



Influenza Vaccine in Children with Cancer Undergoing Chemotherapy

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ABSTRACT

Influenza is a respiratory tract infection caused by a virus that primarily affects children, especially those under 5 years old. Influenza symptoms are generally mild but can worsen in certain conditions such as in immunocompromised patients, including those with cancer. Cancer patients undergoing chemotherapy experience immune system defects, resulting in an inadequate response to infections. It has been reported that children with cancer who contract influenza have longer hospital stays and are at risk of developing pneumonia and respiratory failure. Administration of the influenza vaccine is the most effective prevention to avoid infection and complications from influenza. The inactivated influenza vaccine has been proven safe and can be given to cancer patients undergoing chemotherapy. The challenge in vaccine administration is convincing parents to continue vaccinating their children with cancer.

Keywords: Vaccine, Influenza, Cancer, Chemotherapy

INTRODUCTION

Influenza is a respiratory disease caused by a virus. The influenza virus is an RNA virus consisting of four types: A, B, C, and D. Only types A and B cause infections in humans. Transmission of the influenza virus occurs through droplets when coughing or sneezing, and through direct contact with surfaces contaminated by the virus, which then replicates in the mucosa of the nose and larynx. ⁽¹⁾⁽²⁾ The influenza virus infects 5-15% of the global population. The prevalence of children infected with the influenza virus is 20-30% annually. ⁽³⁾ According to the Centers for Disease Control and Prevention (CDC), hospital visits due to influenza in 2022-2023 were higher compared to 2016-2017, especially in children under 5 years old. ⁽⁴⁾

In children with cancer undergoing chemotherapy, the most common condition found is myelosuppression, which is a decrease in blood cells such as leukocytes, platelets, neutrophils, or hemoglobin. This condition can cause immune system impairment, increasing the risk of complications from influenza infection. A study in Taiwan showed that 82.4 per 100,000 patients under 20 years old with cancer experienced influenza-related hospitalizations. Additionally, 30-60% of immunocompromised patients diagnosed with pneumonia were mostly caused by influenza infection. Influenza infection in children with cancer can cause severe symptoms, complications, intensive care, and even death. Administration of the inactivated influenza vaccine is recommended annually for children undergoing chemotherapy. ⁽⁵⁾⁽⁶⁾

The purpose of influenza vaccination is to prevent severe influenza and its complications. According to the Indonesian Pediatric Society (IDAI), the first injection is given at 6 months to 8 years of age, followed by 2 doses of vaccine containing the same antigen with a 4-week interval, and then repeated annually. ⁽⁷⁾ The influenza vaccine is the most effective prevention to avoid infection and complications from the influenza virus. ⁽⁸⁾

LITERATURE REVIEW

Influenza Vaccine in General

Influenza is an upper respiratory tract disease caused by viral infection, and sometimes the infection can reach the lungs. Influenza virus infection can cause symptoms ranging from mild to severe. According to the CDC, influenza vaccination has been universally recommended since 2010. Previously, the influenza vaccine was only given to certain groups at risk of severe complications and to people who could potentially transmit the influenza virus to high-risk groups. Initially, vaccination was planned for children aged 6-23 months, but a study conducted in 2006 found an increased risk of influenza causing illness in children aged 24-59 months in both inpatient and outpatient settings. Based on this study, influenza vaccination is now recommended for children aged 6-59 months. ⁽⁹⁾

The purpose of influenza vaccination is to prevent severe influenza and its complications by stimulating the production of specific antibodies, resulting in an immune response within 2 weeks after vaccination. Influenza vaccines consist of Live Attenuated Influenza Vaccine (LAIV) and Inactivated Influenza Vaccine (IIV). LAIV contains weakened influenza viruses and is administered intranasally to children aged ≥ 2 years, while IIV contains proteins from killed viruses and is given by intramuscular injection, which can be administered to children aged ≥ 6 months. ⁽³⁾ In Indonesia, the type of vaccine given is IIV. According to the Indonesian Pediatric Society (IDAI) recommendations, it can be given to children aged 6 months to 8 years, with 2 doses of vaccine containing the same antigen given 4 weeks apart. For children aged 9 years and older, only one dose is required. Annual revaccination is recommended at the same month each year. ⁽¹⁰⁾

Cancer and Influenza

Respiratory viral infections are the most common infections in children, with influenza virus being one of the main causes. In both immunocompetent and immunocompromised children, upper respiratory tract infections can also involve lower respiratory tract infections (lungs), especially in children with severe

immunocompromise. Childhood cancer currently ranks second as a leading cause of death in developing countries, with an estimated 300,000-500,000 new cases annually, the most common being leukemia, central nervous system tumors, and lymphoma. However, over time, survival rates have improved with a multidisciplinary approach including chemotherapy, radiotherapy, surgery, and bone marrow transplantation.⁽¹¹⁾ Chemotherapy can cause immunocompromise, which significantly contributes to cytotoxicity and myelosuppression, especially within 6-12 months after treatment completion until recovery.⁽⁶⁾

Immunocompromise is caused by depletion of T and B cells, resulting in defects in the humoral immune system. Children with cancer have varying degrees of immunocompromise, ranging from minimal immune system involvement as seen in solid tumors to severe immunocompromise with pancytopenia in acute leukemia. The degree of immunocompromise depends on the intensity, duration, and type of chemotherapy agents used. For example, in leukemia, there is a decrease in humoral antibody titers in 45-26% of patients and severe neutropenia in almost 100% during chemotherapy. Immune defects can persist for a long time after chemotherapy ends, affecting the ability to fight infections. Therefore, respiratory viral infections are more common in children with cancer undergoing therapy compared to healthy children.⁽¹²⁾⁽⁶⁾⁽¹³⁾

Lymphopenia is commonly found in children with cancer hospitalized due to influenza infection. This condition can reduce vaccine effectiveness due to the loss of some or all protective serum antibodies. Cancer patients are more susceptible to complications from influenza. Children with cancer who contract influenza may have infections lasting twice as long as healthy children and can experience severe complications such as prolonged hospitalization, pneumonia, respiratory failure requiring ventilator support, and sepsis. Influenza infection during chemotherapy can delay chemotherapy processes. During the 2009 influenza pandemic, 55% of patients experienced chemotherapy delays of 3 weeks or more.⁽¹⁴⁾

Influenza Vaccine in Children with Cancer

Influenza infection causes severe morbidity in children with cancer. Children with cancer who contract influenza are more likely to require hospitalization compared to children without cancer. The type of influenza vaccine given is the inactivated vaccine, which is safe for children with cancer undergoing chemotherapy. Children receiving chemotherapy can produce an immune response after influenza vaccination, although the immune response is lower compared to healthy children. ⁽¹⁵⁾ Studies show an increase in antibody titers after influenza vaccination from 38% to 65% in children undergoing chemotherapy, while in healthy children, antibody titers increase from 53% to 89%. Some studies also found that the immune response to the influenza vaccine in children undergoing chemotherapy is weaker compared to children who have completed chemotherapy. ⁽¹⁴⁾

According to the 2013 guidelines from the Infectious Diseases Society of America (IDSA), vaccination is recommended before starting therapy that causes immunocompromise. ⁽¹⁶⁾ Chemotherapy causes immunocompromise, especially during the induction and consolidation phases. Vaccination in children with cancer should be postponed during these phases. ⁽¹⁷⁾ Other recommendations suggest vaccination can be given after 6 months of standard-dose chemotherapy, with the expectation that the immune system has recovered by then. ⁽¹²⁾

Influenza vaccination in children undergoing chemotherapy can be delayed until 3-4 weeks after the intensive chemotherapy phase is completed and when granulocyte and lymphocyte counts are above $1.0 \times 10^9/L$ to ensure a better immune response and reduce vaccine side effects. ⁽¹⁸⁾ An absolute lymphocyte count above the minimum value before vaccination is crucial to indicate that the vaccine will provide protection, and this can be used as a reference for when to vaccinate children undergoing chemotherapy. This is supported by a study by Yen et al., which showed no significant effect of influenza vaccination in patients with lymphocyte counts below $1,500/mm^3$. ⁽¹⁹⁾

Another recommendation from the Indian Academy of Pediatrics Journal states that influenza vaccination can be given during chemotherapy and up to one year after chemotherapy completion based on age: children aged 6 months to 9

years should receive two doses followed by a single dose annually, while those over 9 years receive a single dose annually. However, routine vaccination after the first year post-chemotherapy is not recommended unless the child has high-risk factors such as kidney disease, lung disease, chronic heart disease, or diabetes.⁽¹²⁾

The success of influenza vaccination depends on the immune system's ability to produce antibodies and T-cell responses to antigen exposure. In immunocompromised conditions, serologic responses may not be optimal. Serologic testing can be used to determine antibody formation against the influenza vaccine. Patients with acute myeloid leukemia have a limited serologic response to the vaccine, whereas patients with acute lymphoblastic leukemia have the best serologic response. Additionally, administering a double dose can improve the serologic response to the vaccine.⁽¹⁴⁾⁽²⁰⁾

Most children who have completed chemotherapy experience seronegative status against antigens previously given through vaccination before chemotherapy started. Therefore, revaccination can be considered by giving one additional vaccine dose or by performing serologic testing 6 months after chemotherapy completion. If the result is seronegative, revaccination can be done.⁽¹⁷⁾

Because children with cancer are at high risk of severe influenza, annual routine influenza vaccination is recommended for people who have close contact with children with cancer.⁽¹⁸⁾

Safety of the Influenza Vaccine

The influenza vaccine is very safe, and the majority of children who receive this vaccine experience minimal side effects that resolve on their own. Side effects from the influenza vaccine are usually mild, such as low-grade fever, muscle pain, and pain at the injection site, typically lasting 2-6 days. For the Live Attenuated Vaccine (LAV), nasal congestion and runny nose may occur. Severe allergic reactions, including anaphylaxis to the influenza vaccine, are reported to be rare.⁽³⁾ The inactivated influenza vaccine is safe for immunocompromised patients, including those with cancer, because there is no risk of active infection following vaccination. A study by Ginette et al. involving 391 children with cancer

undergoing chemotherapy who received the influenza vaccine showed that the most common side effects were local reactions at the injection site and mild fever, with no life-threatening side effects. Children undergoing chemotherapy also reported a higher incidence of malaise and decreased appetite after receiving the influenza vaccine. ⁽¹⁵⁾

Parental Awareness of the Influenza Vaccine

A study conducted in Pakistan with 532 respondents, who were parents, showed that more than 80% agreed on the benefits and effectiveness of the influenza vaccine. Educational background was the most significant factor influencing parental awareness of vaccination. Most information about the influenza vaccine was obtained through doctors, clinic visits, and family or relatives. ⁽²¹⁾

In Indonesia, a similar study involving 500 parents across five provinces—Central Kalimantan, Lampung, South Sulawesi, West Java, and Yogyakarta—showed that 92.4% agreed that the influenza vaccine can prevent influenza, with most information about the vaccine coming from the media. ⁽²²⁾

Another study conducted at nine pediatric oncology institutions in the United States found that one of the challenges in vaccinating immunocompromised patients was parental concern, especially regarding vaccine side effects, vaccine safety for cancer patients, and uncertainty about the vaccine. A 2020 study involving 145 parents of children who had completed chemotherapy 3-6 months prior found that one-third did not know which vaccines were needed, and another third did not discuss vaccination with healthcare providers. This study also found that the influenza vaccine was the most commonly administered vaccine after therapy. ⁽²³⁾⁽²⁴⁾

A study by Kersun et al. involving 100 parents at an outpatient oncology clinic showed that 94% of their children had received the influenza vaccine before the cancer diagnosis was confirmed. About 30% of parents were worried their child would still get influenza after vaccination, 23% felt their child was not healthy enough to be vaccinated, and 56% feared vaccine side effects. ⁽¹⁴⁾

CONCLUSION

Administration of the influenza vaccine can reduce the incidence of influenza illness in the community. Although immunocompromised children have a less adequate immune response to the influenza vaccine compared to healthy children, the inactivated influenza vaccine is safe and still recommended. A major challenge in vaccination is convincing parents. Many parents fear vaccine side effects, believe their child has a low risk of infection, or think the vaccine may cause illness. Therefore, collaboration with healthcare workers to provide education about the importance of vaccination is crucial to help reassure parents, especially those with children who have cancer. Vaccination can help reduce symptoms and complications. Side effects of the vaccine in children with cancer are similar to those in healthy children when administered properly. Vaccination not only protects the individual child but also the community as a whole.

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