Guideline Resource Unit
guru@ahs.ca

Influenza Immunization for Adult and Pediatric Patients Undergoing Cancer Treatment

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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 and older), 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.

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.

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 2024 search yielded 43 citations, 3 of which met the criteria to be included in the evidence tables, which are summarized in a supporting document. A comprehensive exploration of gray literature encompassed a review of websites from sources such as Alberta Health, Alberta Health Services, Health Canada, Public Health Agency of Canada, Centers for Disease Control and Prevention, American Academy of Pediatrics, and the World Health Organization. A search for published clinical practice guidelines on oncology websites yielded one updated guideline from the National Comprehensive Cancer Network.[3]

The following recommendations have been adapted from existing practice guidelines, policy documents, and consensus statements, including those from the Alberta BMT Standard Practice Manual,[4] Alberta Health Services Immunization Program Standards Manual,[5] Alberta Influenza Immunization Policy,[6] National Advisory Committee on Immunization,[2] the Public Health Agency of Canada,[7] the Centers for Disease Control and Prevention,[8] and the American Academy of Pediatrics.[9]

Target Population

The recommendations outlined in this guideline apply to adult and pediatric patients with solid tumours or hematologic malignancies.

Recommendations

1. The 2024/2025 quadrivalent inactivated influenza vaccines being used in Alberta contain the following antigenic strains:[6,8,10]

Egg-based (Fluzone®, FluLaval® Tetra, FluZone® High-Dose)	Cell-cultured (Flucelvax® Quad)
• A/Victoria/4897/2022 (H1N1)pdm09-like virus • A/Thailand/8/2022 (H3N2)-like virus • B/Austria/1359417/2021 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B/Yamagata lineage)-like virus	• A/Wisconsin/67/2022 (H1N1)pdm09-like virus • A/Massachusetts/18/2022 (H3N2)-like virus • B/Austria/1359417/2021 (B/Victoria lineage)-like virus • B/Phuket/3073/2013 (B/Yamagata lineage)-like virus

2. Annual administration of the **inactivated** influenza vaccine is recommended for most adult and pediatric patients with cancer. The live attenuated influenza vaccine is not recommended for adults or pediatric patients with immune-compromising conditions.[2,8] Patients considered to be the highest priority are those on active treatment.[2,5]
    - Adults with solid tumours who are 3 months post-chemotherapy and whose cancer is in remission are generally no longer considered immunocompromised. Adults with malignant hematologic disorders who are more than 3 years post-therapy and no longer on immunosuppressive medications are considered healthy and should be assessed for immunizations as per the general population.[11]
    - Children with solid tumours and hematologic malignancies who are 6 months post-chemotherapy and whose cancer is in remission are generally no longer considered immunocompromised.[12]

3. The influenza vaccines included in the 2024/2025 provincially funded program include:[6]

Product	Quadrivalent Inactivated Influenza Vaccine[11]			High-Dose Quadrivalent Inactivated Vaccine[12]
Influenza Vaccine Name	Fluzone® Quadrivalent	FluLaval® Tetra	Flucelvax® Quad	Fluzone® High-Dose Quadrivalent
Dose	0.5 mL			0.7 mL
Indications for use of provincially funded vaccine	Individuals six months of age and older who are living, working, going to school, or visiting Alberta.			Individuals aged 65 years and older who are living, working, or visiting Alberta. Adults 18 years of age and older who are: • Hematopoietic stem cell transplant (HSCT) recipients; • Chimeric antigen receptor T-cell (CAR T) therapy recipients; or • Solid organ transplant (SOT) candidates or recipients.

4. The recommended influenza vaccine schedules by age are:[13,14]
    - Children aged 6 months through 8 years of age who **have never** received the influenza vaccine require 2 doses (0.5 mL per dose) of the **quadrivalent inactivated** influenza vaccine with a minimum interval of 4 weeks between doses.
    - Children aged 6 months through 8 years of age who **have** previously received the influenza vaccine should receive 1 dose (0.5 mL) of the **quadrivalent inactivated** influenza vaccine.
    - For children aged 9 years and older, 1 dose (0.5 mL) of the **quadrivalent inactivated** influenza vaccine should be administered annually.
    - **High-dose quadrivalent inactivated** influenza vaccine is recommended for adults 65 years of age and older and adults 18 years of age and older who are:
        - Hematopoietic stem cell transplant (HSCT) recipients
        - Chimeric antigen receptor T-cell (CAR T) therapy recipients; or
        - Solid organ transplant (SOT) candidates or recipients.
    - Influenza immunization with currently available vaccines is not recommended for infants younger than 6 months of age.

5. **Timing** of inactivated influenza immunization in relation to the therapy cycle and other vaccines:
    - The inactivated influenza vaccine should *ideally* be administered at least 14 days before initiating immunosuppressive therapy.[11]
    - Adult and pediatric patients treated with immune checkpoint inhibitor therapies (e.g., PD-1, PDL-1, CTLA-4) can receive the inactivated influenza vaccine at any time during therapy.[15,16]
    - Adult and pediatric patients who are treated with B-cell or T-cell depleting antibodies (e.g., rituximab, blinatumomab), should be informed that influenza immunization is unlikely to provide effective protection and should be encouraged to ensure their household contacts are all immunized.[4,11,17, 18]
    - Patients treated with CAR T-cell therapy without a prior history of HSCT who received influenza vaccine pre-CAR T-cell therapy are eligible to receive another dose of influenza vaccine at least 3 months for adults and at least 6 months for children post-CAR T-cell therapy. If a clearance letter has been received to proceed with inactivated vaccines, consultation with the healthcare team is not required.[13,14]
    - Patients on clinical trial protocols should continue to follow instructions based on their specific protocol.
    - With the exception of the Respiratory Syncytial Virus (RSV) vaccine, influenza vaccines may be co-administered with, or at any time before or after other vaccines. RSV vaccine should be given with a two-week spacing before or after influenza and/or COVID-19 vaccines.[14] For AHS employees, direction for co-administration of influenza and other vaccines can be found on the internal website at *Home → Teams → Communicable Disease Control → Immunization Program Standards Manual → Biological Product Information.*

6. For adult and 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.[4,11,17-20] For detailed guidance regarding adult HSCT and CAR T-cell therapy recipients, please refer to the "Vaccination" chapter of the Alberta BMT Program Standard Practice Manual.[4]
   a. Recipient: the inactivated influenza vaccine should be administered at least 2 weeks prior to transplant conditioning or mobilization chemotherapy. Live vaccines are contraindicated. The transplant healthcare team should be consulted.
   b. Donor: the inactivated influenza vaccine should be administered at least 2 weeks before stem cell harvest. The transplant healthcare team should be consulted.
   c. For adult HSCT recipients, inactivated influenza vaccine should ideally be administered 6 months post-transplant but can be given as early as 3 months post-transplant at the discretion of the transplant physician during the influenza season. High-dose quadrivalent inactivated influenza vaccine is recommended for patients 18 years of age or older, including pregnant individuals, if available. Once adult HSCT recipients receive clearance for non-live vaccinations (typically between 3-6 months post HSCT), inactivated influenza vaccine can be given in all subsequent years without further clearance needed.
   d. For pediatric HSCT recipients, the quadrivalent inactivated influenza vaccine should be administered 6 months post-transplant.[12]
   e. There is no difference in recommended schedules of influenza vaccine administration between autologous or allogeneic recipients.
   f. Adult and pediatric HSCT recipients who are treated with B-cell or T-cell depleting targeted therapies (e.g., rituximab, blinatumomab) should have the inactivated influenza vaccination postponed until at least 6 months after the last dose of medication.
   g. For HSCT recipients on post-transplant maintenance therapy, inactivated influenza immunization should be postponed until at least 6 months after the last dose of chemotherapy. Maintenance therapies (e.g., lenalinomide) are not a contraindication to influenza immunization.[21]
   h. Individuals receiving CAR T-cell therapy are to be reimmunized with inactivated influenza vaccine as per the standard allogeneic HSCT schedule (see recommendations #6c and #6d above).
   i. HSCT recipients who have started their post-HSCT vaccine series and then had the series interrupted by CAR T-cell therapy should restart their vaccine series. Immunization will be directed by the transplant centre through patient specific letters.
   j. Live influenza vaccine is contraindicated for HSCT patients less than 24 months post-HSCT and not recommended in the later transplant phase. It may be considered on an individual basis in the later transplant phase (greater than 2 years post-transplant).
   k. 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. Household contacts and healthcare workers who

have received the live influenza vaccine (FluMist®) should avoid close association with individuals with severe immunocompromising conditions (e.g., bone marrow transplant recipients requiring protective isolation) for at least 2 weeks following immunization. The live nasal spray influenza vaccine (FluMist®) may be available for purchase in Alberta through community pharmacies.

7. Annual influenza immunization of family members and hospital or clinic staff and volunteers who are in contact with adult and pediatric 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.[2,22]

8. **Contraindications** for influenza immunization in adult and pediatric patients with cancer include:[2,13,14]

    - Known severe hypersensitivity to any component of the vaccine, with the exception of egg (see precautions below).
    - Anaphylactic or other allergic reactions to a previous dose of influenza vaccine.
    - Development of Guillain Barré Syndrome (GBS) within 6 weeks of a previous dose of influenza vaccine, unless another cause of GBS was found.

9. **Precautions** for influenza immunization (standard or high-dose vaccine) in adult and pediatric patients with cancer include:[2,13,14]

    - Egg-allergic individuals may be immunized using inactivated egg-based influenza vaccine without a prior influenza vaccine skin test and with the full dose of vaccine, irrespective of a past severe reaction to egg. Egg-allergic vaccine recipients should be kept under observation for 30 minutes following vaccine administration.
    - Individuals who have experienced oculorespiratory syndrome (ORS) including those with a severe presentation, but without lower respiratory symptoms, may be safely re-immunized. Advice of an expert (e.g., local Medical Officer of Health or designate) should be sought before immunizing individuals who experienced ORS with lower respiratory tract symptoms within 24 hours of influenza immunization.

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 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 the degree of immunosuppression may differ according to the specific therapy regimen, doses, and duration of treatment.[7] Annual administration of the inactivated influenza vaccine is recommended for most adult patients with cancer; however, 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.[23-24] 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).[25] In addition, the immunized patients had significantly fewer interruptions in their chemotherapy cycles, showed a trend toward using fewer healthcare 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 2018 Cochrane review that focused on the effectiveness of influenza vaccination in adults with cancer who had a suppressed immune system because of cancer or chemotherapy, reported lower mortality and infection-related outcomes with influenza vaccination.[26] However, the authors emphasized the evidence was weak due to low number of studies with low methodological quality.

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.[27] 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.[28]

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.[7,29-30] 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.[31] 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.[32] 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.[25,29,33]

There is a growing body of published data on the safety and efficacy of the influenza vaccine in patients with cancer treated with PD-1 (e.g., nivolumab, pembrolizumab), PD-L1 (e.g., atezolizumab), and CTLA-4 (e.g., ipilimumab) inhibitors alone or in combination.[15,34-42] One of the first studies on the safety of influenza vaccination in cancer patients (n=23) receiving immune checkpoint inhibitors (ICIs) caused concern about an increased rate of immunological toxicity.[43] However, the results of a recent systematic review show seroprotection and seroconversion rates in cancer patients receiving ICIs similar to those observed in a low-risk target population.[16] In addition, rates of immune-related adverse events were similar between vaccinated and unvaccinated patients. Most patients in this systematic review received PD-1 inhibitors as a single agent. Patients receiving PD-L1 inhibitors and combination CTLA-4/PD-1 inhibitors are significantly fewer in the reported data. There is some data to suggest the proportion of patients who experience immune-related adverse events, including Grade 3 or 4, is higher among patients treated with combination CTLA-4/PD-1 inhibitors.[34] For this reason, BC Cancer recommends that where possible, patients receiving combination CTLA-4/PD-1 inhibitor therapy should receive the inactivated influenza vaccine prior to beginning treatment and patients who experience a severe immune-related adverse event with combination therapy, should consider deferring influenza vaccination.[44] Finally, the prospective multicentre observational INVIDIa-2 is the first study to demonstrate a higher response rate and more prolonged survival for patients with advanced cancer receiving influenza vaccination during anticancer treatment with ICI.[42] At a median follow-up of 20 months, the influenza vaccination showed a favourable impact on the outcome of patients receiving ICI in terms of median OS (27.0 months [CI 19.5–34.6] in vaccinated vs. 20.9 months [16.6–25.2] in unvaccinated, p=0.003), median progression-free survival (12.5 months [CI 10.4–14.6] vs. 9.6 months [CI 7.9–11.4], p=0.049], and disease-control rate [74.7% vs. 66.5%, p=0.005]. In this trial, 94.4% of patients were treated with single agent ICI.

Adult patients with hematologic malignancies are at significant risk for infections prior to immune regeneration.[45-46] This patient population may also face additional risk because of their weakened postvaccination immune responses. For patients with multiple myeloma, the risk of infection is already increased at the stage of monoclonal gammopathy of undetermined significance (MGUS), and rises even further in patients with active disease when beginning anti-myeloma therapies.[47] It is recommended that all patients with multiple myeloma, MGUS, and smouldering myeloma, as well as their family members and caregivers, be immunized against influenza.[47] There are several published guideline statements that recommend that patients with multiple myeloma without a documented immune response to the influenza vaccine should automatically receive a second dose of the vaccine within a 4-week time interval.[47-48] A recent prospective cohort study of 84 patients with multiple myeloma treated with daratumumab reported that a two-injection strategy (4 weeks apart) of the

standard-dose influenza vaccine demonstrated potential benefits against specific strains (A-H3N2); the authors suggested that the overall low response rates in this patient population necessitates the development of alternative vaccination and prophylaxis strategies.[49]

For patients undergoing autologous or allogeneic HSCT, preparation 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.[50] Kumar *et al.* 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 over a 5-year study period and reported that the annual incidence of pneumonia ranged between 11.3% to 35.0%, while ICU admission rates ranged between 8.1% to 14.3%.[51] 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.[51] No significant differences were noted between SOT and HSCT patients with regards 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 × 105 copies/mL vs 8.04 × 103 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.[52-53] 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.[54] 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.[55] 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 5 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.[56] 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.[57] Patients who are treated with rituximab or other B-cell or T-cell depleting antibodies should therefore be informed that vaccination is unlikely to provide effective protection and should be encouraged to ensure that their household contacts are all immunized.[17,56-58]

Lower-respiratory tract infection (LRTI) is a complication of influenza infection that frequently leads to lung injury and death.[59] The intensive chemotherapy regimens used in HSCT can lead to a long period of profound lymphopenia, which is a significant risk factor for the progression of upper- to lower-respiratory tract involvement. Data from a systematic review and meta-analysis of the impact of influenza infection among adult and pediatric populations with hematologic malignancy and HSCT reported an overall rate of viral LRTI of 35.44%, with a statistically significant difference between adult and children (46.1% vs. 19.92, $p<0.001$).[60]

It is recommended that both the recipient and donor (for allogeneic transplants) receive inactivated influenza immunization at least 2 weeks prior to the transplant; if available, high-dose quadrivalent inactivated influenza vaccine is recommended for adults 65 years of age and older and adults 18 years of age and older who are HSCT recipients, CAR T-cell therapy recipients, or SOT candidates or recipients. [6,59,61]

The efficacy of the influenza vaccine in HSCT recipients is influenced by the duration since the transplantation, showing response rates ranging from 20% to 40% within the first 6 months, which subsequently increase to 20% to 72%.[20] Approximately 2 years post-transplantation, response rates closely resemble those observed in healthy individuals.[20] Graft versus host disease (GVHD), and the treatment thereof, prolongs the duration of immunosuppression. Although adult transplant patients with chronic GVHD may require up to 24 months or more post-transplant to recover CD4+ counts, inactivated influenza vaccination should not be delayed due to GVHD.

To reduce the risk of disease transmission, annual influenza immunization is recommended for close contacts (e.g., family members and hospital staff) of patients who are at high risk for severe or complicated influenza. Influenza immunization rates of healthcare workers is associated with a reduction in influenza infections in cancer patients.[62] Healthcare workers and other caregivers who could potentially transmit influenza to individuals at high risk should receive annual vaccination with non-live influenza vaccine, regardless of whether the high-risk individual has been vaccinated.[7]

Immunization of close contacts of HSCT recipients is also of particular importance because these patients are severely immunocompromised. The annual influenza vaccine is strongly recommended for close contacts both pre- and post-transplant.[11,19] 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.[11,19]

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.[63] In addition, hospitalization rates due to influenza infection for children under the age of 5 years with chronic health conditions have been reported to be significantly higher than for healthy children in the same age group.[64]

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 response varies 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 children who had completed their chemotherapy regimen and in healthy controls.[65] Seroconversion rates have also been reported to be influenced by the type of cancer (solid tumour vs. hematologic malignancy)[66] and the type of chemotherapy.[67] However, these studies are based on small numbers of patients. Like the recommendations for adults with cancer, it is likely most beneficial to immunize children with cancer at least 14 days weeks prior to beginning chemotherapy to allow for sufficient antibody production. 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).[68]

The recommendations for pediatric patients undergoing HSCT are like those for adult patients.[17,18,50,61] It is recommended that both the recipient and donor (for allogeneic transplants) receive the inactivated influenza vaccine 2 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 GVHD. Although inactivated influenza vaccine may be administered as early as 3 months after HSCT is complete, the Children's Oncology Group (COG) Taskforce recommends that all boosters and revaccinations be administered at 6 months post-HSCT in pediatric patients, as some studies suggest increased efficacy at this timepoint.[12] Children younger than 9 years of age receiving the influenza vaccine for the first time post-transplant are recommended to receive 2 doses administered at least 4 weeks apart.[13]

Immunization of child HSCT transplant recipients' close contacts (e.g., family members and healthcare workers) is particularly important because these patients are severely immunocompromised and cannot be immunized themselves for at least three months post-transplant. In this situation, annual influenza vaccine (either inactivated or live) is strongly recommended for close contacts both pre- and post-transplant.[18,61] If close contacts will only accept the live nasal spray influenza vaccine, they should wait for at least 2 weeks following immunization before continuing to provide care to severely immunocompromised individuals.[61]

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Appendix A: Additional Resources

Canadian Resources

Alberta Health Services:

- Get Immunized Against Influenza
- Immunization Program Standards Manual
- Influenza Information for Health Professionals
- Alberta Bone Marrow and Blood Cell Transplant Program: Standard Practice Manual

Government of Alberta: Alberta Immunization Policy

Public Health Agency of Canada:

- Canadian Immunization Guide
- An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI). Statement on Seasonal Influenza Vaccine for 2024-2025.

International Resources

American Academy of Pediatrics: Recommendations for Prevention and Control of Influenza in Children, 2024-2025

Centers for Disease Control and Prevention:

- Cancer and Flu
- Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2024-25 Influenza Season

National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections, version 3.2024. To access content, registration (free) is required.

World Health Organization: Global Influenza Programme

Appendix B: Search Strategy

Database	Date	Search Strategy	Results
PubMed	September 10, 2024	1. carcinoma[MeSH Terms]	755,798
		2. neoplasm[MeSH Terms]	4,014,998
		3. cancer[Title/Abstract]	2,339,405
		4. tumor[Title/Abstract]	1,515,156
		5. tumour[Title/Abstract]	252,538
		6. ((((carcinoma[MeSH Terms]) OR (neoplasm[MeSH Terms])) OR (cancer[Title/Abstract])) OR (tumor[Title/Abstract])) OR (tumour[Title/Abstract])	5,064,590
		7. influenza A virus[MeSH Terms]	50,879
		8. influenza B virus[MeSH Terms]	4,798
		9. influenza, human[MeSH Terms]	60,120
		10. ((influenza A virus[MeSH Terms]) OR (influenza b virus[MeSH Terms])) OR (influenza, human[MeSH Terms])	85,463
		11. immunization[MeSH Terms]	218,544
		12. vaccination[MeSH Terms]	116,138
		13. immun*[Title/Abstract]	3,002,147
		14. vaccin*[Title/Abstract]	451,336
		15. (((immunization[MeSH Terms]) OR (vaccination[MeSH Terms])) OR (immun*[Title/Abstract])) OR (vaccin*[Title/Abstract])	3,253,334
		16. (((((immunization[MeSH Terms]) OR (vaccination[MeSH Terms])) OR (immun*[Title/Abstract])) OR (vaccin*[Title/Abstract])) AND (((influenza A virus[MeSH Terms]) OR (influenza b virus[MeSH Terms])) OR (influenza, human[MeSH Terms]))) AND (((((carcinoma[MeSH Terms]) OR (neoplasm[MeSH Terms])) OR (cancer[Title/Abstract])) OR (tumor[Title/Abstract])) OR (tumour[Title/Abstract]))	1,102
		17. Limit #16 to English, from 2023/8/1 – 2024/12/31	43
		18. Excluded case reports, studies w ≤10 patients, duplicates from 2023, covid 19, non-cancer or non-human subjects (i.e., mice, in vitro), vaccine uptake and equity, vaccine design, unrelated to guideline question (i.e., recommendations, response, timing)	3

Please refer to the Literature Review: Influenza Immunization for Adult and Pediatric Patients Undergoing Cancer Treatment (2024) 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 hematologists, surgical oncologists, radiation oncologists, medical oncologists, pediatric oncologists, 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, October 2022, October 2023, and November 2024.

Maintenance

An annual review of the evidence will be conducted in August 2025. The guideline will be revised and updated accordingly at that time unless critical new evidence emerges.

Abbreviations

ACIP, Advisory Committee on Immunization Practices; ALL, acute lymphoblastic leukemia; CAR T, chimeric antigen receptor T-cell therapy; 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; SEER, Surveillance, Epidemiology, and End Results database; SOT, solid organ transplant.

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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