar changes, but at a slower rate compared to influenza A. Influenza virus, particles have a diameter of 80-120 nanometers and have a spherical shape. The composition of the virus particle includes a capsule containing two types of glycoproteins that envelop a central core. This core contains RNA genomes and other viral proteins that encapsulate the RNA.[34,35]

Symptoms and Signs

Seasonal influenza infections are characterized by sudden onset of fever, dry

cough, headache, muscle and joint pain, severe malaise, sore throat, and runny nose. Cough can be severe and persist for 2 weeks or more. Influenza virus transmission can occur easily, especially in crowded places such as schools or nursing homes, and it is transmitted through respiratory droplets. The virus incubation period is approximately 2 days, varying from 1 to 4 days. Generally, infected individuals recover from fever and other symptoms within 1 week without requiring special attention. However, influenza can cause severe illness and death in high-risk groups. These high-risk groups include pregnant women, children under 59 months of age, elderly population, individuals with chronic diseases such as chronic heart disease, chronic kidney disease, metabolic disorders (diabetes mellitus, liver disorders, or hematological conditions), individuals with immunocompromised conditions (e.g., HIV, undergoing chemotherapy or taking steroids, and malignancies), healthcare workers that are at high risk of contracting the influenza virus due to their high exposure to patients and are also susceptible to transmitting to high-risk individuals.[36,37]

Epidemiology

Worldwide, influenza is estimated to cause severe illness in 3-5 million cases annually and result in 290,000 to 650,000 deaths each year. A surveillance study of influenza in Indonesia from 2003 to 2007 reported 21,030 cases with clinical manifestations resembling influenza. Out of this total, 4,236 cases (20.1%) were confirmed to be infected with influenza viruses, with a similar proportion among outpatient and inpatient cases. The age group most affected by influenza was school-aged children. This study also found that 64.9% of all identified influenza cases were caused by influenza A viruses (with subtypes H3N2 accounting for 64.6%, H1N1 for 34.9%, and H5N1 for 0.4%), while the remaining 35.1% were caused by influenza B viruses. Seasonal activity of influenza A viruses was observed, with peak incidence occurring in December and January during the rainy season, particularly in western and central Indonesia. In eastern Indonesia, both influenza A and B viruses were found to be active.[37,38]

Diagnosis

In general, influenza infection is clinically diagnosed. However, infections from other respiratory viruses, such as rhinovirus, respiratory syncytial virus (RSV), parainfluenza, and adenovirus, can also cause symptoms similar to influenza (influenza-like illness/ILI). This makes it challenging to differentiate clinical symptoms caused by influenza infection from other pathogens. Obtaining a good respiratory sample for laboratory diagnostic testing is necessary to establish a definitive diagnosis. Laboratory confirmation from throat, nasal, and nasopharyngeal samples is commonly performed using examinations such as antigen tests or PCR.[35,37]

Treatment and Prevention

Patients who are not at high risk can be managed with symptomatic treatment. Patients with severe symptoms can be treated with antiviral medications such as neuraminidase inhibitors (e.g., oseltamivir), which are recommended to be administered as soon as possible within 48 hours of symptom onset and continued for at least 5 days, depending on clinical improvement. Corticosteroids are not commonly administered unless in specific cases such as the presence of asthma. The use of corticosteroids also has the potential to cause immunosuppression and prolong viral clearance. The most effective prevention method is vaccination. Influenza vaccination is safe and highly effective. The World Health Organization (WHO) recommends annual influenza vaccination for the following groups: pregnant women, children aged 6 months to 5 years, the elderly population, individuals with chronic diseases, and healthcare workers.[34,37]

INFLUENZA INFECTION AND DIABETES MELLITUS

Patients with diabetes mellitus (DM) have weakened immune responses, impairments in chemotaxis, phagocytosis, and antigen presentation in response to infections. This leads to disruptions in the function and proliferation of T cells, ultimately exacerbating the symptoms of infectious diseases.[39] Impairments in innate immunity in DM patients are associated with the complement system, cytokines, and

hyperglycemia. A study conducted on 86 patients found that 26% of them had low complement levels (C4), resulting in neutrophil dysfunction and inadequate cytokine responses. Lower secretion of interleukin-1 (IL-1) and interleukin-6 (IL-6) by mononuclear cells and monocytes was also observed in DM patients when stimulated by bacterial components such as lipopolysaccharides (LPS) activated through phagocytosis.[40] In conditions of hyperglycemia, reduced neutrophil degranulation, complement activation, and impaired phagocytosis have been reported. This results in more severe symptoms of respiratory infections, including influenza.[41] A study in Canada reported that DM patients had a threefold higher risk of experiencing severe symptoms and hospitalization during the H1N1 pandemic in 2009. ICU admissions were four times higher in DM patients compared to non-DM patients.[8] A study in Germany by Wilking et al. reported that deaths due to the influenza strain circulating in 2009 were twice as high in DM patients compared to non-DM patients. Influenza infection can also worsen blood glucose control and increase DM complications.[39] Apart from causing more severe complications, influenza infections are known to trigger the onset of DM. A study by Nenna et al. in Rome found an increased incidence of newly diagnosed type 1 DM following the H1N1 pandemic (October 2009 to January 2010) compared to the years 2004-2005. Additionally, an increase in newly diagnosed type 1 DM was reported in the 1970s following an influenza epidemic.[42]

Respiratory tract infections caused by influenza viruses are transmitted through droplets and aerosols, making them highly contagious and capable of causing serious complications in individuals with weakened immune systems.[7] The disease burden of influenza in the diabetic population, compared to influenza patients without diabetes, increases significantly, resulting in up to a six-fold greater risk of hospitalization, a four-fold increase in the risk of intensive care unit (ICU) admission[8], and a six-fold increase in the risk of death.[9]

Furthermore, a retrospective study indicates that the rate of diabetes complications increases following exposure to the influenza virus. Patients who have been infected with influenza tend to have significantly higher average Diabetes Complications Severity Index (DCSI) scores compared to those in the non-influenza group.[10] The same study also highlights a higher utilization of healthcare services, including outpatient visits, emergency department visits, and hospitalizations, resulting in an overall surge in healthcare costs for individuals with diabetes who also contract influenza.

Based on the research by Kosen et al. in 2017, the impact caused by lower respiratory tract infections attributed to influenza in Indonesia is highly significant. The disease burden is estimated to reach 3,358,418 cases of influenza-related lower respiratory tract infections, including 40,435 hospitalizations and 4,097 deaths. The estimated cost incurred is approximately US$ 866.7 million. This total includes indirect costs of US$ 847.5 million associated with productivity loss and direct costs of US$ 19.2 million related to treatment expenses.[3] Meanwhile, according to the study by Akin et al. in Turkey, increasing influenza vaccination coverage to 20% in the adult population with type 2 diabetes mellitus (DM) is predicted to prevent 19,777 cases of influenza, 2,376 hospitalizations, and 236 deaths. The cost savings from influenza treatment are estimated to be 8.3 million Turkish lira, while the cost of vaccination amounts to approximately 8.4 million Turkish lira.[21] Furthermore, research conducted by Wang et al. in Taiwan demonstrates that influenza vaccination provides considerable cost benefits for patients with DM. An estimated 1,283 USD can be saved per hospitalization event in DM patients who receive the influenza vaccine compared to those who do not.[20] Influenza vaccination is a primary preventive measure in reducing the incidence of hospitalizations and deaths due to influenza virus.[11] Influenza vaccination is indicated for adults and is highly recommended for the elderly, pregnant women, children under 5 years of age, travelers, people with chronic diseases, and healthcare workers.[12]

INFLUENZA VACCINE TYPES

The World Health Organization (WHO) issues recommendations every February and

September each year to suggest the strains of the influenza virus be included in vaccines for the Northern and Southern hemispheres. In Indonesia, influenza vaccination can be administered throughout the year using the available influenza vaccines at that time. For travelers, vaccines are tailored to the destination region. Influenza vaccines are categorized into three types: live-attenuated influenza vaccine (LAIV), inactivated influenza vaccine (IIV), and recombinant influenza vaccine (RIV), with their usage tailored to different age groups.[13] In Indonesia, the available influenza vaccine is the Inactivated Influenza Vaccine (IIV). Based on the contained strain types, there are two main types of influenza vaccines. First, Trivalent Inactivated Influenza Vaccine (IIV3) provides protection against two influenza A strains (A/H1N1 and A/H3N2) and one influenza B strain (B/Victoria or B/Yamagata). Second, Quadrivalent Inactivated Influenza Vaccine (IIV4) offers protection against two influenza A strains (A/H1N1 and A/H3N2) and two influenza B strains (B/Victoria and B/Yamagata). Quadrivalent influenza vaccines provide additional protection compared to trivalent vaccines because they cover both influenza B strains (B/Victoria and B/Yamagata) that co-circulate in the wild.[14]

BENEFITS OF INFLUENZA VACCINATION IN THE DIABETES POPULATION

Patients with diabetes are considered a high-risk population and are more likely to experience complications, hospitalizations, and mortality due to influenza infections. Therefore, influenza vaccination for diabetes patients is recommended as the standard of care for managing all patients with type 1 and 2 diabetes.[15] Furthermore, diabetes patients with comorbid conditions are strongly advised to receive influenza vaccination. The comorbidities include chronic respiratory system disorders, chronic kidney disease, cardiovascular disorders (heart failure, coronary heart disease, acute coronary syndrome, hypertension, arrhythmia, heart valve disorders, congenital defects), immunocompromised conditions (HIV/AIDS, cancer, etc), cancer, anemia/hemoglobinopathies, morbid obesity and elderly individuals.[12]

The immune response of diabetes patients (seroprotection and seroconversion) after influenza vaccination is quite comparable to that of healthy adults. One month after vaccination, the seroconversion rate reaches 58.0%, and seroprotection reaches 99.0%. These review findings indicate that influenza vaccination protects them from severe infections and complications.[16]

Meta-analyses have shown that influenza vaccination in adult diabetes patients (aged 18-64 years) can reduce mortality rates and the incidence of hospitalization due to pneumonia.[17] Other studies have assessed that influenza vaccination in adult diabetes patients can significantly reduce the number of influenza cases and hospitalizations related to influenza events.[18] The benefits of influenza vaccination in elderly diabetes patients (aged 65 and above) also significantly reduce the incidence of influenza-like illness, hospitalization due to pneumonia or other reasons, and a decrease in mortality due to respiratory tract infections or any other cause.[17] A study conducted in the UK with 124,503 diabetic patients between 2003-2010 showed that influenza vaccination was associated with lower rates of hospitalization and mortality in vaccinated patients compared to those who did not receive vaccination. This study found a significant reduction in cardiovascular events, including acute myocardial infarction (19%), stroke (30%), heart failure (22%), and pneumonia (15%).[43] Another study by Wang et al. in elderly diabetic patients showed a reduction in hospitalization rates of up to 11% in patients who received influenza vaccination compared to those who did not receive vaccination.[44]

For diabetes patients with cardiovascular disease, influenza vaccination has been linked to a reduction in overall mortality risk, cardiovascular disease-related mortality risk, and the incidence of cardiovascular events.[19] Data from various countries also show that increasing influenza vaccination coverage in the diabetes population and reducing the number of cases, hospitalizations, and deaths can result in significant cost savings.[20,21]

INFLUENZA VACCINE ADMINISTRATION

In Indonesia, influenza vaccination can be administered throughout the year, using the available influenza vaccines at the time.[12] Annual influenza vaccination for type 1 and type 2 diabetes patients can begin at the age of 6 months and should be administered every year.[22] The American Diabetes Association (ADA) recommends the use of inactivated and recombinant influenza vaccines for diabetes patients and advises against the use of live attenuated vaccines (LAIV).[23] The influenza vaccines available in Indonesia are of the inactivated type and are administered intramuscularly (IM).

Influenza vaccination is needed annually because the influenza virus continues to mutate (antigenic drift), affecting various strains.[24] Therefore, influenza vaccines are updated yearly to protect against the viruses that will circulate in the upcoming season. Receiving an influenza vaccination more than one year after the previous vaccination is still beneficial, but the immune response from the previous vaccination will decrease over time.[25] Hence, if the virus strains remain unchanged, annual influenza vaccination is still necessary to maximize protection. In certain situations where the strains in the vaccine differ from the circulating strains in a specific region, revaccination can be administered before one year to enhance protection.[26] The CDC recommends that travelers going abroad should receive influenza vaccination at least 2 weeks before their trip.[27]

In general, there are no absolute contraindications to influenza vaccination, except for a history of severe hypersensitivity reactions to previous influenza vaccines. In specific situations, vaccination should be postponed if there are severe acute conditions.[13] Severe acute conditions in patients with diabetes include hypoglycemia, diabetic ketoacidosis, and hyperosmolar hyperglycemic state. As long as these conditions are not present, vaccination is still recommended even if blood sugar levels are not well controlled. Influenza vaccination can be administered simultaneously with other vaccines. If the next influenza vaccination is given less than 1 year after the previous vaccination, it is generally safe and does not have significant cross-reactivity.[12]

Influenza vaccination should also be considered in diabetic patients as part of hospital care after a myocardial infarction episode. Influenza vaccination can be administered within 72 hours after a myocardial infarction episode. Besides diabetic patients, it is important for healthcare workers handling these patients to receive influenza vaccination because they are at higher risk of being exposed to the influenza virus, which could pose a risk of spreading it to other vulnerable patients.[29] In addition to healthcare workers, vaccination is also recommended for individuals living near people with diabetes, including family members of patients and caregivers.[30]

SAFETY PROFILE AND CONSIDERATIONS IN INFLUENZA VACCINATION

In addition to being effective, influenza vaccination is also safe and well-tolerated by adult and elderly diabetic patients.[16] 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.[12] One study noted that there is a possibility of elevated blood sugar levels up to 24 hours after vaccination, but this is temporary and returns to the patient's previous blood sugar range one day after vaccination.[31] This reaffirms that the benefits of influenza vaccination outweigh the risks and addresses concerns among diabetic patients which can lead to decreased vaccination rates. However, diabetic patients with the following conditions should not receive influenza vaccination. First, individuals with a life-threatening allergy to any component of the influenza vaccine (whether it's egg protein or other components) should not receive the vaccine. Second, individuals who have experienced a severe allergic reaction to one dose of the influenza vaccine should not receive that specific vaccine again and may be unable to receive other influenza vaccines.[32]

Individuals who use immunosuppressants are generally safe to receive inactivated vaccines,

including influenza. However, their immune response to the vaccine may be reduced.[33] Diabetic patients with a history of non-severe egg allergy can receive licensed and recommended influenza vaccines, such as Inactivated Influenza Vaccine (IIV) and Recombinant Influenza Vaccine (RIV). The choice of vaccine should be administered under strict medical supervision. Vaccine administration should be monitored by healthcare providers capable of recognizing and managing severe allergic reactions.[34]

RECOMMENDATION

Influenza remains a disease with a significant burden in terms of both direct and indirect costs. Influenza infection in populations with diabetes mellitus (DM) poses a higher risk of morbidity and mortality.

Prevention is crucial, and one proven preventive measure is influenza vaccination. Influenza vaccination has been shown to prevent or reduce the severity of symptoms in DM patients if they become infected with influenza.

Influenza vaccination has a good safety profile when administered to individuals with comorbidities, particularly in populations with DM.

Recommended influenza vaccines include inactivated and recombinant types and should be administered annually.

CONCLUSION

This consensus provides a comprehensive guideline for healthcare practitioners to navigate the complexities of influenza management in patients with diabetes mellitus. The collaborative effort of the multidisciplinary team underscores the importance of a unified approach in addressing the heightened risks diabetes patients face during influenza. The integration of these recommendations into daily practice holds the potential to significantly reduce the overall healthcare burden associated with influenza in this vulnerable population.

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DECLARATION OF COMPETING INTEREST

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