

Influenza Immunization for Adult and Pediatric Patients Undergoing Cancer Treatment

Effective Date: October, 2022



Background

Seasonal influenza is an important cause of morbidity and mortality in Canada.¹ An estimated 12,200 hospitalizations and 3,500 deaths can be attributed to influenza annually.² People at greatest risk of influenza-related complications are children 6 to 59 months of age, pregnant individuals, older adults (>65 years), residents of congregate living facilities and other chronic care facilities, Indigenous peoples and people with underlying medical conditions.² Adult and pediatric patients with cancer are considered immunosuppressed, either as a result of their underlying disease or secondary to their treatment, and are therefore included in this high risk group. Influenza infection not only causes primary illness but also can lead to severe secondary medical complications, including viral pneumonia, secondary bacterial pneumonia, and worsening of underlying medical conditions.

Guideline Questions

1. What are the recommendations for influenza immunization for adult and pediatric patients with solid tumours or hematologic cancers in Alberta?
2. What is the current evidence for response to the influenza vaccine among adult and pediatric patients with cancer receiving chemotherapy or other systemic therapy?
3. What is the best timing for administering the influenza vaccine in relation to the therapy cycle and other vaccines for adult and pediatric patients with cancer?

Search Strategy

The PubMed database was searched according to the strategy outlined in Appendix B. The 2022 search yielded 111 citations, two of which met the criteria to be included in the evidence tables presented in a supporting document. A systematic search of grey literature included websites from the World Health Organization, Health Canada, the Public Health Agency of Canada, Alberta Health Services, Alberta Health, Centers for Disease Control and Prevention, and the American Academy of Pediatrics. A search for published clinical practice guidelines from within the oncology field yielded one result from the National Comprehensive Cancer Network.³

Target Population

The recommendations outlined in this guideline apply specifically to children and adults with solid tumours or hematologic malignancies.

Recommendations

The following recommendations have been adapted from existing practice guidelines, policy documents, and consensus statements, including those from the [Alberta Health Services Immunization Program Standards Manual](#), [Alberta Influenza Immunization Policy](#), the National Advisory Committee on Immunization,² the Public Health Agency of Canada,⁴ the Centers for Disease Control and Prevention⁵, and the American Academy of Pediatrics.⁶ Evidence from the peer-reviewed literature was also reviewed and considered.

This guideline outlines the recommendations for influenza immunization among adult and pediatric patients with cancer. For the most current Alberta Health Services information, clinical guidelines, and schedules on influenza immunization for the general population, please visit the [Influenza Immunization Information for Health Professionals](#) webpage. For information specific to COVID-19 immunization for Alberta cancer patients and families, please refer to [COVID-19 and Cancer Treatment](#). For general COVID-19 immunization information, please refer to [Health Professional Immunization Information \(COVID-19\)](#).

The 2022/2023 standard and high dose quadrivalent inactivated influenza vaccines being used in Alberta contain the following antigenic strains:^{2,5,7,8}

- A/Victoria/2570/2019 (H1N1)pdm09-like virus;
- A/Darwin/9/2021 (H3N2)-like virus;
- B/Austria/1359417/2021 (B/Victoria lineage)-like virus; and
- B/Phuket/3073/2013 (B/Yamagata lineage)-like virus.

Influenza vaccines that are included in the 2022/23 Provincially Funded Program⁸

Product	Standard dose Quadrivalent Inactivated Influenza Vaccine (SD-QIV)	High dose Quadrivalent Inactivated Vaccine (HD-QIV)
Influenza Vaccine Name	Fluzone® FluLaval® Tetra	Fluzone® High Dose
Presentation	Multidose Vial Pre-filled syringe	Pre-filled syringe
Dose	0.5 mL	0.7 mL
Age Group	Six months of age and older Note: Individuals 65 years of age and older should be offered Fluzone® High Dose influenza vaccine as first option. ⁹	65 years of age and older

Influenza Immunization: Adult Patients with Cancer

1. Annual administration of the **inactivated** influenza vaccine is recommended for most adult patients with cancer. Patients considered to be the highest priority are those on active treatment.^{2,5,10} Individuals with malignant solid tumours (and on immunosuppressive therapy) who are three months post-chemotherapy and the cancer is in remission are no longer considered immunocompromised.¹¹ Individuals with malignant hematologic disorders who are more than three years post therapy and no longer on immunosuppressive medications are considered healthy and should be assessed for immunizations as per the general population.

2. Age, duration, type of systemic therapy (except for rituximab or other B-cell or T cell depleting antibodies), and curative versus palliative treatment intent do not appear to influence the response of adult patients with cancer to the influenza immunization. Adult patients with hematologic malignancies may have lower responses to immunization when compared to adult patients with solid tumours.
3. Timing of inactivated influenza immunization in relation to the therapy cycle and other vaccines:
 - a) The vaccine should ideally be given at least two weeks before commencing any immune-suppressing cancer treatment, including chemotherapy and ICI therapy, or delayed until at least three months after such treatment has stopped or is at the lowest possible level.¹¹ While administration of the vaccine at any time before, during or after immune-suppressing cancer treatment is safe, its efficacy may be reduced.
 - b) Patients who are treated with rituximab (or other B-cell or T cell depleting antibodies), should have all their inactivated vaccines postponed until at least six months after the last dose of rituximab. A clearance letter is required before starting immunization.¹²⁻¹⁵
 - c) Patients on high-dose systemic steroids (i.e., 20 mg/day or more of prednisone or its equivalent, for 14 days or more) should wait four weeks after discontinuation of therapy before the vaccine is administered.¹¹
 - d) For AHS employees, direction for co-administration of influenza and COVID-19 vaccines can be found on the internal website at Home → Teams → Communicable Disease Control → Immunization Program Standards Manual → Biological Product Information → COVID-19.
 - e) Patients on clinical trial protocols should continue to follow instructions based on their specific protocol.
4. For adult patients undergoing hematopoietic stem cell transplant (HSCT) the recipient and donor immunization status pre-transplant both have an impact on post-transplant immunity. Immunity established prior to HSCT may increase immune response following transplant.^{14,16,17}
 - a) **Recipient:** the inactivated influenza vaccine should be administered at least two weeks prior to transplant conditioning or mobilization chemotherapy. **Consult the attending transplant physician. Live influenza vaccine is contraindicated.**
 - b) **Donor:** the inactivated influenza vaccine should be administered at least two weeks before stem cell harvest. **Consult the attending transplant physician. Live influenza vaccine is contraindicated.**
 - c) There is no difference in recommended schedules between autologous or allogeneic recipients. Although a current topic of research, the differences in immunity post-transplant for the two types of recipients are not enough to justify two separate schedules.
 - d) Immune system recovery post-HSCT is variable and requires assessment by the transplant physician. The majority of HSCT recipients will have a detectable antibody response to the influenza vaccine at six months post-transplant which continues to

increase over the next 12 to 24 months. Graft versus host disease (GVHD) may prolong the duration of immunosuppression.

- e) For HSCT recipients, inactivated influenza vaccine should ideally be administered six months post-transplant. Inactivated influenza vaccine can be given as early as three to four months post-transplant in outbreak situations at the discretion of the transplant physician. In such case, two doses should be given, at least four weeks apart.
 - f) For patients on post-transplant maintenance therapy, all immunizations should be postponed until at least six months after the last dose of chemotherapy. It is not known how new agents used for maintenance therapy (e.g., lenalinomide/revlimid) impact patients' ability to respond to vaccines; some physicians elect to have their patients immunized. **A clearance letter is required before starting immunization.**
 - g) HSCT recipients who have started their post-HSCT vaccine series and then had the series interrupted by Chimeric Antigen Receptor T (CAR-T) cell therapy will need to restart their vaccine series. Inactivated influenza immunization can be restarted as early as three months post CAR-T cell therapy.
 - h) Inactivated immunization should not be delayed due to GVHD/immunosuppressive therapy, unless due to high-dose steroids (see above). Live vaccines are contraindicated in patients with active GVHD.
 - i) Household contacts and healthcare workers should be up to date for routine immunizations as per the Alberta Immunization Schedule, including annual influenza, to reduce the risk of disease transmission to transplant recipients.
 - j) Individuals who have received the live nasal spray influenza vaccine (FluMist® Quadrivalent) should avoid close association with individuals with severe immunocompromising conditions (e.g., bone marrow transplant recipients requiring protective isolation) for at least two weeks following immunization.¹⁴ The live nasal spray influenza vaccine (FluMist®) may be available for purchase in Alberta through community pharmacies.
5. Annual influenza immunization of family members and hospital or clinic staff and volunteers who are in contact with adult patients with cancer is strongly recommended. In many cases, this may be more important than immunizing the patients themselves, as some patients may be less likely to respond to the vaccine. Transmission of influenza between infected healthcare workers and their vulnerable patients results in significant morbidity and mortality; therefore, healthcare workers should consider it their responsibility to provide the highest standard of care, which includes receiving the annual **inactivated** influenza vaccine.^{2,18}
6. **Contraindications** for influenza immunization (standard or high-dose vaccine) in adult patients with cancer include:^{2,9,19}
- Known hypersensitivity to any component of the vaccine excluding eggs.
 - Anaphylactic or other allergic reactions to a previous dose of influenza vaccine.

- Known history of **severe** oculorespiratory syndrome (ORS) symptoms that included lower respiratory symptoms within 23 hours of receiving influenza vaccine pending consultation with the Medical Officer of Health to review the risks and benefits of further influenza immunization.
- Known history of Guillain Barré Syndrome (GBS) within six weeks of a **previous dose of influenza vaccine**.
- Individuals presenting with a serious acute febrile illness
 - Recommendations should be provided for these individuals to be immunized when their symptoms have resolved.
 - Individuals with non-serious febrile illness may be immunized.

7. **Precautions** for influenza immunization (standard or high-dose vaccine) in adult patients with cancer include:^{2,9,19}

- Egg allergy is not considered a contraindication for inactivated influenza vaccine.
- Egg-allergic individuals may be safely immunized using inactivated influenza vaccine without a prior influenza vaccine skin test and with the full dose of vaccine, irrespective of a past severe reaction to egg. They can be immunized in any setting and should be kept under observation for 30 minutes following vaccine administration.

As with all vaccine administration, immunizers should have the necessary anaphylaxis equipment and protocols, and be prepared to always respond to a vaccine emergency. Vaccine recipients who have had an anaphylactic reaction to *any* agent should be kept under observation for at least 30 minutes post-immunization.

Individuals who report they have experienced severe lower respiratory symptoms (wheeze, chest tightness, difficulty breathing) within 24 hours of a previous influenza immunization, had an apparent significant allergic reaction to the vaccine or any other symptoms (e.g., throat constriction or difficulty swallowing) should have a report sent to the [Adverse Event Following Immunization Reporting | Alberta Health Services](#), please follow the reporting requirements laid out on this webpage. Follow up will then occur directly with the patient.

Influenza Immunization: Pediatric Patients with Cancer

1. Annual administration of the **inactivated** influenza vaccine is indicated for most pediatric patients with cancer who are six months of age and older. A standard dose quadrivalent influenza vaccine, Fluzone® or FluLaval® Tetra for children six months of age and older should be used.² The live attenuated influenza vaccine is not recommended for children with immune-compromising conditions.^{2,5} Immunization with currently available influenza vaccines is **not** recommended for infants younger than six months of age. The recommended doses by age are as follows:

- Children nine years or older should receive one dose of influenza vaccine.

- Children previously unimmunized with influenza vaccine who are older than six months and less than nine years of age require **two** doses of influenza vaccine in the first year they are immunized, with a minimum interval of four weeks between doses.
 - Children six months to less than nine years of age who have been previously immunized with influenza vaccine in another season require only one dose of influenza vaccine.
 - A full dose (0.5 mL) of influenza vaccine should be used for all people who are receiving influenza immunization.
2. Although the data is limited, age, duration, and type of systemic therapy (except for rituximab or other B-cell or T cell depleting antibodies) do not appear to influence the response of pediatric patients to influenza vaccine. Pediatric patients with hematologic malignancies may have lower responses to immunization when compared to pediatric patients with solid tumours. Patients who are treated with rituximab or other B-cell or T cell depleting antibodies should have all their inactivated vaccines postponed until at least six months after the last dose of rituximab. A clearance letter is required before starting immunization.¹²⁻¹⁵
 3. Timing of inactivated influenza immunization in relation to the therapy cycle and other vaccines:
 - a) Influenza vaccine should ideally be given at least two weeks before the administration of any immune-suppressing cancer treatment, to allow the patient to develop a sufficient antibody response. If early immunization is not possible or feasible, administration of the inactivated vaccine less than two weeks before the start of immune-suppressing cancer treatment, or between treatment cycles has been reported to be safe and is recommended over not receiving the vaccine at all, although the efficacy of the vaccine may be reduced in this situation.
 - b) For AHS employees, direction for co-administration of influenza and COVID-19 vaccines can be found on the internal website at Home → Teams → Communicable Disease Control → Immunization Program Standards Manual → Biological Product Information → COVID-19.
 4. For pediatric patients undergoing hematopoietic stem cell transplant (HSCT) the recipient and donor immunization status pre-transplant both have an impact on post-transplant immunity. Immunity established prior to HSCT may increase immune response following transplant:^{11,14,20}
 - a) **Recipient:** the inactivated influenza vaccine should be administered at least two weeks prior to transplant conditioning or mobilization chemotherapy. **Consult the attending transplant physician. Live influenza vaccine is contraindicated.**
 - b) **Donor:** the inactivated influenza vaccine should be administered at least two weeks before stem cell harvest. **Consult the attending transplant physician. Live influenza vaccine is contraindicated.**
 - c) There is no difference in recommended schedules between autologous or allogeneic recipients. Although a current topic of research, the differences in immunity post-transplant for the two types of recipients are not enough to justify two separate schedules.

- d) Immune system recovery post-HSCT is variable and requires assessment by the transplant physician. The majority of HSCT recipients will have a detectable antibody response to the influenza vaccine at six months post-transplant which continues to increase over the next 12 to 24 months. GVHD, may prolong the duration of immunosuppression.
 - e) For HSCT recipients, inactivated influenza vaccine should ideally be administered six months post-HSCT but can be given as early as three to four months post-transplant in outbreak situations at the discretion of the transplant physician. In such case, two doses should be given, at least four weeks apart.
 - k) For patients on post-transplant maintenance therapy all immunizations should be postponed until at least six months after the last dose of chemotherapy. It is not known how new agents used for maintenance therapy (e.g., lenalinomide/revlimid) impact patients' ability to respond to vaccines; some physicians elect to have their patients immunized. **A clearance letter is required before starting immunization.**
 - l) HSCT recipients who have started their post-HSCT vaccine series and then had the series interrupted by Chimeric Antigen Receptor T (CAR-T) cell therapy will need to restart their vaccine series. Inactivated influenza immunization can be given as early as three months post CAR-T cell therapy.
 - f) Inactivated immunization should not be delayed due to GVHD/immunosuppressive therapy, unless due to high-dose steroids (i.e., 2 mg/kg per day for children under 10 kg or 20 mg/day for children over 10 kg or more of prednisone or its equivalent, for 14 days or more). Live vaccines are contraindicated in patients with active GVHD.
 - g) Household contacts and healthcare workers should be up to date for routine immunizations as per the Alberta Immunization Schedule, including annual influenza, to reduce the risk of disease transmission to pediatric transplant recipients.
 - h) Individuals who have received the live nasal spray influenza vaccine (FluMist® Quadrivalent) should avoid close association with individuals with severe immunocompromising conditions (e.g., transplant recipients requiring protective isolation) for at least two weeks following immunization.¹⁴ The live nasal spray influenza vaccine (FluMist®) may be available for purchase in Alberta through community pharmacies.
5. Annual influenza immunization of family members, out-of-home caregivers, and hospital or clinic staff and volunteers in contact with pediatric patients with cancer is strongly recommended. In many cases, this may be more important than immunizing the patient themselves, as some patients may be less likely to respond to the vaccine. Transmission of influenza between infected healthcare workers and their vulnerable patients results in significant morbidity and mortality; therefore, healthcare workers should consider it their responsibility to provide the highest standard of care, which includes receiving the annual **inactivated** influenza vaccine.^{2,18}
6. **Contraindications** for influenza immunization in pediatric patients with cancer include:^{2,19}

- Known hypersensitivity to any component of the vaccine excluding eggs.
- Anaphylactic or other allergic reactions to a previous dose of influenza vaccine.
- Known history of **severe** oculorespiratory syndrome (ORS) symptoms that included lower respiratory symptoms within 23 hours of receiving influenza vaccine pending consultation with the Medical Officer of Health to review the risks and benefits of further influenza immunization.
- Known history of Guillain Barré Syndrome (GBS) within six weeks of a **previous dose of influenza vaccine**.
- Individuals presenting with a serious acute febrile illness
 - Recommendations should be provided for these individuals to be immunized when their symptoms have resolved.
 - Individuals with non-serious febrile illness may be immunized.

7. **Precautions** for influenza immunization in pediatric patients with cancer include:^{2,19}

- Egg allergy is not considered a contraindication for inactivated influenza vaccine.
- Egg-allergic individuals may be safely immunized using inactivated influenza vaccine without a prior influenza vaccine skin test and with the full dose of vaccine, irrespective of a past severe reaction to egg. They can be immunized in any setting and should be kept under observation for 30 minutes following vaccine administration.

As with all vaccine administration, immunizers should have the necessary anaphylaxis equipment and protocols, and be prepared to always respond to a vaccine emergency. Vaccine recipients who have had an anaphylactic reaction to *any* agent should be kept under observation for at least 30 minutes post-immunization.

Individuals who report they have experienced severe lower respiratory symptoms (wheeze, chest tightness, difficulty breathing) within 24 hours of a previous influenza immunization, had an apparent significant allergic reaction to the vaccine or any other symptoms (e.g., throat constriction or difficulty swallowing) should have a report sent to the [Adverse Event Following Immunization Reporting | Alberta Health Services](#), please follow the reporting requirements laid out on this webpage. Follow up will then occur directly with the patient.

Discussion

Influenza Immunization: Adult Patients with Cancer

Cancer treatments can produce acute and profound immunosuppression, although published literature suggests that the degree may differ according to the specific regimen, doses, and duration of treatment. Annual administration of the inactivated influenza vaccine is recommended for most adult patients with cancer.

Interpreting the results of influenza vaccine efficacy in adult patients with cancer is difficult because patient characteristics, cancer types, vaccine strains, and assessment of responses vary between published studies. In a review of 1,225 patients from the Surveillance, Epidemiology, and End Results (SEER) and Medicare databases, Earle *et al.* reported that among patients undergoing chemotherapy for stage IV colorectal cancer, those who had been immunized had lower rates of influenza and pneumonia than those who were not immunized (1.1% vs. 3.8%, $p=0.004$).²¹ In addition, the immunized patients had significantly fewer interruptions in the chemotherapy cycles, showed a trend toward using fewer health care resources, and were more likely to survive to the next influenza season (HR for death=0.88, 95% CI 0.77-0.99). Similarly, a 2013 Cochrane review of four studies involving 2,124 adult patients with cancer receiving chemotherapy concluded that influenza immunization was associated with lower mortality and that infection rates were lower or similar in patients who were vaccinated versus those who were not.²²

Patients with cancer who develop influenza are at high risk for serious complications and death. In a review of 11 published studies involving adult patients undergoing chemotherapy treatment or hematopoietic stem cell transplantation (HSCT), Kunisaki *et al.* reported case fatality rates ranging from 11% to 33% for the studies involving chemotherapy.²³ Similarly, in a report of 168 critically ill patients admitted to Canadian intensive care units at the peak of the 2009-2010 H1N1 influenza outbreak, Kumar *et al.* reported that 8.2% of these patients had one or more major co-morbidities, including immunosuppression due to cancer or cancer therapies.²⁴

It is most beneficial to immunize patients with malignant solid tumours at least two weeks prior to beginning chemotherapy to allow for sufficient antibody production by the patient.^{4,25-27} In a study involving patients with breast cancer, geometric mean titers were significantly lower among individuals immunized at day 16 of chemotherapy versus those immunized at day 4.²⁸ However, a pilot study of 18 patients with solid tumours immunized either one week before or on the first day of chemotherapy reported that all patients mounted an immune response to the vaccine, and there were no significant differences in seroconversion or seroprotection rates against the three influenza strains between the two groups of patients.²⁹ If early immunization is not possible, administration of the inactivated vaccine *between* chemotherapy cycles has been reported to be safe and is recommended over not receiving the vaccine at all, although the efficacy of the vaccine may be reduced in this situation.^{21,25,30} In such situations, administration of the vaccine is preferable when therapy is at the lowest level possible.⁴

There is a growing body of published data on the safety and efficacy of the influenza vaccine in patients with cancer treated with ICI therapies, including CTLA-4 inhibitors (e.g., ipilimumab) or PD-1 and PD-L1 inhibitors (e.g., nivolumab, pembrolizumab).³¹⁻⁴⁰ One of the first studies on the safety of influenza vaccination in cancer patients receiving ICIs caused concern about an increased risk of severe immunological complications.⁴¹ While data were based on a small number of lung cancer patients (n=23), because of this data many clinicians began to advise patients on ICIs against vaccination. A 2021 systematic review that included ten studies assessing the safety and eight assessing the efficacy of influenza vaccination in cancer patients receiving ICIs has since moderated these concerns.³⁸ The systematic review showed that in most subsequent and larger studies, the overall safety and efficacy of influenza immunization in cancer patients receiving ICIs is not markedly different from that observed in the general population. Therefore, it is the consensus of the Alberta Provincial Tumour Teams that patients receiving ICIs can receive the influenza vaccine at any time during therapy.

Adult patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) are at significant risk for infections prior to immune regeneration. Preparation for both autologous and allogeneic HSCT involves intensive high-dose regimens of chemotherapy and/or radiotherapy, which leaves the patient acutely and profoundly immunocompromised for several months following transplantation. The impact of seasonal influenza on HSCT recipients can be devastating. Llungman *et al.* reported a case fatality rate of 23% among over 1,900 patients in Europe over three influenza seasons.¹⁶ Kumar and colleagues reported the results of a multicentre prospective observational study of pediatric and adult solid organ transplant (SOT) and HSCT patients carried out across 20 sites from the United States, Canada, and Spain. They documented 616 patients with confirmed influenza (477 SOT; 139 HSCT) over a 5-year study period. The annual incidence of pneumonia ranged between 11.3-35.0% and ICU admission rates ranged between 8.1% to 14.3%. The receipt of vaccine in the same influenza season was associated with a decrease in disease severity as determined by the presence of pneumonia, and antiviral treatment within 48 hours was associated with improved outcomes.⁴² No significant differences were noted between SOT and HSCT patients with regard to pneumonia and ICU care. However, HSCT patients had a higher 6-month mortality (13.8% vs 4.8%, p<0.001) and viral load at disease onset (median viral load 1.04×10^5 copies/mL vs 8.04×10^3 copies/mL, p=0.001) compared to SOT patients.

There is variability in the efficacy of influenza immunization in HSCT patients reported in the literature. One study documented serologic responses ranging from 0% in allogeneic transplant patients to 32% in autologous transplant patients. Another study reported immune responses of 29% to 34% in patients who underwent HSCT, and 46% to 62% in a group of healthy matched controls.^{43,44} In a study of 82 allogeneic HSCT recipients who received the 2009-2010 H1N1 vaccine, Issa *et al.* reported that seroprotective antibody titers were detected in 51% of patients, and this rate was not affected by the presence of chronic graft-versus-host disease or type of conditioning regimen.⁴⁵ Patients were more likely to have higher seroprotective titers the further away they were from the transplant (OR=1.79 per year, 95% CI 1.12-2.85), and rituximab administration prior to

immunization was associated with lower seroprotective titers (OR=0.11, 95% CI 0.01-0.97). Bedognetti *et al.* reported the results of a study comparing response to the seasonal influenza vaccine in 31 patients with non-Hodgkin lymphoma in complete remission after treatment with rituximab-containing regimens to 34 age-matched healthy subjects.⁴⁶ They reported that CD27+ memory B-cells were significantly reduced in patients treated with rituximab-based chemotherapies, and this reduction correlated with lower responses to influenza immunization. Similarly, in a study of 67 patients with lymphoma who were treated with rituximab alone or in combination with chemotherapy, Yri *et al.* reported that only five patients had a measurable but non-protective antibody titer after immunization, and the remaining 62 patients had no detectable titers at all, giving a seroprotection rate of 0%. This is in comparison to the 82% seroprotection rate for the healthy control patients. The investigators suggest that the non-responsiveness was due to the B-cell depletion caused by rituximab therapy.⁴⁷ Similarly, Berglund and colleagues reported the results of a subgroup analysis of rituximab-treated patients among 96 adult outpatients with cancer who were undergoing treatment. Of the 13 patients treated with rituximab, only one responded to immunization against influenza A (H1N1) and none responded to immunization against seasonal influenza.¹³ Patients who are treated with rituximab or other B-cell depleting antibodies should therefore have all immunizations postponed until at least six months after the last dose of rituximab or other B-cell depleting therapies.^{12-14,47}

Lower-respiratory tract infection (LRTI) is a complication of influenza infection that frequently leads to lung injury and death, and profound lymphopenia is one of the most significant risk factors for progression from upper- to lower-respiratory tract involvement.⁴⁸ Risk factors for progression of H1N1 influenza to LRTI in patients with hematologic malignancies are unknown at the present time.

It is recommended that both the recipient and donor (for allogeneic transplants) receive inactivated influenza immunization at least two weeks prior to the transplant.^{4,16,49} While only 10% to 30% of HSCT recipients will have a detectable antibody response to the influenza vaccine at six to 24 months post-transplant, over 60% will have a detectable response at 24 months or more post-transplant.⁵⁰ Immune system recovery post-transplant is variable and requires individual assessment by the transplant physician. For example, patients treated with rituximab post-transplant will have a delay in their B-cell recovery by at least six months following the final dose.^{16,46} In addition, adult transplant patients with chronic graft-versus-host disease may require up to 24 months or more post-transplant to recover CD4+ counts. It is recommended that HSCT patients receive annual seasonal inactivate influenza immunization beginning at six months post-transplant.^{4,16,49}

To reduce the risk of disease transmission, immunization of family members and hospital staff in contact with patients who are at high risk for severe or complicated seasonal influenza is strongly recommended. Influenza immunization rates of health care workers is associated with a reduction in influenza infections in cancer patients.⁵¹ The Public Health Agency of Canada (PHAC) states that people who are potentially capable of spreading influenza to those who are at high risk should be immunized, regardless of whether the high-risk person has been immunized.⁴ Immunization of family members and hospital staff who are in contact with HSCT recipients is also of particular importance,

as these patients are severely immunocompromised. Family members and health care providers should receive the inactivated influenza vaccine beginning the season before the transplant and annually for 24 months or more post-transplant.⁴⁹ If the family member or healthcare worker will only accept the live nasal spray influenza vaccine, they should wait two weeks following immunization before continuing to provide care to severely immunocompromised individuals.¹⁷

Influenza Immunization: Pediatric Patients with Cancer

Pediatric patients with cancer are highly susceptible to influenza infections and have an increased rate of influenza infection compared to healthy children.⁵² In addition, hospitalization rates due to influenza infection for children under the age of five years with chronic health conditions have been reported to be significantly higher than for healthy children in the same age group.⁵³ Annual administration of the inactivated influenza vaccine is indicated for all pediatric patients with cancer over the age of six months. Immunization with currently available influenza vaccines is **not** recommended for infants younger than six months of age.

Recommendations regarding influenza vaccine doses in healthy children state that those nine years of age and older should receive one dose of the vaccine annually. Children younger than nine years of age who have not previously received the trivalent or quadrivalent influenza vaccine require two doses of the vaccine **in the first year** they are immunized, with the second dose being administered four weeks or more after the first dose. The live vaccine is contraindicated in children with immune compromising conditions.²

Like the literature regarding adult patients with cancer, interpreting the limited published results of influenza vaccine efficacy in pediatric patients with cancer is difficult because patient characteristics, cancer types, vaccine strains, and assessment of responses vary between published studies. In a meta-analysis of nine controlled clinical trials and one randomized controlled trial involving 770 children, Goossen *et al.* reported that immune responses to the seasonal influenza vaccine in children receiving chemotherapy were consistently weaker than in those children who had completed their chemotherapy regimen and in healthy controls.⁵⁴ Several studies have reported that pediatric patients with cancer who have completed their chemotherapy regimens have increased rates of seroconversion, suggesting that the timing of influenza immunization with regards to the chemotherapy cycle is an important factor in this population.^{52,55} Seroconversion rates are also influenced by the type of cancer (solid tumour vs. hematologic malignancy)⁵⁶ and the type of chemotherapy.⁵⁷ Similar to the recommendations made for adults with cancer, it is likely most beneficial to immunize pediatric patients with cancer two weeks prior to beginning chemotherapy, to allow for sufficient antibody production by the patient. Shahgholi *et al.* assessed the immune response of 32 pediatric patients with acute lymphoblastic leukemia (ALL) and compared them to a control group of 30 healthy siblings. The trivalent influenza vaccine was well tolerated in the patients with ALL, and the immune responses were acceptable but limited. The percentage of ALL patients versus healthy controls with a fourfold increase in antibody titers were 56.2% versus 80% for H1N1

($p=0.04$), 40.6% versus 53.3% for H3N2 ($p=0.31$), and 59.4% versus 83.3% for influenza B ($p=0.038$).⁵⁸

The recommendations for pediatric patients undergoing HSCT are like those for adult patients.^{14,16,20,49} It is recommended that both the recipient and donor (for allogeneic transplants) receive the inactivated influenza vaccine two weeks prior to the transplant. Immune system recovery following transplant is variable and depends on factors such as the types of therapies administered and the presence of graft-versus-host disease; therefore, individual assessment is required by the transplant physician. Influenza vaccine should ideally be administered six months post-HSCT in pediatric patients. Inactivated influenza vaccine can be given as early as three to four months post-transplant in outbreak situations, at the discretion of the transplant physician. In such case, two doses should be given, at least four weeks apart.⁵⁹

Similar to the recommendations made for adult patients with cancer, immunization of family members, caregivers, and hospital staff in contact with pediatric patients who are at high risk for severe or complicated influenza is **strongly recommended**.⁴ Immunization of family members and hospital staff who are in contact with pediatric HSCT recipients is also of particular importance, as these patients are severely immunocompromised and cannot be immunized themselves for at least four months post-transplant. In this situation, family members and health care providers should receive the inactivated influenza vaccine beginning the season before the transplant and annually for 24 months or more post-transplant.^{20,49} If the family member or healthcare worker will only accept the live nasal spray influenza vaccine, they should wait two weeks following immunization before continuing to provide care to severely immunocompromised individuals.²⁰

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Appendix A: Additional Resources

Canadian Resources

Alberta Health Services. Immunization Program Standards Manual:

<https://www.albertahealthservices.ca/info/page10802.aspx>

Alberta Health Services, Influenza Immunization:

www.albertahealthservices.ca/influenza/influenza.aspx

Alberta Health Services. Influenza Information for Health Professionals:

www.albertahealthservices.ca/influenza/Page12438.aspx

Alberta Bone Marrow and Blood Cell Transplant Program. Standard Practice Manual:

www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-bmt-manual.pdf

Public Health Agency of Canada. National Advisory Committee on Immunization (NACI) Advisory Committee. Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2022-2023:

<https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2022-2023.html>

Public Health Agency of Canada. Canadian Immunization Guide:

<https://www.canada.ca/en/public-health/services/canadian-immunization-guide.html>

International Resources

World Health Organization. Global Influenza Programme:

<https://www.who.int/teams/global-influenza-programme>

Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP): Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2022-23 Influenza Season:

<https://www.cdc.gov/mmwr/volumes/71/rr/rr7101a1.htm>

Centers for Disease Control and Prevention. Cancer, the Flu, and You. What Cancer Patients, Survivors, and Caregivers Should Know About the Flu:

www.cdc.gov/cancer/flu/

National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections, version 2.2022 (requires free registration and login):

https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

American Academy of Pediatrics (AAP). Policy Statement: Recommendations for the Prevention and Control of Influenza in Children, 2022-2023:

<https://publications.aap.org/pediatrics/article/doi/10.1542/peds.2022-059274/189385/Recommendations-for-Prevention-and-Control-of?autologincheck=redirected?nfToken=00000000-0000-0000-0000-000000000000>

Appendix B: Search Strategy

Database	Date	Search Strategy	Results
PubMed	Aug. 26, 2022	<ol style="list-style-type: none"> 1. carcinoma[MeSH Terms] 2. neoplasm[MeSH Terms] 3. cancer[Title/Abstract] 4. tumor[Title/Abstract] 5. tumour[Title/Abstract] 6. (((tumour[Title/Abstract]) OR (tumor[Title/Abstract])) OR (cancer[Title/Abstract]) OR (neoplasm[MeSH Terms])) OR (carcinoma[MeSH Terms]) 7. influenza A virus[MeSH Terms] 8. influenza B virus[MeSH Terms] 9. influenza, human[MeSH Terms] 10. influenza[Title/Abstract] 11. (((influenza[Title/Abstract]) OR (influenza, human[MeSH Terms])) OR (influenza B virus[MeSH Terms])) OR (influenza A virus[MeSH Terms]) 12. immunization[MeSH Terms] 13. vaccination[MeSH Terms] 14. immun*[Title/Abstract] 15. vaccin*[Title/Abstract] 16. (((vaccin*[Title/Abstract]) OR (immun*[Title/Abstract])) OR (vaccination[MeSH Terms])) OR (immunization[MeSH Terms]) 17. (((((vaccin*[Title/Abstract]) OR (immun*[Title/Abstract])) OR (vaccination[MeSH Terms])) OR (immunization[MeSH Terms])) AND (((influenza[Title/Abstract]) OR (influenza, human[MeSH Terms]) OR (influenza B virus[MeSH Terms]) OR (influenza A virus[MeSH Terms]))) AND (((((tumour[Title/Abstract]) OR (tumor[Title/Abstract])) OR (cancer[Title/Abstract]) OR (neoplasm[MeSH Terms])) OR (carcinoma[MeSH Terms])) <p>***Limit 17 to Humans, English, from 2021/8/1 to present ***Excluded case reports, duplicates from 2021, covid 19, non-cancer or non-human subjects (i.e., mice, in vitro), vaccine uptake and equity, vaccine design</p>	<p>712,272 3,723,199 2,033,334 1,339,093 233,293 4,602,569 48,112 4,554 55,595 109,909 119,912 200,362 102,321 2,688,037 386,195 2,903,841 2,466 111 2</p>

Please refer to the Literature Review: Influenza Immunization for Adult and Pediatric Patients Undergoing Cancer Treatment (2022) document for a summary of relevant results.

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Tumour Teams. Members include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Tumour Teams, external participants identified by the Working Group Lead, and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Resource Unit Handbook](#).

This guideline was originally developed and posted to the website in November 2009. The guideline was revised and reposted in September 2010, October 2011, October 2012, September 2013, September 2014, October 2015, October 2016, October 2017, October 2018, October 2019, October 2020, October 2021, and October 2022.

Maintenance

An annual review will next be conducted in August 2023. If critical new evidence is brought forward before that time, however, the guideline will be revised and updated accordingly.

Abbreviations

ACIP, Advisory Committee on Immunization Practices; ALL, acute lymphoblastic leukemia; CI, confidence interval; GBS, Guillain-Barre Syndrome; HR, hazard ratio; HSCT, hematopoietic stem cell transplant; ICI, immune checkpoint inhibitor; LRTI, lower respiratory tract infection; NACI, National Advisory Committee on Immunization; OR, odds ratio; ORS, oculo-respiratory syndrome; PHAC, Public Health Agency of Canada; QIV, quadrivalent inactivated influenza vaccine; SEER, Surveillance, Epidemiology, and End Results database; SOT, solid organ transplant; TIV, trivalent inactivated influenza vaccine

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Tumour Teams and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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