INFLUENZA IMMUNIZATION FOR
ADULT AND PEDIATRIC PATIENTS
UNDERGOING CANCER TREATMENT

Effective Date: October, 2016

The recommendations contained in this guideline are a consensus of members of the Alberta Provincial Tumour Council and members of the Alberta Health Services Province-wide Immunization Program Standards and Quality and represent 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.
BACKGROUND

In a given year, between 10% and 20% of the Canadian population becomes infected with influenza, and an estimated 12,200 hospitalizations and 3,500 deaths can be attributed to an epidemic of influenza; these include deaths related to pneumonia due to influenza virus or a secondary pathogen like Streptococcus pneumoniae. Rates of influenza infection are highest in children between the ages of five and nine years, but rates of serious illness and death are highest in children under the age of two years, older persons (>65 years), and persons with underlying medical conditions.2,3 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

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

DEVELOPMENT AND REVISION HISTORY

The 2016 update of this guideline was reviewed and endorsed by members the Alberta Provincial Tumour Council, which includes medical oncologists, radiation oncologists, and surgeons, as well as content experts from the Alberta Health Services Province-wide Immunization Program Standards and Quality, Communicable Disease Control. Updated evidence was selected and reviewed by the working group and the Guideline Resource Unit (GURU). 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, and October 2016.

SEARCH STRATEGY

For the original guideline published in 2009, the MEDLINE, PubMed, Cochrane, CINAHL, and EMBASE databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials published between 1965 and October 2010. Websites from health organizations including the World Health Organization, Health Canada, the Public Health Agency of Canada, Alberta Health Services, Alberta Health, the BC Cancer Agency, the National Comprehensive Cancer Network, the American Academy of Pediatrics, the Centers for Disease Control and Prevention, the National Guideline Clearinghouse, and the Département D’Oncologie Pédiatrique (France) were also searched for relevant guidance. The search terms for influenza immunization included: influenza vaccine or H1N1 vaccine AND neoplasms or radiotherapy or therapy or surgery or drug therapy. The search terms for immunocompromised patients included influenza vaccine or H1N1 vaccine AND cancer or oncology AND immunocompromise*. The search yielded 41 relevant studies on influenza vaccine and 18 relevant
studies on immunocompromised patients; 11 of these were included in the evidence tables presented in Appendix B.

For subsequent annual guideline updates, the PubMed and Cochrane databases were searched using the search terms “cancer” OR “neoplasm” OR “oncology” AND “influenza vaccination” OR “H1N1” OR “H3N2” OR “influenza A” OR “influenza B”. Limits for the literature search included publication date (September 2015 – December 2016), language (English) and species (human). The 2016 search yielded 94 citations; one relevant publication was added to the evidence tables presented in Appendix B.

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 2016/2017 Alberta Health Services Immunization Program, 2016/2017 Alberta Health Influenza Immunization Policy, Health Canada, the Public Health Agency of Canada, the Centers for Disease Control and Prevention, and the American Academy of Pediatrics. Evidence from published clinical trials, retrospective reviews, and case study reports 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 refer to www.albertahealthservices.ca/influenza/influenza.aspx.

The 2016/2017 trivalent influenza vaccine contains the following antigenic strains: an A/California/7/2009 (H1N1) pdm09-like virus, an A/Hong Kong/4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus. The 2016/17 quadrivalent influenza vaccine also contains a B/Phuket/3073/2013-like virus.

Influenza Immunization: Adult Patients with Cancer

1. Annual administration of the inactivated influenza vaccine is indicated for most adult patients with cancer. Patients considered to be the highest priority are those on active treatment; the next priority group includes patients who have been treated within the past one year. Given the burden of influenza A (H3N2) disease and evidence of better efficacy in adults aged 65 years and older, it is expected that the trivalent inactivated adjuvanted influenza vaccine (FLUAD ®) should provide superior protection compared with the standard-dose intramuscular vaccine, and is recommended for all individuals aged 65 years and older. The inactivated quadrivalent influenza vaccine (FLUZONE ®) is recommended for individuals over 6 months and under 65 years of age.

2. Age, duration, type of systemic therapy (with the exception of rituximab or other B-cell depleting antibodies, and immuno-oncology therapies including ipilimumab, nivolumab, and pembrolizumab), 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 influenza immunization:
   a. Influenza vaccine should be given two weeks before the start of any immune-suppressing cancer treatment, to allow for sufficient antibody production by the patient. If early immunization is not possible, administration of the inactive vaccine between chemotherapy cycles when therapy is at the lowest level is recommended, although the efficacy of the vaccine may be reduced in this situation.
   b. Patients who are treated with rituximab or other B-cell depleting antibodies should have all immunizations postponed until at least six months after the last dose of rituximab.7-10
   c. Patients treated with CTLA-4 inhibitors (e.g., ipilimumab) alone or in combination with other anti-cancer agents and those who have discontinued treatment in the past six months should not receive the influenza vaccine.
   d. Patients treated with PD-1 and PD-L1 inhibitors (e.g., nivolumab, pembrolizumab) and those who have discontinued treatment in the past six months may receive the inactivated influenza vaccine one week post-administration of these agents so as not to mask any immune related effects related to administration of cancer therapies.
   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, autologous and allogeneic):11,12
   a. The inactivated influenza vaccine should be administered at least two weeks prior to harvest (allogeneic donor), in the first half of the interval between mobilization chemotherapy and harvest (autologous recipient), or at least two weeks prior to transplant conditioning (allogeneic recipient).
      **Live vaccines are contraindicated.**
   b. Immune system recovery post-HSCT is variable and requires physician assessment. Between 10% and 30% of HSCT recipients will have a detectable antibody response to the influenza vaccine at 6 to 24 months post-transplant, while over 60% will have a detectable response at 24 months or more post-transplant.
   c. For HSCT recipients, influenza vaccine should ideally be administered six months post-HSCT. Inactivated influenza vaccine can be given as early as four months post-transplant in outbreak situations; if given less than six months post-transplant, a second dose can be given four weeks later if there is ongoing circulation of influenza virus in the community.
   d. Close contacts of HSCT patients should be strongly encouraged to be immunized annually against 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 annual influenza vaccination.2 It is important for transplant recipients to know that people receiving the live nasal spray influenza vaccine virus can shed vaccine virus in small amounts which are generally below the levels needed to spread vaccine virus to others. In rare cases, vaccine virus can be spread from vaccine recipients to unimmunized people but is not likely to cause illness. However, it is recommended that anyone who has a severely weakened immune system (e.g., bone marrow transplant recipients requiring isolation) avoid contact with people who have received the live nasal spray influenza vaccine for a time period of two weeks.
5. Family members of and hospital staff working with severely immune suppressed individuals in a protected environment should receive the inactivated annual influenza vaccine. If the family member or healthcare worker will only accept the live attenuated influenza vaccine, they should wait two weeks following immunization before continuing to provide care to severely immunocompromised individuals.2,13

6. Contraindications and precautions for influenza immunization in adult patients with cancer are:
- a previous anaphylactic reaction to an influenza vaccine.
- a known hypersensitivity to any component of the vaccine, with the exception of egg.
- a history of severe oculo-respiratory syndrome that included lower respiratory symptoms within 24 hours of receiving the influenza vaccine, pending consultation with the Medical Officer of Health to review the risks and benefits of further immunization.
- a history of developing Guillain-Barré syndrome within six weeks of a previous dose of influenza vaccine.
- individuals with severe acute febrile illness should not be immunized until the symptoms have resolved; individuals with mild-to-moderate febrile illness may be immunized.
- egg-allergy is no longer considered a contraindication for the influenza vaccine:1
  - egg-allergic adults with cancer may be immunized using the inactivated vaccine without a prior influenza vaccine skin test and with the full dose of the vaccine, irrespective of a past severe reaction to egg, and without any particular consideration such as immunization setting.
  - egg allergic vaccine recipients should be kept under observation for 30 minutes following the administration of the inactivated influenza vaccine.
  - as with all vaccine administration, immunizers should have the necessary equipment and be prepared to respond to a vaccine emergency at all times.

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. Given the burden of influenza B in children, a quadrivalent influenza vaccine should be used for children.2,4 The live attenuated influenza vaccine is not recommended for children with immune-compromising conditions.2 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.
- a full dose (0.5mL) of influenza vaccine should be used for all persons, including children 6 to 35 months of age, who are receiving influenza immunization.

2. Although the data is limited, age, duration, and type of systemic therapy (with the exception of rituximab or other B-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 depleting antibodies should have all immunizations postponed until at least six months after the last dose of rituximab.7-10
3. Current recommendations for pediatric patients with cancer suggest that influenza vaccine should ideally be given at least two weeks before the start of the next round of chemotherapy, to allow the patient to develop a sufficient antibody response. If early immunization is not possible, administration of the inactive vaccine between chemotherapy cycles when therapy is at the lowest level is recommended, although the efficacy of the vaccine may be reduced in this situation.

4. For pediatric patients undergoing hematopoietic stem cell transplant (HSCT, autologous and allogeneic):
   a. Administer the inactivated influenza vaccine at least two weeks prior to harvest (allogeneic donor), in the first half of the interval between mobilization chemotherapy and harvest (autologous recipient), or at least two weeks prior to transplant conditioning (allogeneic recipient). The live nasal spray influenza vaccine is contraindicated.
   b. Immune system recovery post-HSCT is variable and requires physician assessment. Between 10% and 30% of HSCT recipients will have a detectable antibody response to the influenza vaccine at 6 to 24 months post-transplant, while over 60% will have a detectable response at 24 months or more post-transplant.
   c. For HSCT recipients, influenza vaccine should ideally be administered six months post-HSCT. Inactivated influenza vaccine can be given as early as four months post-transplant in outbreak situations; if given less than six months post-transplant, a second dose can be given four weeks later if there is ongoing circulation of influenza virus in the community.
   d. Close contacts of pediatric HSCT patients should be strongly encouraged to be immunized annually against influenza.

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 annual influenza vaccination.² It is important for transplant recipients to know that people receiving the live attenuated influenza vaccine can shed vaccine virus in small amounts which are generally below the levels needed to spread vaccine virus to others. In rare cases vaccine virus can be spread from vaccine recipients to unimmunized people but is not likely to cause illness. However, it is recommended that if a family member or healthcare worker will only accept the live attenuated influenza vaccine, they should wait two weeks following immunization before continuing to provide care to severely immunocompromised individuals.²,¹³

6. Contraindications and precautions for influenza immunizations in pediatric patients with cancer include:
   - age less than six months.
   - a previous anaphylactic reaction to an influenza vaccine.
   - a known hypersensitivity to any component of the vaccine, with the exception of egg.
   - a history of severe oculo-respiratory syndrome that included lower respiratory symptoms within 24 hours of receiving the influenza vaccine, pending consultation with the Medical Officer of Health to review the risks and benefits of further immunization.
   - a history of developing Guillain-Barré syndrome within six weeks of a previous dose of influenza vaccine.
   - children with severe acute febrile illness should not be immunized until the symptoms have resolved; children with mild-to-moderate febrile illness may be immunized.
• egg allergy is no longer considered a contraindication for the annual influenza vaccine: 1
  o egg-allergic children with cancer may be immunized using the inactivated annual influenza
    vaccine without a prior influenza vaccine skin test and with the full dose of vaccine,
    irrespective of a past severe reaction to egg and without any particular consideration such
    as immunization setting.
  o egg allergic vaccine recipients should be kept under observation for 30 minutes following
    the administration of inactivated influenza vaccine.
  o as with all vaccine administration, immunizers should have the necessary equipment and
    be prepared to respond to a vaccine emergency at all times.

DISCUSSION

In general, there is a paucity of evidence from well-controlled studies on influenza immunization in adult
and pediatric patients with cancer. Articles included in this review repeatedly cite the need for universally
accepted guidelines on: the types of vaccines that produce best immunologic response, the number of
administrations, the timing of administration in relation to severity of immunosuppression, and the timing of
administration in relation to chemotherapy schedules. The recommendations included in the current
guidelines are based, in part, on data extrapolated from healthy populations and combined with the best
practices and opinions of experts in Alberta.

Influenza Immunization: Adult Patients with Cancer

Annual administration of the inactivated influenza vaccine is recommended for most adult patients with
cancer, with the exception of patients treated with b-cell depleting antibodies (e.g., rituximab) and CTLA-4
immo-oncology therapies (e.g., ipilimumab). Chemotherapy can produce acute and profound
immunosuppression in this patient population, although published literature suggests that the degree may
differ according to the specific regimen, doses, and duration of treatment. There is currently limited
published evidence to support the administration of a second dose of the seasonal influenza vaccine to
adults during the same influenza season, though data specific to adults with cancer is scarce.14-17 The
VACANCE trial published in 2012 compared one dose of AS03A-adjuvanted H1N1v vaccine with two
doses, among patients receiving cytotoxic and/or targeted therapies (n=65) and showed that
seroprotection increased from 48% after one dose to 73% after two doses, while seroconversion
increased from 44% after one dose to 73% after two doses.18

Interpreting the results of influenza vaccine efficacy in adult patients with cancer is difficult, as patient
characteristics, cancer types, vaccine strains, and assessment of responses vary between published
studies. In a thorough review of the literature, Arrowood et al. reported seasonal influenza immunization
response rates to be between 29% and 88% for patients with cancer, and responses were generally
higher for patients with solid tumours compared to those with hematologic malignancies.19 In a small
prospective cohort study comparing pH1N1 vaccine (one dose) response among patients with
hematological malignancies (n=26) and those with solid tumours (n=20), Mackay and colleagues reported
that seroprotection and seroconversion rates were higher among patients with solid tumours (50% vs.
27%, p=0.11 and 45% vs. 19%, p=0.06, respectively).20 In a review of 1225 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=.004).21 In
addition, the immunized patients had significantly fewer interruptions in the chemotherapy cycles, showed
a trend towards 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). In a 2013 Cochrane review of four studies involving 2124 adult patients with cancer receiving chemotherapy, the authors 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

The results of a growing body of literature suggest that patients with cancer who develop influenza are at a 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 98.2% of these patients had one or more major co-morbidities, including immunosuppression due to cancer or cancer therapies.24

There is some controversy regarding the timing of influenza immunization with respect to chemotherapy administration. The majority of research studies, reviews, and published guidelines included in this review suggest that since immunosuppressive chemotherapy regimens may depress the patients' immune response to vaccines, it is likely most beneficial to immunize patients early (i.e., approximately 10 to 14 days prior to beginning chemotherapy), to allow for sufficient antibody production by the patient.3,19,25-27 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 (63.7 vs. 29.5, 28.2 vs. 19.6, and 29.8 vs. 16.0, for H3N2, H1N1, and B/Brisbane, respectively).28 If early immunization is not possible, however, 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.3,21,26,29 In such situations, administration of the vaccine is preferable when therapy is at the lowest level possible.25,30

There is no clear data on safety of the influenza vaccine (live or inactivated) in patients with cancer treated with immuno-oncology therapies including CTLA-4 inhibitors (e.g., ipilimumab) or PD-1 and PD-L1 inhibitors (e.g., nivolumab, pembrolizumab). Many of the clinical trial protocols evaluating ipilimumab did not routinely allow for influenza immunization. Therefore, until more evidence is available, it is the consensus of the Alberta Provincial Tumour Teams that patients currently receiving ipilimumab alone or in combination with other anti-cancer agents, as well as those who have discontinued ipilimumab in the past six months should not receive the influenza vaccine. It is the consensus of the Alberta Provincial Tumour Teams that patients receiving nivolumab or pembrolizumab alone or in combination with other anti-cancer agents may be immunized with the inactive influenza vaccine; the timing of the immunization is not clearly studied in this population, but can be considered one week post-administration of these agents. Patients should be advised to monitor themselves closely, and to report any adverse events to their oncologist.

Adult patients with hematologic malignancies undergoing hematopoietic stem cell transplantation (HSCT) are at a 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 leave 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 1900 patients in Europe over three influenza seasons.31 Very few controlled studies of the efficacy of influenza immunization in HSCT patients have been 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.32,33 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.34 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. recently 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.35 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.36 Similarly, Berglund and colleagues recently 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.9 Patients who are treated with rituximab or other B cell depleting antibodies should therefore have all immunizations postponed until at least 6 months after the last dose of rituximab or other B cell depleting therapies.7-10

Retrospective case series of HSCT patients who were immunized during the 2009-2010 H1N1 influenza pandemic are also emerging in the literature. George et al. reported that between May and September 2009, among the 31 transplant recipients and 235 follow-up patients seen at their centre, two developed H1N1 influenza less than 100 days post-transplant, four developed H1N1 while preparing for the transplant, and seven developed H1N1 100 days or more post-transplant. All four patients in this series who died due to complications from H1N1 had developed a lower-respiratory tract infection (LRTI).37 Similarly, Espinosa-Aguilar et al. reported a 30-day mortality rate of 43% (n=6/14) in transplant patients who had confirmed H1N1 influenza and LRTI. All of the patients with only upper-respiratory tract involvement survived without long-term complications associated with H1N1 influenza.38 Similar results were also recently published by Mohty et al., who reported H1N1 infection in 10 of 51 allogeneic transplant recipients followed at their outpatient clinic. Upper respiratory tract infections were present in eight of the patients, while lower respiratory infections were present in five patients.39 In contrast, in a recent analysis of 21 HSCT patients who developed H1N1 infection at the Memorial-Sloan Kettering Cancer Center in the United States, only 8% developed LRTI, and none of these patients required mechanical ventilation or died due to influenza.40 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.41 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 influenza immunization at least two weeks prior to the transplant.12,25,42-44 While only 10 to 30% of HSCT recipients will have a detectable antibody response to the influenza vaccine at 6 to 24 months post-transplant, over 60% will have a detectable response at 24 months or more post-transplant.45 Immune system recovery post-transplant is variable and requires individual assessment by a 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.12,35 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 influenza immunization beginning at least four months post-transplant. In an effort 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. 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. 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 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. If the family member or healthcare worker will only accept the live attenuated influenza vaccine, they should wait two weeks following immunization before continuing to provide care to severely immunocompromised individuals.

A survey among cancer centre hospital workers showed that factors associated with vaccine acceptance included the desire to protect relatives (30.3%) and to protect oneself (30.3%), while factors associated with refusal included fear of side effects (43.1%) and doubt regarding efficacy (25.8%); institutional campaigns and colleagues' advice were significant factors influencing vaccine uptake, suggesting that promotional efforts aimed at dispelling myths about side effects or poor vaccine efficacy may increase immunization rates among hospital workers.

Adult patients with cancer who should not receive influenza immunization include those who have had a previous serious reaction to an influenza vaccine or a known hypersensitivity to any component of the vaccine (with the exception of egg), and those who have previously developed Guillain-Barré syndrome within six weeks of getting an influenza immunization. In addition, for adult oncology patients with severe febrile neutropenia, the vaccine should be administered after symptoms have diminished. The 2016-2017 statements from the Canadian National Advisory Committee on Immunization (NACI), the American Advisory Committee on Immunization Practices (ACIP), and the Alberta Health Services Immunization program all state that egg allergy is no longer considered a contraindication for the influenza vaccine. Egg-allergic individuals may be immunized without a prior influenza vaccine skin test and with the full dose of vaccine irrespective of a past severe reaction to egg, and without any particular consideration such as immunization setting. Egg-allergic individuals should be kept under observation for 30 minutes following the administration of inactivated influenza vaccine.

**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. 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. 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.

Given the burden of influenza B in children, NACI continues to recommends that a quadrivalent influenza vaccine be used. Current 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. Although the NACI statement recommends that either the quadrivalent live attenuated influenza vaccine or the quadrivalent inactivated influenza vaccine can be used in children and adolescents aged 2-17 years of age, the live vaccine is contraindicated in individuals with immune compromising conditions due to underlying disease and/or therapy.  

Similar to the literature regarding adult patients with cancer, interpreting the limited published results of influenza vaccine efficacy in pediatric patients with cancer is difficult, as patient characteristics, cancer types, vaccine strains, and assessment of responses vary between published studies. In a meta-analysis of eight controlled clinical trials and one randomized controlled trial, 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.49 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.47,50 Bate et al. reported that among 54 pediatric patients who received two doses of the 2009-2010 H1N1 influenza monovalent AS03(B)-adjuvanted vaccine (days 0 and 21), the seroconversion rate tended to be higher for those with solid tumours than those with hematological malignancies (66.7% for patients with brain tumours; 71.4% for patients with other solid tumours; 36.4% for patients with lymphoma or other leukemias).51 With regards to the optimal number of doses, a small study by Cheng et al. among pediatric patients receiving chemotherapy or who had completed chemotherapy within the past 12 months (n=12) showed that seroprotection and seroconversion rates were higher after two doses of vaccine to influenza A/California/07/2009 (H1N1)-like virus, versus one dose: 100% vs. 58% and 75% vs. 41%, respectively; at this time however, larger studies are needed to confirm these results.52 Overall, there are currently very limited recommendations regarding the optimal timing of seasonal influenza immunization for pediatric patients with cancer. Based on the results of the studies included in this review, the ability of children with solid tumours to develop a protective immune response depends on whether the chemotherapy is administered during or within two weeks of their immunizations. Seroconversion rates have also been shown to vary according to the type of chemotherapy. Reilly et al. reported that, in patients with acute lymphoblastic leukemia (ALL), responses to the vaccine were greater when it was given early in the course of treatment.53 After cessation of chemotherapy, adequate immune responses were reported within three months to one year. 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. recently assessed the immune response of 32 pediatric patients with 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).54

The recommendations for pediatric patients undergoing HSCT are similar to those for adult patients, with appropriate adjustments made for vaccine doses.12,43 It is recommended that both the recipient and donor (for allogeneic transplants) receive the inactivated influenza vaccine two weeks prior to the transplant.25,43 Post-transplant, the majority of recipients will have a detectable antibody response to the vaccine beginning at four months, and this response will continue to increase over the next 12 to 24 months. As with adult patients, immune system recovery following transplant is variable, and depends on factors such as the types of therapies administered post-transplant, and the presence of graft-versus-host disease; therefore individual assessment is required by a physician. 12 It is recommended that pediatric HSCT
patients receive annual seasonal influenza immunizations beginning no earlier than four months post-transplant.\textsuperscript{12,25,43,55}

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.\textsuperscript{25} 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.\textsuperscript{25,43,44} If the family member or healthcare worker will only accept the live attenuated influenza vaccine, they should wait two weeks following immunization before continuing to provide care to severely immunocompromised individuals.\textsuperscript{2,13}

The influenza vaccine is not approved for use in Canada among children under the age of six months. Other contraindications include: children with moderate-to-severe febrile illness, children who have previously developed a severe reaction to the influenza vaccine, and children who have previously developed Guillain-Barré syndrome within six weeks of receiving an influenza vaccine.\textsuperscript{2} The 2016-2017 statements from NACI, ACIP and the Alberta Health Services Immunization Program all state that egg allergy is no longer considered a contraindication for the influenza vaccine.\textsuperscript{2,4,5} Egg-allergic children may be immunized without a prior influenza vaccine skin test and with the full dose of vaccine irrespective of a past severe reaction to egg, and without any particular consideration such as immunization setting. Egg-allergic children should be kept under observation for 30 minutes following the administration of inactivated influenza vaccine.

GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACIP</td>
<td>Advisory Committee on Immunization Practices</td>
</tr>
<tr>
<td>ALL</td>
<td>acute lymphoblastic leukemia</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
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<tr>
<td>HSCT</td>
<td>hematopoietic stem cell transplant</td>
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<tr>
<td>LRTI</td>
<td>lower respiratory tract infection</td>
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<tr>
<td>NACI</td>
<td>National Advisory Committee on Immunization</td>
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<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PHAC</td>
<td>Public Health Agency of Canada</td>
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<tr>
<td>QIV</td>
<td>quadrivalent inactivated influenza vaccine</td>
</tr>
<tr>
<td>SEER</td>
<td>Surveillance, Epidemiology, and End Results database</td>
</tr>
<tr>
<td>TIV</td>
<td>trivalent inactivated influenza vaccine</td>
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</table>

DISSEMINATION

- Circulate the guideline internally to all CancerControl Alberta staff.
- Post the guideline and accompanying tools on the Alberta Health Services website.
- Circulate the guideline and accompanying tools to nurses at immunization clinics throughout Alberta, as well as daycare units at the tertiary, associate, and community cancer centres in Alberta.
MAINTENANCE

An annual review will next be conducted in September 2017. If critical new evidence is brought forward before that time, however, the guideline will be revised and updated accordingly.

CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Tumour Council in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Tumour Council are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


APPENDIX A: ADDITIONAL RESOURCES

Canadian Resources

Alberta Health Services, Influenza Immunization:

Alberta Health Services. Influenza Information for Health Professionals:
http://www.albertahealthservices.ca/influenza/Page12438.aspx

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


Public Health Agency of Canada. Canadian Immunization Guide:

International Resources

World Health Organization. Global Influenza Programme:
www.who.int/influenza/en/

http://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm?s_cid=rr6505a1_w

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/

www.nccn.org/professionals/physician_gls/f_guidelines.asp

http://pediatrics.aappublications.org/content/138/4/e20162527
## Table 1. Published Literature on Influenza Immunization in Adult Patients with Cancer, January 2000 – September 2016

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Type</th>
<th>Disease Site and Comparisons</th>
<th>N</th>
<th>Immunization Details</th>
<th>Results and Recommendations</th>
</tr>
</thead>
</table>
| Jamshed S, 2016<sup>26</sup> | randomized controlled trial | cancer patients <65 years of age receiving chemotherapy: 1. standard dose influenza vaccine 2. high-dose influenza vaccine | 51  54 | | • no severe adverse events reported  
• seroconversion rates for all 3 influenza antigens and post-vaccination GMTs for H3N2 and B strains were significantly improved in patients receiving high-dose vs. standard-dose |
| Berglund A, 2014<sup>4</sup> | prospective trial | cancer outpatients receiving ongoing treatments with chemotherapy, monoclonal antibodies, tyrosine kinase inhibitors or corticosteroids | 96  | 2009 influenza A(H1N1) AS03-adjuvanted split virion vaccine x 2 doses + 2009 trivalent non-adjuvanted seasonal influenza vaccine x 1 dose | • 100% (N=13) of patients treated with rituximab did not respond to immunization  
• For the patients not treated with rituximab:  
  o H1N1 vaccine: seroconversion = 84% (N=63), seroprotection = 87% (N=65)  
  o Seasonal influenza vaccine (A/Bri): seroconversion = 42% (N=28), seroprotection = 70% (N=46)  
  o Seasonal influenza vaccine (A/Uru): seroconversion = 50% (N=33), seroprotection = 59% (N=39) |
| Strowd RE, 2014<sup>27</sup> | prospective cohort | CNS tumours (GBM = 21, high-grade gliomas = 5, low-grade gliomas = 6, primary CNS lymphoma = 6) treated with CT, RT, +/- glucocorticoids | 38  | Seasonal trivalent inactivated influenza vaccine | • At 28 days post-vaccine, seroconversion rates for A/H1N1, A/H3N2, and B strains = 37%, 23%, and 23%, respectively; seroprotection rates = 80%, 69%, and 74%, respectively |
| Vinograd I, 2013<sup>28</sup> | prospective non-intervention trial | patients with solid tumours receiving CT and hematologic patients with active disease | 806 | 2011 seasonal trivalent killed influenza vaccine | • Immunization rate= 387/806 (48%)  
• Hospitalization rate for fever or acute respiratory infections, pneumonia, and/or infection-related CT interruptions = 111/387 (28.7%) vaccinated patients vs. 112/419 (26.7%) unvaccinated patients (p=0.54)  
• Mortality rate = 46/387 (11.9%) vaccinated patients vs. 80/419 (19.1%) unvaccinated patients (p= 0.005) |
| Chu C, 2013<sup>29</sup> | prospective trial | Ovarian cancer: 1. in remission receiving a dendritic cell vaccine + cyclophosphamide 2. in remission not receiving treatment undergoing standard therapy 3. undergoing standard therapy | 31  | Seasonal trivalent killed influenza vaccine | • 4-fold response for H1N1 in 20% of patients, for H3N2 in 26% of patients, and for influenza B in 6% of patients  
• Pre-existing exposure to influenza was predictive of responders |
| Lagler H, 2012<sup>30</sup> | prospective trial | 1. Hematologic malignancies + cytotoxic, targeted, or hormone therapy 2. Solid tumours + | 25  17 | Unadjuvanted whole-virion pandemic influenza A (H1N1) vaccine | • 260/285 (91.2%) patients with solid tumours who were offered free immunization during their therapy declined  
• Seroprotection: 96% healthy, 90% solid tumours, 67% hematologic malignancies (p<0.05) |
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</tr>
</thead>
</table>
| Mariotti J, 2013  | prospective trial| 1. Hematologic malignancies 2. Healthy controls                                                | 47 | Monovalent adjuvanted 2009 H1N1 vaccine                                                | • At 28 days post-vaccine, rates of seroprotection (95.2% vs. 75.2%, p<0.01) and seroconversion (88.7% vs. 51.1%, p<0.01), as well as GMT (256 vs. 134, p<0.05), were lower for pts with hematologic malignancies vs. health controls  
• Patients not receiving CT had seroprotection and GMTs similar to controls in all time points, while patients receiving CT or allogeneic HSCT had lower seroprotection and seroconversion levels than controls on day 28 and 50. |
| Hottinger AF, 2012 | prospective controlled open-label                                                              | 1. Lymphoma and solid tumours (34.5% active CT) 2. Healthy controls                          | 197| AS03A-adjuvanted split influenza A/H1N1/09 vaccine x 2 doses for cancer patients and x 1 dose for healthy controls | • Seroprotection: 87.4% cancer patients vs. 87% controls (p=0.16)  
• Seroconversion: 82.3% cancer patients vs. 87% controls (p=0.33)  
• Active CT (p=0.01), lymphoma (p=0.03), rituximab (p<0.001), and steroid treatment (p=0.02) associated with lesser antibody responses in cancer pts |
| Xu Y, 2012        | prospective case series                                                                         | 1. Healthy controls 2. Solid tumour + myelosuppressive CT 3. Solid tumour + non-myelosuppressive CT 4. Hematologic | 44 | Monovalent unadjuvanted influenza A (H1N1) 2009 vaccine                                  | • Seroprotection: 95.5% group 1, 75% group 2, 90.5% group 3, 90.1% group 4; no significant differences between groups  
• Seroconversion: 80% group 1, 72.2% group 2, 87% group 3, 75% group 4; no significant differences between groups |
| Rousseau B, 2012  | prospective cohort                                                                               | Patients receiving cytotoxic and/or targeted therapies                                       | 65 | AS03A-adjuvanted H1N1v vaccine x 1 or 2 doses                                          | • Seroprotection: 48% after one dose; 73% after two doses  
• Seroconversion: 44% after one dose; 73% after two doses  
• Vaccine-related adverse events were mild to moderate |
| Puthillath A, 2011 | prospective case series                                                                         | Colorectal cancer: 1. CT 2. no CT                                                             | 58 | 2006-2007 trivalent influenza vaccine x 1 dose                                          | • Immune response: 70.6% overall population, 69% CT group, 74.1% non-CT group (OR=0.78; p=0.8)  
• Seroconversion: 12.1% CT group vs. 11.1% non-CT group  
• No difference in responses by chemo regimen or timing of immunization with regards to CT administration |
| Miraglia JL, 2011  | multicentre prospective cohort                                                                  | Cancer (tumour type not specified) compared to elderly and immuno-compromised patients       | 319| Monovalent unadjuvanted influenza A (H1N1) 2009 vaccine                                  | • Seroprotection: 52.4% (95% CI: 46.7–57.9)  
• Seroconversion: 49.2% (95% CI: 43.6–54.8)  
• No comparisons made by tumour type or CT regimen |
| Yri OE, 2011      | prospective controlled trial                                                                     | 1. Lymphoma treated with rituximab + CT 2. Healthy controls                                 | 67 | Monovalent adjuvanted influenza A (H1N1) vaccine x 1 dose                               | • Seroprotection: 0% lymphoma vs. 82% controls |
| Monkman K, 2011   | prospective cohort                                                                               | Hematologic malignancies: 1. Vaccinated 2. Unvaccinated                                      | 62 | AS03A-adjuvanted H1N1 vaccine x 1 dose                                                  | • Seroconversion : 21% vaccinated vs. 0% unvaccinated (p<0.001)  
• Seroprotection : 40% vaccinated vs. 22% unvaccinated (p=0.058)  
• 10/46 vaccinated patients on active CT seroconverted and 16/46 mounted seroprotective titers  
• 2/12 vaccinated patients on active rituximab seroconverted and 4/12 mounted seroprotective titers  
• 1/3 vaccinated stem cell transplant recipients seroconverted  
• No differences in response rates between patients on or off CT, on or off rituximab, or between pts with lymphoid vs. non-lymphoid malignancies |
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<tr>
<th>Author, Year</th>
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| de Lavallade H, 2011<sup>47</sup> | prospective cohort | 1. Hematological (B-cell malignancies, CML, and ASCT recipients) 2. Healthy controls | 97 | AS03A-adjuvanted H1N1v vaccine x 1 dose + trivalent seasonal influenza vaccine x 1 dose | • Seroprotection Day 21: 100% controls vs. 39.3% B-cell malignancies (p<0.001), 45.5% ASCT recipients (p=0.001), 85.0% CML (p=0.086); rates in CML patients significantly higher vs. B-cell malignancies (p=0.003) and ASCT recipients (p=0.011)  
• Seroprotection Day 49: 100% controls vs. 67.9% B-cell malignancies (p=0.002), 72.7% ASCT recipients (p=0.008), 95.0% CML (p=0.46)  
• Seroconversion Day 21: 100% controls vs. 35.7% B-cell malignancies (p<0.001), 45.5% ASCT recipients (p=0.001), 80% CML (p=0.036)  
• Seroconversion Day 49: 100% controls vs. 64.3% B-cell malignancies (p=0.001), 72.7% ASCT recipients (p=0.008), 90% CML (p=0.20)  
• Adverse reactions in 90.5% of hematology patients and 88% of controls; 2.1% and 3.2% of local and systemic reactions in hematology patients respectively rated as severe |
| Loulergue P, 2011<sup>48</sup> | prospective cohort | 1. Breast – docetaxel Prostate – docetaxel | 13 | Trivalent inactivated influenza vaccine x 1 dose | • Seroconversion: 28% (95% CI: 23.1-33.3; H1N1), 8% (95% CI: 7.7-8.3; H3N2), 16% (95% CI: 7.7-25; B strain)  
• GMT: 2.16 (H1N1), 1.3 (H3N2), 1.58 (B)  
• No serious adverse events related to the vaccine. |
| Mackay HJ, 2011<sup>49</sup> | prospective cohort | 1. Hematologic malignancies 2. Solid tumours | 26 | pH1N1 vaccine x 1 dose | • Seroconversion: 45% (95% CI: 38.2-51.7) vs. 35.7% B-cell malignancies (p=0.002), 72.7% ASCT recipients (p=0.008), 90% CML (p=0.011)  
• Highest titres: mid-cycle immunization in pts w/solid tumours and start of cycle for hematological pts.  
• Immunization was well tolerated. |
| Sasson M, 2011<sup>50</sup> | prospective cohort | Palliative care patients | 13 | Trivalent influenza vaccine Vaxigrip x 1 dose | • Seroprotection: increased from 15.4% to 61.5% after immunization  
• Serum response: 53.8% for all the three strains of vaccine  
• GMT: from 8.3 to 159.4 after immunization for A-H3N2; from 5.2 to 124.3 for A-H1N1; from 5.7 to 44.6 for influenza B. |
| Stadtmauer EA, 2011<sup>70</sup> | randomized controlled trial | Multiple myeloma | 21 | 1. Influenza-primed autologous T-cell product (HSCT) 2. Nonspecifically primed autologous T-cell product (HSCT) | • Seroconversion: influenza-primed autologous T-cell product group more likely to respond to influenza vaccine (P=0.001)  
• No differences in the global quantitative recovery of T-cell and B-cell subsets or in global T-cell and B-cell function |
| Chadha MK, 2011<sup>71</sup> | prospective cohort | Prostate cancer | 35 | Trivalent influenza vaccine (Fluzone) x 1 dose | • Seroconversion: 28% (95% CI: 23.1-33.3; H1N1), 8% (95% CI: 7.7-8.3; H3N2), 16% (95% CI: 7.7-25; B strain)  
• GMT: from 8.3 to 159.4 after immunization for A-H3N2; from 5.2 to 124.3 for A-H1N1; from 5.7 to 44.6 for influenza B. |
| Mulder SF, 2011<sup>72</sup> | case control | 1. mRCC - sunitinib 2. mRCC - sorafenib 3. mRCC - no CT 4. Healthy controls | 16 | Seasonal influenza inactivated vaccine x 1 dose | • Seroprotection: similar between sunitinib and sorafenib vs. controls.  
• Functional T-cell reactivity: sorafenib patients had a decreased rate of proliferation, decreased IFN-γ/IL-2, and increased IL-10 vs. controls. |
| Bedognetti D, 2011<sup>73</sup> | case control | 1. Non-Hodgkin lymphoma – post rituximab controls 2. Healthy controls | 31 | Trivalent seasonal influenza vaccine x 1 dose | • Response: lower in patients vs. controls for each strain, especially in patients treated with fludarabine (European immunogenic criteria not met); CD27(+) memory B cells reduced among patients vs. controls. |
| Meerveld-Eggink A, 2011<sup>74</sup> | case control | 1. Breast cancer – FEC therapy healthy controls | 38 | Influenza vaccine 1. Early (day 4 of chemo; n=20) 2. Late (day 16 of chemo; n=18) | • Response rate: significantly lower in patient group vs. controls; early group had higher antibody titers vs. late group (not sig)  
• GMT: 63.7 vs. 29.5 (early vs. late, H3N2), 28.2 vs. 19.6 (early vs. late, H1N1), 29.8 vs. 16.0 (early vs. late, B/Brisbane). |
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</table>
| Avetisyan G, 2008 | comparative study  | 1. Healthy volunteers                                                                       | 18 | Inactivated trivalent 2005/2006 influenza vaccine x 1 dose                                             • 29% of SCT patients demonstrated protective antibody levels to influenza A H1N1 serotype  
• critical period is later than 90 days post-SCT, when patients gradually return to contact with the community and are more exposed to infection by circulating respiratory viruses  
• Authors recommend the influenza immunization 3 months or longer after allo-SCT, as long as they do not have GVHD or ongoing immunosuppression |
|                   |                    | 2. Allo-SCT patients                                                                       | 14 |                                                                                                         |                                                                                                                                                                                                                                                                                       |
| Ljungman P, 2005  | open, randomized   | Hematologic malignancies (N=59 receiving active CT against malignancy)                      | 36 | 1. one-dose vaccine                                                                                     • Response rates:  
• H1N1:14/70 (20%)  
• H3N2: 14/70 (20%)  
• Influenza B: 16/70 (23%)                                                                                             | • 4/70 patients responded and became immune to all three influenza subtypes after immunization  
• Proportion of immune patients after 1-dose vs. 2-doses:  
• H1/N1:25% vs. 26% (NS)  
• H3/N2: 22% vs. 21% (NS)  
• Influenza B: 14% vs. 18% (NS)  
• Patients with myeloproliferative disorders responded better to H1N1 vs. multiple myeloma patients (p<.002) and patients with lymphoma also responded better than patients with multiple myeloma (p<.001)  
• Trend for better responses in patients with less intensive CT  
• Authors recommend immunization of family members and hospital staff |
|                   |                    |                                                                                              | 34 | 2. two-doses vaccine  
minimum of 1 week between immunization and the next scheduled CT course                           |                                                                                                         |                                                                                                                                                                                                                                                                                       |
|                   |                    |                                                                                              |                                                                 |                                                                                                         |                                                                                                                                                                                                                                                                                       |
| Machado CM, 2005  | prospective cohort study | Hematologic malignancies: 1. < 6 months post-BMT, not eligible for immunization  
2. ≥ 6 months post-BMT | 134| Trivalent seasonal influenza vaccine x 1 dose                                                            • 25/134 (18.6%) in group 1 developed influenza  
• 19/43 (44.2%) in group 2 were vaccinated, and vaccine efficacy was 80%  
• 12/24 (50%) unvaccinated in group 2 developed influenza  
• Multivariate analysis:  
• Seasonal exposure and conditioning regimens independently associated with increased risk for influenza  
• influenza vaccine and steroid therapy showed a protective role  
• Gender, BMT type, underlying disease and GVHD not associated with risk of influenza infection | • SEER database and the Center for Medicare and Medicaid Services database accessed for immunization rates among patients undergoing CT in September – December between 1993-1996  
• Patients who developed influenza while undergoing CT: 3.8% unvaccinated vs. 1.1% vaccinated, p<.004  
• Influenza immunization associated with an HR for death of 0.88 (95%CI, 0.77-0.99)  
• 68% of patients who were immunized received their immunization through a primary care physician, yet oncologists are often these patients’ most consistent medical contacts. As a result, it is critical that oncologists actively provide routine influenza immunization to their patients with advanced cancer as part of delivering comprehensive, high-quality cancer care. |
<p>| Earle CC , 2003   | cohort study       | 1. Stage IV colorectal cancer patients who received seasonal influenza vaccine                 | 626| Seasonal influenza vaccine                                                                               |                                                                                                         |                                                                                                                                                                                                                                                                                       |
|                   |                    | 2. Stage IV colorectal cancer patients who were not immunized                                 | 951|                                                                                                         |                                                                                                                                                                                                                                                                                       |</p>
<table>
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<tr>
<th>Author, Year</th>
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<th>N</th>
<th>Immunization Details</th>
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</tr>
</thead>
</table>
| Nordoy T, 2002 | controlled clinical trial | 1. Solid tumours or malignant lymphoma; mild-moderate immunosuppressive CT 2. Healthy controls | 35  | Trivalent inactivated seasonal influenza vaccine x 1 dose + 23-valent polysaccharide pneumococcal vaccine | • After 1 immunization, 25 patients (72%) and 34 controls (87%) were serologically protected against 2 of the 3 flu strains  
• A higher proportion of the patients with solid tumours (81%) than lymphoma (38%) achieved protection  
• Age, duration of CT, and curative vs. palliative treatment did not influence immunization response |

**Table 2. Published Literature on Influenza Immunization in Pediatric Patients with Cancer, January 2000 – September 2016**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Study Type</th>
<th>Disease Site</th>
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</thead>
</table>
| Ottóffy G, 2014 | prospective cohort | Patients receiving CT for solid tumours (15) and hematologic malignancies (12) | 27  | Inactivated, whole-virion, adjuvanted pandemic H1N1 vaccine administered simultaneously with 2009 seasonal influenza vaccine x 1 dose | • Pre- and post-immunization seroprotective rates were H1N1: 33–48%, H3N2: 56–78%, influenza B: 0–15% for seasonal influenza, and for pandemic H1N1: 15–37%.  
• Seropositivity rates for seasonal influenza H1N1, H3N2, and B were 22%, 37%, and 22%, respectively, and 30% for the pandemic H1N1 vaccine  
• Determinants of responsiveness were lymphocyte count and serum immunoglobulin-G  
• Only influenza B vaccine elicited significant differences in differences in pre- and post-immunization seroprotective rates |
| McManus M, 2014 | randomized, double-blind, phase I safety trial | ALL (80% on maintenance therapy) | 34  | 1. High-dose TIV (60 µg)  
Standard-dose TIV (15 µg) | • no significant differences reported in local or systemic symptoms  
• No severe adverse events attributed to vaccine  
• No significant differences in immune response between the high- and standard-dose TIV groups |
| Dotan A, 2014 | prospective cohort | Patients with leukemia (16), lymphoma (10), neuroblastoma (4), and other malignancies (10) admitted to hospital with fever +/- other influenza A or H1N1 symptoms | 40  | Vaccinated patients received Pandemrix— influenza vaccine (H1N1) (split virion, inactivated, adjuvanted) before hospitalization | • 57 total episodes; 13/57 (22.8%) were influenza A/H1N1 positive  
• 2/13 (15%) H1N1-positive episodes were previously immunized versus 4/4 (4%) H1N1-negative episodes (p=0.3)  
• No sig demographic differences between groups with and without influenza A/H1N1 infection; no difference in proportion who received CT in the influenza A/H1N1-positive group vs. the H1N1-negative group (69.2% vs. 65.1% (p=0.8)  
• Proportion of children who underwent BMT= 7.7% in influenza A/H1N1-positive children vs. 4.8% in influenza A/H1N1-negative children  
• 7/16 (44%) episodes in vaccinated children presented with fever and URI symptoms vs. 24/41 (59%) episodes in unvaccinated children (p=0.38) |
| Leahy TR, 2013 | prospective cohort | ALL | 45  | Patients received 2 doses of the inactivated split-virion AS03-adjuvanted vaccine. Serological response measured before each vaccine dose (days 0 & 28) and 3 months after the second dose. | • Pre and post titres were available from 45 children after 1 vaccine dose and 39 children after 2 doses. The seroconversion rates were 11.1% after 1 dose and 25.6% after 2 doses.  
• Significantly higher (p=0.01) seroconversion rate among children who received the adult vaccine dose (0.5ml) in univariate analyses, and a trend towards significance (p=0.07) in multivariate analyses  
• Factors including age, gender, lymphocyte count, treatment phase and regimen did not significantly affect the seroconversion rate  
• Children who received the adult dose demonstrated significantly greater magnitude of serological response after 1 dose (p = 0.04) and 2 doses (p = 0.001). |
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</tr>
</thead>
</table>
| Mavinkurve, Groothuis AM, 2013 | prospective cohort | Children with hematologic malignancies (N=20) or solid tumours (N=11) treated with CT or within 6 months after the end of CT | 31  | Inactivated split-virion preparation of the A/California/07/2009(H1N1)v-like strain x 2 doses (3-week interval) | • No sig. difference in the immunization response between patients with hematologic cancer vs. solid tumours.  
• Sig. difference in the absolute lymphocyte count prior to the first immunization between patients with protective vs. no protective response (p= 0.012).  
• Absolute lymphocyte counts for above the lower normal limits (LNL) for age were seen in 13/28 patients (46%). In 12/13 patients (92%), a protective response to immunization was seen. In the 15 patients with absolute lymphocyte counts below the LNL for age, only 5 (33%) had a protective response to immunization (p=0.002).  
• No protective immunization response observed in patients with CD4+ T cell count less than 200/mm^3. |
| Karras NA, 2012 | randomized trial | Vaccine-naive patients >60 days post-allogeneic HSCT | 33  | Single dose inactivated trivalent seasonal influenza vaccine (H3N2 + H1N1pdm09 +influenza B Victoria lineage) vs. Double dose inactivated trivalent seasonal influenza vaccine (H3N2 + H1N1pdm09 +influenza B Victoria lineage), separated by 1 month | • Seroprotection: no significant differences at 8 weeks for H3N2 (19% 1-dose vs. 19% 2-doses), H1N1 (32% 1-dose vs. 32% 2-doses), and influenza B (32% 1-dose vs. 23% 2-doses)  
• Seroconversion: no significant differences at 8 weeks for H3N2 (13% of 1-dose vs. 22% 2-doses), H1N1 (31% 1-dose vs. 31% 2-doses), and influenza B (16% 1-dose vs. 25% 2-doses)  
• None of the patients vaccinated <1 yr from SCT showed seroconversion to the H3N2 virus vs. 39% of patients vaccinated >1 yr (p=0.001); similarly, only 6% and 8% of patients in the <1 yr group seroconverted to H1N1 and influenza B, respectively, whereas 64% (p=0.001) and 39% (p=0.003) seroconverted in the >1 yr group |
| Kersun LS, 2012 | prospective trial | ALL | 177 | Inactivated trivalent influenza vaccine x dose in repeat vaccinees and x 2 doses in vaccine-naive patients | • Patients vaccinated during induction phase had superior vaccine responses compared to patients vaccinated during post-induction or maintenance phases (p=0.0237).  
• Higher aggregate HAI titer responses associated with a higher baseline B-cell count (p=0.0240), and higher CD4 and CD8 influenza-specific T-cell responses, suggesting prior antigen exposure is a significant contributor. |
| Wong-Chew RM, 2012 | prospective cohort | AML, solid tumours, or lymphoma | 56  | Inactivated trivalent seasonal vaccine | • Seropositivity from pre- to post-vaccine: 43% to 63% for H1N1 serotype (p=0.02), 68% to 85% for H3N2 serotype (p=0.05) and 0% to 14% for B serotype (p=0.006)  
• GMT from pre- to post-vaccine: 47 (95% CI, 128-378) to 138 (95% CI, 363-685) for H1N1 virus (p=0.009), 99 (95% CI, 208-485) to 277 (95% CI, 466-775; p=0.009) for H3N2 virus, and 10 (95% CI, 9-10) to 14 (95% CI, 5-58) for influenza B virus (p=0.11) |
| Shahin K, 2012 | prospective cohort | Patients receiving CT for solid tumours | 20  | A503-adjuvanted or nonadjuvanted monovalent vaccine x 2 doses at day 0 and 21; most often administered on day 1 of CT | • Seroprotection: 90%  
• Seroconversion: 65%  
• 8.8-fold increase in GMT from pre- to post-vaccine |
| Hakim H, 2012 | prospective observation | Solid and hematological, receiving CT | 37  | 2009 H1N1 influenza monovalent vaccine x 1 or 2 doses (age dependent) | • Seroprotection: achieved in 52% of hematology patients and 75% of solid tumour patients after the last dose  
• Seroconversion: achieved in 48% of hematology patients and 50% of solid tumour patients after the last dose  
• No significant differences in seroconversion or seroprotection rates between patients who received one dose versus two doses |
<table>
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<th>Author, Year</th>
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| Carr S, 2011<sup>ae</sup> | randomized trial | Solid and hematological, receiving or received CT or RT within last 3 months | 28 | 1. LAIV x 1 or 2 doses  
2. TIV x 1 or 2 doses | • Seroprotection: H3N2 (80.7% LAIV vs. 92.3% TIV, p=0.41), H1N1 (34.6% vs. 73.0%, p=0.01), influenza B (3.8% LAIV vs. 15.3% TIV, p=0.34)  
• Seroconversion: H3N2 (7.6% LAIV vs. 46.1% TIV, p=0.004), H1N1 (7.6% vs. 26.9%, p=0.13), influenza B (0% LAIV vs. 3.8% TIV, p=0.999)  
• Two serious adverse events reported (febrile illness and seizure) |
| Yen TY, 2011<sup>ab</sup> | prospective cohort | Solid and hematological, receiving CT | 25 | 2009 H1N1 influenza monovalent vaccine x 1 or 2 doses (age dependent) | • Seroprotection: 52% pre-vaccine; 72% post-vaccine (p=0.24)  
• Sero-response: 32% post-vaccine; greater in pts without pre-vaccine seroprotective titer than those with (50% vs. 15%, p=0.07) and greater in those with lymphocyte counts >1,500/µl (p=0.008)  
• GMT: increased post-immunization in patients <10 yrs receiving two immunizations (21.4 to 60.6; p=0.025) |
| Cheng FW, 2011<sup>ad</sup> | prospective cohort | Patients receiving CT or completed ≤12 mos | 12 | Haemagglutinin of influenza A/Caldifornia/07/2009 (H1N1)-like virus x 2 | • Seroprotection: 58% after 1<sup>st</sup> dose (7/12 patients); 100% after 2<sup>nd</sup> dose  
• Seroconversion: 41% after 1<sup>st</sup> dose; 75% after 2<sup>nd</sup> dose |
| Bate J, 2010<sup>ae</sup> | prospective cohort | Solid and hematological | 54 | 2009 H1N1 influenza monovalent AS03(B)-adjuvanted vaccine x 2 doses, days 0 and 21 | • Seroconversion: 44.4% of patients  
• 33.3% among those w/acute lymphoblastic leukemia  
• 36.4% among those w/lymphoma or other leukemias  
• 66.7% among those w/brain tumors  
• 71.4% among those w/other solid tumours  
• 28.6% among those receiving acute lymphoblastic leukemia maintenance therapy  
• Non-factors (multivariate): age, cancer type, and lymphopenia |
| Goossen GM, 2009<sup>ef</sup> | meta-analysis (Cochrane Review) | Pediatric malignancies | 708 | 8 controlled clinical trials and 1 RCT were included in the review  
In 5 studies, immune responses to influenza vaccine were compared in 272 children on CT with 166 children not on CT  
In 3 studies, responses to influenza vaccine were assessed in 204 children on CT compared with responses in 112 healthy children  
Immune responses in children receiving CT were consistently weaker (four-fold rise of 25% to 52%) than in those children who had completed CT (50% to 86%) and in healthy children (71% to 89%)  
Concerning adverse effects, 359 pediatric oncology patients received influenza vaccine and the side effects described were mild local reactions and low grade fever  
Authors concluded that although pediatric oncology patients receiving CT are able to generate an immune response to the influenza vaccine, it is unclear whether this immune response protects them from influenza infection or its complications |
| Bektas O, 2007<sup>e</sup> | case series | Patients with solid tumours aged 1-18 years on CT or within 6 months of completing CT | 45 | 2 doses of the trivalent split vaccine 1 month apart | • Fourfold rise in the percentage of post-immunization antibody titers was detected for: H1N1 (84.4%), H3N2 (77.8%), and influenza B (60%)  
• Stratification of patients on active CT versus within 6 months of completion of CT in terms of fourfold rise in antibody titers showed a statistically significant difference for only influenza B (p = .34)  
• Post-immunization protective rates were 86 to 97% |
| Matsuzaki A, 2005<sup>g</sup> | controlled clinical trial | Pediatric malignancies | 44 | 2 doses of influenza vaccine 2-4 weeks apart | • Response rates: H1N1 65%; H3N2 40%; influenza B: 46%  
• Patients on CT showed a significantly lower response than those who were immunized after completing CT; protection titers were: H1N1=42% vs. 80% (p=0.006), H3N2=25% vs. 83% (p=.019)  
• For influenza B, patients with low IgG showed a lower response rate than those with higher IgG (29% vs. 61%, p=.040)  
• Multivariate analysis showed that factors associated with low immune response were: H1N1= low IgG (p<.001) and admin. of CT (p=.003); H3N2= admin. Of CT (p=.008); influenza B= low WBC count (p=.03) and low IgG (p=.030) |
**Author, Year** | **Study Type** | **Disease Site** | **N** | Comparisons | Results and Recommendations
--- | --- | --- | --- | --- | ---
Chisholm J, 2005<sup>17</sup> | controlled clinical trial | Pediatric patients with solid tumours or lymphoma actively receiving CT or who were within 6 months of completing CT | 66 | 1 or 2 doses of influenza vaccine, in autumn 2001 and/or 2002 | • Following immunization:
  o 25/64 patients (38%) were protected against all three viruses, representing a full response
  o Protective responses to one or two viral strains were seen in 12/64 (19%) patients
  o 27 (41%) patients showed no protective response to immunization, including 5 patients who remained fully susceptible to all 3 viruses following immunization
• Estimated increases in percentage protected against each viral subtype following immunization were:
  o H1N1: 29% (95% CI 17–42%, p<.0001)
  o H3N2: 22% (95% CI 10–33%, p=.0002)
  o Influenza B: 43% (95% CI 29–57%, p< .0001)
• N= 27 patients were transfused with blood and/or platelets during the study:
  o N=10 (38%) showed no response
  o N=6 (23%) showed a protective response to 1-2 viral subunits
  o N=10 (38%) were protected against all 3 viruses
• in multivariate analysis, lymphopenia was associated with improved response for H1N1 (OR=11.4, 95% CI 1.11–117.37; p= .041), though the authors caution that the number of patients with lymphopenia was small
• There was no significant difference in response rates among children on treatment and off treatment and by intensity of CT regimen
Porter CC, 2004<sup>19</sup> | controlled clinical trial | 1. ALL in 1st remission, maintenance CT, completed last delayed intensification at least 4 weeks earlier 2. Healthy controls 49 | 2001–2002 inactivated trivalent influenza vaccine x 1 dose for children >9 yrs of age and those previously vaccinated, and x 2 doses (1 month apart) for previously unimmunized children or those <9 yrs of age | • Although post-immunization geometric mean titres were lower in group 1 versus group 2 children for the H1N1 antigen (p<.001), H3N2 antigen (p=.03), and influenza B antigen (p=.003), at least 60% of children with ALL had at least a 4-fold increase in HAI titres to each of the influenza antigens
• group 1 developed significant antibody titers to H3N2 antigen 4 weeks after the 2<sup>nd</sup> immunization
• Seroconversion rates after 2 doses of vaccine were 57.1 to 84.6% and serorespore rates were between 24 and 60% in group 1
• Compared to group 2, group 1 had less seroconversion and lower serorespore rates to H1N1
• Seroconversion and serorespore rates to influenza B and H3N2 antigens were comparable in group 1 and group 2 children
• Antibody response in group 1 children who received reinduction CT suggests that the therapy did not impair serorespore rates
Hseih YC, 2002<sup>20</sup> | controlled clinical trial | 1. Pts with ALL in maintenance stage; received 6-mercaptopurine + methotrexate, and reinduction with vincristine + prednisolone 2. Pts with asthma 3. Healthy controls previously unvaccinated | 49 | TIV x 2 doses for children younger than 8 yrs, 1 dose for children older than 8 yrs | • 2001–2002 inactivated trivalent influenza vaccine x 1 dose for children >9 yrs of age and those previously vaccinated, and x 2 doses (1 month apart) for previously unimmunized children or those <9 yrs of age | • group 1 developed significant antibody titers to H3N2 antigen 4 weeks after the 2<sup>nd</sup> immunization
• Seroconversion rates after 2 doses of vaccine were 57.1 to 84.6% and serorespore rates were between 24 and 60% in group 1
• Compared to group 2, group 1 had less seroconversion and lower serorespore rates to H1N1
• Seroconversion and serorespore rates to influenza B and H3N2 antigens were comparable in group 1 and group 2 children
• Antibody response in group 1 children who received reinduction CT suggests that the therapy did not impair serorespore rates

**Abbreviations:** ALL = acute lymphocytic leukemia, AML = acute myeloid leukemia, ASCT = autologous stem cell transplantation, BMT = blood and marrow transplant, CI = confidence interval, CML = chronic myeloid leukemia, CT = chemotherapy, FEC = 5-FU + epirubicin + cyclophosphamide, GMT = geometric mean titers, GVHD = graft-versus-host disease, HAI = hemagglutination inhibition, HSCT = hematopoietic stem cell transplant, HR = hazard ratio, IgG= immunoglobulin G, LAIV = live attenuated influenza vaccine, NS = not statistically significant, OR = odds ratio, RCT = randomized controlled trial, RT = radiotherapy, SCT = stem cell transplant, TIV = trivalent inactivated influenza vaccine, WBC = white blood cells.
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