

INFLUENZA IMMUNIZATION FOR ADULT AND PEDIATRIC PATIENTS UNDERGOING CANCER TREATMENT

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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.

All cancer drugs described in the guidelines are funded in accordance with the Outpatient Cancer Drug Benefit Program, at no charge, to eligible residents of Alberta, unless otherwise explicitly stated. For a complete list of funded drugs, specific indications, and approved prescribers, please refer to the [Outpatient Cancer Drug Benefit Program Master List](#).

Participation of members of the Alberta Provincial Tumour Teams 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 Teams 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.

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*.¹ 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

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 for adult and pediatric patients with cancer?

DEVELOPMENT AND REVISION HISTORY

The 2019 update of this guideline was reviewed and endorsed by members of the Alberta Provincial Tumour Teams, which includes medical oncologists, radiation oncologists, hematologists, 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, October 2016, October 2017, October 2018, and October 2019.

SEARCH STRATEGY

The MEDLINE database was searched according to the strategy outlined in Table 3, Appendix B. The 2019 search yielded 71 citations, 4 of which met the criteria to be included in the evidence tables presented in Appendix B; an additional 3 articles were identified through searching the reference lists of the included publications. A systematic search of grey literature included websites from the World Health Organization, Health Canada, the Public Health Agency of Canada, Alberta Health Services, Alberta Health, Centers for Disease Control and Prevention, and the American Academy of Pediatrics. A search for published clinical practice guidelines yielded results from the Infectious Diseases Society of America⁴, the National Comprehensive Cancer Network,⁵ and the Italian Society of Medical Oncology.⁶

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 [2019 Alberta Health Services Immunization Program Standards Manual](#), 2019/20 [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.ahs.ca/influenza/influenza.aspx.

The 2019/2020 quadrivalent inactivated influenza vaccine being used in Alberta contains the following antigenic strains:^{2,7-9}

- A/Brisbane/02/2018 (H1N1) pdm09-like virus
- A/Kansas/14/2017 (H3N2)-like virus
- B/Colorado/06/2017-like virus (B/Victoria/2/87 lineage)
- B/Phuket/3073/2013-like virus (B/Yamagata/16/88 lineage)

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.^{2,7,10} The inactivated quadrivalent influenza vaccine (Fluzone® Quadrivalent or Flulaval® Tetra) is recommended for all individuals over six months of age.⁹
2. Age, duration, type of systemic therapy (with the exception of rituximab or other B-cell depleting antibodies, and CTLA-4, PD-1, or PD-L1 immune checkpoint inhibitor therapies), 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 ideally be given two weeks before the administration of any immune-suppressing cancer treatment, to allow for sufficient antibody production by the patient. If early immunization is not possible or feasible, administration of the inactivated vaccine less than two weeks before the start of immune-suppressing cancer treatment, or between treatment cycles has been reported to be safe and is recommended over not receiving the vaccine at all, although the efficacy of the vaccine may be reduced in this situation.

- b. 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.^{4,11-13}
 - c. Given the lack of safety information and the potential risk of a significant immune response, patients treated with CTLA-4 inhibitors (e.g., ipilimumab) alone or in combination with other anti-cancer agents and those who have discontinued treatment with CTLA-4 inhibitors 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 with PD-1 and PD-L1 inhibitors 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):^{12,14}
- 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 assessment by the transplant physician. 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-transplant. 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. Household contacts and healthcare workers should be up-to-date for routine immunizations as per the Alberta Health Immunization Schedule, including annual influenza, to reduce the risk of disease transmission to transplant recipients.
 - e. Individuals who have received the live nasal spray influenza vaccine (FluMist®) should avoid close association with individuals with severe immunocompromising conditions (e.g., transplant recipients requiring protective isolation) for at least two weeks following immunization.¹² The live nasal spray influenza vaccine (FluMist®) is not available in Canada this year.
5. Annual influenza immunization of family members and hospital or clinic staff and volunteers who are in contact with adult patients with cancer is strongly recommended. In many cases, this may be more important than immunizing the patients themselves, as some patients may be less likely to respond to the vaccine. Transmission of influenza between infected healthcare workers and their vulnerable patients results in significant morbidity and mortality; therefore, healthcare workers should consider it their responsibility to provide the highest standard of care, which includes receiving the annual **inactivated** influenza vaccine.^{1,2,15}

6. Contraindications and precautions for influenza immunization in adult patients with cancer are:^{2,16,17}
- a previous anaphylactic reaction to an influenza vaccine.
 - a known hypersensitivity to any component of the vaccine, with the exception of egg.
 - Egg-allergic adults with cancer may be safely immunized using inactivated influenza vaccine without a prior influenza vaccine skin test and with the full dose of vaccine, irrespective of a past severe reaction to egg. They can be immunized in any setting and should be kept under observation for 30 minutes following the administration the vaccine.
 - 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.

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

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 and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, the quadrivalent influenza vaccine (Fluzone® Quadrivalent or Flulaval® Tetra) should be used for children.^{2,18} The live attenuated influenza vaccine is not recommended for children with immune-compromising conditions.^{2,7} Immunization with currently available influenza vaccines is **not** recommended for infants younger than six months of age. The recommended doses by age are as follows:
 - children nine years or older should receive one dose of influenza vaccine.
 - children previously unimmunized with influenza vaccine who are older than six months and less than nine years of age require **two** doses of influenza vaccine in the first year they are immunized, with a minimum interval of four weeks between doses.
 - children less than nine years of age who have been previously immunized with influenza vaccine in another season require only one dose of influenza vaccine.
 - a full dose (0.5mL) 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.^{4,11-13}

3. Influenza vaccine should ideally be given at least two weeks before the administration of any immune-suppressing cancer treatment, to allow the patient to develop a sufficient antibody response. If early immunization is not possible or feasible, administration of the inactivated vaccine less than two weeks before the start of immune-suppressing cancer treatment, or between treatment cycles has been reported to be safe and is recommended over not receiving the vaccine at all, although the efficacy of the vaccine may be reduced in this situation.
4. For pediatric patients undergoing hematopoietic stem cell transplant (HSCT, autologous and allogeneic):^{12,18}
 - 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). **Live vaccines are contraindicated.**
 - b. Immune system recovery post-HSCT is variable and requires assessment by the transplant physician. 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, with the approval of the transplant physician; 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. Household contacts and healthcare workers should be up-to-date for routine immunizations as per the Alberta Health Immunization Schedule, including annual influenza, to reduce the risk of disease transmission to pediatric transplant recipients.
 - e. Individuals who have received the live nasal spray influenza vaccine (FluMist®) should avoid close association with individuals with severe immunocompromising conditions (e.g., transplant recipients requiring protective isolation) for at least two weeks following immunization.¹² The live nasal spray influenza vaccine (FluMist®) is not available in Canada this year.
5. Annual influenza immunization of family members, out-of-home caregivers, and hospital or clinic staff and volunteers in contact with pediatric patients with cancer is strongly recommended. In many cases, this may be more important than immunizing the patient themselves, as some patients may be less likely to respond to the vaccine. Transmission of influenza between infected healthcare workers and their vulnerable patients results in significant morbidity and mortality; therefore, healthcare workers should consider it their responsibility to provide the highest standard of care, which includes receiving the annual **inactivated** influenza vaccine.^{1,2,15}
6. Contraindications and precautions for influenza immunizations in pediatric patients with cancer include:^{2,16,17}
 - 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.
 - Egg-allergic children with cancer may be safely immunized using inactivated influenza vaccine without a prior influenza vaccine skin test and with the full dose of vaccine, irrespective of a past severe reaction to egg. They can be immunized in any setting and should be kept under observation for 30 minutes following the administration the vaccine.

- 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.

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

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

Cancer treatments 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. Annual administration of the inactivated influenza vaccine is therefore recommended for most adult patients with cancer, with the exception of patients treated with B-cell depleting antibodies (e.g., rituximab) and CTLA-4 immune checkpoint inhibitor therapies (e.g., ipilimumab).

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 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%, $p=.004$).¹⁹ 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). Similarly, a 2013 Cochrane review of four studies involving 2124 adult patients with cancer receiving chemotherapy concluded that influenza immunization was associated with lower mortality and that infection rates were lower or similar in patients who were vaccinated versus those who were not.²⁰ 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.²¹ 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.²²

There is conflicting evidence regarding the timing of influenza immunization with respect to chemotherapy administration. The majority of research studies, reviews, and published guidelines suggest that since immunosuppressive chemotherapy regimens may depress the patients' immune response to vaccines, it is most beneficial to immunize patients approximately 10 to 14 days prior to beginning chemotherapy, to allow for sufficient antibody production by the patient.^{3,16,23,24} 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 4.²⁵ However, a recent pilot study of 18 patients with solid tumours immunized either one week before or on the first day of chemotherapy reported that all patients did mount 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.²⁶ If early immunization is not possible, administration of the inactivated vaccine *between* chemotherapy cycles has been reported to be safe and is recommended over not receiving the vaccine at all, although the efficacy of the vaccine may be reduced in this situation.^{3,5,19,27} In such situations, administration of the vaccine is preferable when therapy is at the lowest level possible.¹⁶

There is limited published data on safety of the influenza vaccine (live or inactivated) in patients with cancer treated with immune checkpoint inhibitor therapies including CTLA-4 inhibitors (e.g., ipilimumab) or PD-1 and PD-L1 inhibitors (e.g., nivolumab, pembrolizumab).²⁸⁻³⁴ 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. A recent study of 23 lung cancer patients treated with a PD-1 or PD-L1 inhibitor who received the seasonal influenza vaccine reported an adequate humoral immune response to the vaccine and a high rate of seroconversion rate compared to healthy controls. However, the frequencies of severe immune-related adverse events in the long-term clinical course following vaccination were significantly higher than those reported in the safety data of PD-1 immune checkpoint inhibitor trials.³⁵⁻³⁷ 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.¹⁴ Kumar and colleagues recently reported the results of a multicentre prospective observational study of pediatric and adult solid organ transplant (SOT) and HSCT patients carried out across 20 sites from the United States, Canada, and Spain. They documented 616 patients with confirmed influenza (477 SOT; 139 HSCT) over a 5-year study period; the annual incidence of pneumonia ranged between 11.3-35.0% and ICU admission rates ranged between 8.1-14.3%. The receipt of vaccine in the same influenza season

was associated with a decrease in disease severity as determined by the presence of pneumonia, and antiviral treatment within 48 hours was associated with improved outcomes.³⁸ No significant differences were noted between SOT and HSCT patients with regard to pneumonia and ICU care. However, HSCT patients had a higher 6-month mortality (13.8% vs 4.8%, $p < 0.001$) and viral load at disease onset (median viral load 1.04×10^5 copies/mL vs 8.04×10^3 copies/mL, $p = 0.001$) compared to SOT patients.

There is variability in the efficacy of influenza immunization in HSCT patients reported in the literature. One study documented serologic responses ranging from 0% in allogeneic transplant patients to 32% in autologous transplant patients. Another study reported immune responses of 29% to 34% in patients who underwent HSCT, and 46% to 62% in a group of healthy matched controls.^{39,40} 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.⁴¹ 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.⁴² 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.⁴³ Similarly, Berglund and colleagues reported the results of a subgroup analysis of rituximab-treated patients among 96 adult outpatients with cancer who were undergoing treatment. Of the 13 patients treated with rituximab, only one responded to immunization against influenza A (H1N1) and none responded to immunization against seasonal influenza.¹³ Patients who are treated with rituximab or other B-cell depleting antibodies should therefore have all immunizations postponed until at least 6 months after the last dose of rituximab or other B-cell depleting therapies.^{4,11-13,43}

Lower-respiratory tract infection (LRTI) is a complication of influenza infection that frequently leads to lung injury and death, and profound lymphopenia is one of the most significant risk factors for progression from upper- to lower-respiratory tract involvement.⁴⁴ 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.^{14,16,45,46} While only 10-30% of HSCT recipients will have a detectable antibody response to the influenza vaccine at 6-24 months post-transplant, over 60% will have a detectable response at 24 months or more post-transplant.⁴⁷ Immune system recovery post-transplant is variable and requires individual assessment by the transplant physician. For example, patients treated with rituximab post-transplant will have a delay in their B-cell recovery by at least six months following the final dose.^{14,42} 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.^{14,16,45,46}

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. Influenza immunization rates of health care workers is associated with a reduction in influenza infections in cancer patients.⁴⁸ 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.¹⁶ 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.^{45,46} 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.^{2,15}

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.⁴⁹ 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.⁵⁰ 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, and the potential for lineage mismatch between the predominant circulating strain of influenza B and the strain in a trivalent vaccine, NACI continues to recommend that a quadrivalent influenza vaccine be used.^{2,10} 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. The live vaccine is contraindicated in children with immune compromising conditions.²

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 nine controlled clinical trials and one randomized controlled trial involving 770 children, Goossen *et al.* reported that immune responses to the seasonal influenza vaccine in children receiving chemotherapy were consistently weaker than in those children who had completed their chemotherapy regimen and in healthy controls.⁵¹ 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.^{49,52} Seroconversion rates are also influenced by the type of cancer (solid tumour vs. hematologic malignancy)⁵³ and the type of chemotherapy.⁵⁴ Similar to the recommendations made for adults with cancer, it is likely most beneficial to immunize pediatric patients with cancer two weeks prior to beginning chemotherapy, to allow for sufficient antibody production by the patient. Shahgholi *et al.* assessed the immune response of 32 pediatric patients with 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 ($p=0.038$).⁵⁵

The recommendations for pediatric patients undergoing HSCT are similar to those for adult patients, with appropriate adjustments made for vaccine doses.^{12,14,18,45} It is recommended that both the recipient and donor (for allogeneic transplants) receive the inactivated influenza vaccine two weeks prior to the transplant. Immune system recovery following transplant is variable, and depends on factors such as the types of therapies administered and the presence of graft-versus-host disease; therefore individual assessment is required by the transplant physician. Influenza vaccine should ideally be administered six months post-HSCT in pediatric patients. Inactivated influenza vaccine can be given as early as four months post-transplant in outbreak situations, with the approval of the transplant physician; 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.^{18,45,56}

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**.¹⁶ 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.^{18,45} 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.^{2,12}

GLOSSARY OF ABBREVIATIONS

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

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 2020. If critical new evidence is brought forward before that time, however, the guideline will be revised and updated accordingly.

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APPENDIX A: ADDITIONAL RESOURCES

Canadian Resources

Alberta Health Services. Immunization Program Standards Manual:
<https://www.albertahealthservices.ca/info/page10802.aspx>

Alberta Health Services, Influenza Immunization:
www.albertahealthservices.ca/influenza/influenza.aspx

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

Alberta Bone Marrow and Blood Cell Transplant Program. Standard Practice Manual:
www.albertahealthservices.ca/assets/info/hp/cancer/if-hp-cancer-guide-bmt-manual.pdf

Public Health Agency of Canada. National Advisory Committee on Immunization (NACI) Advisory Committee. Canadian Immunization Guide Chapter on Influenza and Statement on Seasonal Influenza Vaccine for 2019-2020:
<https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/canadian-immunization-guide-statement-seasonal-influenza-vaccine-2019-2020.html#11>

Public Health Agency of Canada. Canadian Immunization Guide:
www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php

International Resources

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

Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices (ACIP): Prevention and Control of Seasonal Influenza with Vaccines: Recommendations of the Advisory Committee on Immunization Practices — United States, 2019–20 Influenza Season.
https://www.cdc.gov/mmwr/volumes/68/rr/rr6803a1.htm?s_cid=rr6803a1_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/

National Comprehensive Cancer Network. Prevention and Treatment of Cancer-Related Infections, version 1.2019 (Requires Free Registration and Login):
www.nccn.org/professionals/physician_gls/f_guidelines.asp

American Academy of Pediatrics. Policy Statement: Recommendations for the Prevention and Control of Influenza in Children, 2019-2020:
<https://pediatrics.aappublications.org/content/early/2019/08/29/peds.2019-2478#T1>

APPENDIX B: SELECT EVIDENCE FROM CLINICAL TRIALS AND CASE STUDIES

Table 1. Published Literature on Influenza Immunization in Adult Patients with Cancer, January 2000 – September 2019^{13,19,25,26,28-35,42,43,56-84}

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
Chong, 2019	retrospective review	Patients with solid tumours (lung=165, melanoma=71, other=134) treated with immune checkpoint inhibitors	370	2014-15, 2015-16, or 2016-17 inactivated trivalent (N=207) or quadrivalent (N=163) standard (N=199) or high dose (N=171) influenza vaccine within 65 days of cancer therapy	<ul style="list-style-type: none"> N=75 (20%) experienced a new onset immune related AE (any grade): N=5 (7%) grade 1, N=40 (53%) grade 2, N=27 (36%) grade 3, N=3 (4%) grade 4; no grade 5 Main types of immune related AEs: endocrine (28% of all AEs) pneumonitis (25%), colitis (13%), transaminitis (12%) Proportion of patients who experienced any immune related AE was highest among those treated with ipilimumab+nivolumab (25/82, 30%) For patients on an anti-PD1 agent only, the overall immune related AE rate was 17% (38/227) The proportion of patients who experienced serious (grade 3 or 4) immune related AEs was higher among those treated with ipilimumab+nivolumab (11/82, 13%) vs. those treated with anti-PD1 agents alone (15/227, 6.6%)
Gwynn, 2019	prospective case series	Patients with solid tumours treated with immune checkpoint inhibitors	24	2017-18 inactivated quadrivalent influenza vaccine	<ul style="list-style-type: none"> N=7 patients with immune mediated AEs (any grade) in 60 day follow up period (1 patient experienced 2) <ul style="list-style-type: none"> N=3 grade 1-2 rash N=1 grade 1-2 hypothyroidism N=1 grade 1-2 myalgia N=1 grade 1-2 colitis N=2 severe immune mediated AEs (grade 3 nephritis, grade 4 diabetes) No significant changes in serum cytokine or chemokine concentrations no patients discontinued treatment due to AEs or disease progression
Awadalla, 2019	retrospective case control	Patients with solid tumours or Hodgkin lymphoma treated with immune checkpoint inhibitors: 1. Cases: developed myocarditis 2. Controls: no myocarditis	101 201	Various	<ul style="list-style-type: none"> Influenza vaccination was administered to 25% of the cases vs. 40% of the controls (p=0.01) 36% of vaccinated cases vs. 55% of unvaccinated cases had further immune side effects during treatment (p=0.10), including lower rates of pneumonitis (12 vs. 36%, p=0.03) N=47/101 cases experienced a major adverse cardiac event during the median 175 day follow-up; 24% vaccinated vs. 59% unvaccinated cases, p=0.002)
Bersanelli, 2018	multicentre retrospective cohort	Patients with advanced cancer (NSCLC=103, RCC=112, melanoma=55, other=30) treated with immune checkpoint inhibitors 1. Vaccinated 2. Unvaccinated	79 221	2016-17 inactivated trivalent or quadrivalent influenza vaccine	<ul style="list-style-type: none"> Incidence of influenza=24.1% vaccinated vs. 11.8% unvaccinated (OR=2.4; 95% CI 1.23–4.59,p=0.009) In the NSCLC subgroup, incidence of influenza=27% vaccinated vs. 17% unvaccinated (OR=1.81; 95% CI 0.67–4.86, p=0.29) In the elderly subgroup (>71 years, N=103), incidence of influenza=37.8% vaccinated vs. 6.1% unvaccinated (OR=9.28, 95% CI 2.77–31.14, p<0.0001) No significant differences were seen in response rate, disease control rate, or time to treatment failure between vaccinated vs. unvaccinated patients or between patients developing vs. not developing influenza
Strowd, 2018	prospective cohort	CNS tumours (high-grade glioma=23, CNS	27	2013-14 inactivated quadrivalent high-dose influenza vaccine	<ul style="list-style-type: none"> No grade III-IV toxicity reported

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		lymphoma=3, meningioma =1) treated with RT, CT, or glucocorticoids			<ul style="list-style-type: none"> Seroconversion rates for the A/H1N1=65%, A/H3N2=69%, and B strains=50%, and all were significantly higher than 2014 study ($p < 0.04$) Baseline seroprotection in $\geq 67\%$ of patients; rose to $\geq 93\%$ to all strains and remained stable at 3-months post-vaccination Seroconversion was universally poor in patients with post-treatment lymphopenia
<i>Wijn, 2018</i>	retrospective cohort	Patients with NSCLC treated with nivolumab: 1. Vaccinated 2. Unvaccinated	42 85	2015-16 or 2016-17 trivalent inactivated influenza vaccine	<ul style="list-style-type: none"> Incidence of irAEs = 26% vaccinated vs. 22% unvaccinated patients (Rate Ratio 1.20, 95% CI 0.51-2.65) Incidence of serious irAEs = 7% vaccinated vs. 4% unvaccinated patients (Rate Ratio 2.07, 95% CI 0.28-15.43) No significant differences in the rates of discontinuation, death, clinical deterioration or tumour response between groups
<i>Bitterman, 2018</i>	systematic review	6 studies conducted between 2013-2017 including adults with hematologic and solid tumours	2275	Various	<ul style="list-style-type: none"> Observational data suggest lower mortality and infection-related outcomes with vaccination The evidence, although weak, shows that the benefits outweigh the potential risks when vaccinating adults with cancer against influenza. There is no conclusive evidence regarding the use of adjuvanted versus non-adjuvanted influenza vaccine in this population
<i>Waqar, 2018</i>	prospective cohort	Patients with non-hematologic malignancies receiving CT: 1. Vaccinated on day of CT 2. Vaccinated 1 week before CT	8 10	2011-12 trivalent inactivated influenza vaccine	<ul style="list-style-type: none"> Seroconversion against H1N1, H3N2, and B strains was observed in 63% (5/8), 50% (4/8), and 38% (3/8) of patients in group 1, and 50% (5/10), 70% (7/10), and 60% (6/10) in group 2 Seroconversion and seroprotection rates against the 3 influenza strains were not significantly different between the 2 groups All of the patients (8/8) vaccinated in group 1 demonstrated seroprotection to at least 1 strain, compared with 60% of patients in group 2 Seroprotection rates were 50% for all 3 strains in group 1, and they were 20% (2/10), 40% (4/10), and 50% (5/10) for strains H1N1, H3N2, and B, respectively in group 2
<i>Läubli, 2018</i>	prospective trial	1. Patients with lung cancer receiving immune checkpoint inhibitors 2. Age-matched healthy controls	23 11	Inactivated, unadjuvanted trivalent vaccine containing: Influenza/A/H1N1/California/2009, Influenza/A/H3N2/Texas/2012, Influenza/B/Brisbane/2008	<ul style="list-style-type: none"> No significant differences between patients and healthy controls in vaccine-induced antibody titers against all 3 viral antigens Vaccination resulted in protective titers in more than 60% of patients/participants Post-vaccine frequency of immune-related adverse events (irAEs) was 52.2% with a median time to occurrence of 3.2 months after vaccination 6/23 patients (26.1%) showed severe grade 3 or 4 immune-related adverse events, including N=2 colitis, N=2 encephalitis, N=1 peripheral neuropathy, N=1 pneumonitis; other adverse events included N=3 rash, N=3 arthritis, and N=1 hypothyroidism
<i>Branagan, 2017</i>	prospective trial	Patients with multiple myeloma (N=49) or Waldenström's Macroglobulinemia (N=2); 41 patients had disease requiring therapy	51	Two doses of 2014-15 trivalent Fluzone® high-dose influenza vaccination, administered 30 days apart	<ul style="list-style-type: none"> Total seroprotection rate against all 3 influenza strains = 4% at baseline, 47% after initial dose ($p < 0.001$), and 65% after the second dose ($p < 0.01$) Seroconversion rates after initial dose: 69% (35/51) H3N2, 73% (37/51) H1N1, 67% (34/51) influenza B, and 39% (20/51) combined strains Seroconversion against influenza B improved significantly after the second dose (67% to 96%, $p < 0.001$) and seroconversion against all three strains increased from 39% to 55% after second vaccination ($p=0.02$) Rate of laboratory-confirmed influenza infection=6%

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<i>Nakashima, 2017</i>	prospective cohort	Patients with lung cancer undergoing CT (25) or COPD (controls, 26)	51	2013-14 trivalent inactivated influenza vaccine	<ul style="list-style-type: none"> A/H1N1 seroprotection rate=84% lung cancer vs. 81% COPD; (not significant) A/H3N2 seroprotection rate=84% lung cancer vs. 96% COPD (not significant); B strain seroprotection rate = 64% lung cancer vs. 92% COPD (p=0.019) Patients with lung cancer receiving platinum doublet treatment exhibited lower seroprotection rates than those receiving a single agent
<i>Keam, 2017</i>	randomized controlled trial	Breast & lung cancer patients receiving CT: 1. vaccinated on day 1 of CT cycle 2. vaccinated on day 11 of CT cycle	43 54	2014-15 trivalent inactivated influenza vaccine	<ul style="list-style-type: none"> Seroprotection rates day 1 group vs. day 11 group: H1N1, 67% vs. 75%, p= 0.403; H3N2, 77% vs 80%, p=0.772; strain B, 21% vs. 27%, p=0.472 Seroconversion rates day 1 group vs. day 11 group: H1N1, 41% vs 57%, p= 0.151; H3N2, 44% vs 52%, p=0.429; strain B, 10% vs 18%, p=0.306 Adverse events day 1 group vs. day 11 group = 13% vs. 32%, p=0.040
<i>La Torre, 2016</i>	systematic review and meta-analysis	22 studies conducted between 1993-2016 including adult and pediatric patients with hematologic malignancies	N/A	Various	<ul style="list-style-type: none"> Protection rate of H1N1 booster dose=30% (95% CI=6-62%) Pooled prevalence protection rate available for meta-analysis only for first dose = 42.6% (95% CI=23.2–63.3 %) for H3N2 and 39.6 % (95% CI=26%-54.1%) for B strain Response rate of booster dose=35% (95% CI=19.7-51.2%) for H1N1, 23% (95% CI=16.6-31.5%) for H3N2, and 29% (95% CI=21.3- 37%) for B strain
<i>Sanada, 2016</i>	multicentre prospective trial	Patients with solid tumours or hematologic malignancies receiving CT	109	2013-14 trivalent inactivated influenza vaccine; second vaccinations administered to patients who did not respond to all 3 viral strains after the first vaccination	<ul style="list-style-type: none"> Proportion of patients with protective titres against all 3 viral strains increased from 3 to 27% following vaccination (p< 0.01) 79 patients received a second vaccination; the proportion of those with protective titres against the individual strains increased by 10% (H1N1), 8% (H3N2), and 3% (B) from the first vaccination No serious adverse events observed
<i>Sun, 2016</i>	prospective cohort	CLL patients treated with ibrutinib	19	2013-14 trivalent inactivated influenza vaccine	<ul style="list-style-type: none"> Seroconversion rates for A/H1N1, A/H3N2, and B strains = 16%, 26%, and 11%, respectively Significant increases in GMTs for all three strains Significant increase in seroprotection rate for A/H3N2 (32% vs. 74%, p=0.004) 7 patients developed influenza-like illness within 6 months of immunization
<i>Jamshed, 2016</i>	randomized controlled trial	cancer patients <65 years of age receiving chemotherapy: 1. standard dose influenza vaccine 2. high-dose influenza vaccine	51 54	2012-13 (year 1) and 2013-14 (year 2) trivalent inactivated influenza vaccines	<ul style="list-style-type: none"> 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

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<i>Berglund, 2014</i>	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	<ul style="list-style-type: none"> 100% (N=13) of patients treated with rituximab did not respond to immunization For the patients not treated with rituximab: <ul style="list-style-type: none"> H1N1 vaccine: seroconversion = 84% (N=63), seroprotection = 87% (N=65) Seasonal influenza vaccine (A/Bri): seroconversion = 42% (N=28), seroprotection = 70% (N=46) Seasonal influenza vaccine (A/Uru): seroconversion = 50% (N=33), seroprotection = 59% (N=39)
<i>Strowd, 2014</i>	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	<ul style="list-style-type: none"> 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
<i>Vinograd, 2013</i>	prospective non-intervention trial	patients with solid tumours receiving CT and hematologic patients with active disease	806	2011 seasonal trivalent killed influenza vaccine	<ul style="list-style-type: none"> 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)
<i>Chu, 2013</i>	prospective trial	Ovarian cancer: 1. in remission receiving a dendritic cell vaccine ± cyclophosphamide 2. in remission not receiving treatment 3. undergoing standard therapy	31	Seasonal trivalent killed influenza vaccine	<ul style="list-style-type: none"> 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
<i>Lagler, 2012</i>	prospective trial	1. Hematologic malignancies + cytotoxic, targeted, or hormone therapy 2. Solid tumours + cytotoxic, targeted, or hormone therapy 3. Healthy controls	25 17 23	Unadjuvanted whole-virion pandemic influenza A (H1N1) vaccine	<ul style="list-style-type: none"> 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) Seroconversion: 70% healthy, 52% solid tumours, 13% hematologic malignancies (p<0.05) GMT ratios: 4.1healthy, 4.3 solid tumours 1.5 hematologic malignancies (p<0.05)
<i>Mariotti, 2012</i>	prospective trial	1. Hematologic malignancies 2. Healthy controls	47 77	Monovalent adjuvanted 2009 H1N1 vaccine	<ul style="list-style-type: none"> 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.

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
<i>Hottinger, 2012</i>	prospective controlled open-label	1. Lymphoma and solid tumours (34.5% active CT) 2. Healthy controls	197 138	AS03A-adjuvanted split influenza A/H1N1/09 vaccine x 2 doses for cancer patients and x 1 dose for healthy controls	<ul style="list-style-type: none"> 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
<i>Xu, 2012</i>	prospective case series	1. Healthy controls 2. Solid tumour + myelosuppressive CT 3. Solid tumour + non-myelosuppressive CT 4. Hematologic	44 38 42 22	Monovalent unadjuvanted influenza A (H1N1) 2009 vaccine	<ul style="list-style-type: none"> 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
<i>Rousseau, 2012</i>	prospective cohort	Patients receiving cytotoxic and/or targeted therapies	65	AS03A-adjuvanted H1N1v vaccine x 1 or 2 doses	<ul style="list-style-type: none"> 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
<i>Puthillath, 2011</i>	prospective case series	Colorectal cancer: 1. CT 2. no CT	58 27	2006-2007 trivalent influenza vaccine x 1 dose	<ul style="list-style-type: none"> 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
<i>Miraglia, 2011</i>	multicentre prospective cohort	Cancer (tumour type not specified) compared to elderly and immunocompromised patients	319	Monovalent unadjuvanted influenza A (H1N1) 2009 vaccine	<ul style="list-style-type: none"> 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
<i>Yri, 2011</i>	prospective controlled trial	1. Lymphoma treated with rituximab ± CT 2. Healthy controls	67 51	Monovalent adjuvanted influenza A (H1N1) vaccine x 1 dose	<ul style="list-style-type: none"> Seroprotection: 0% lymphoma vs. 82% controls
<i>Monkman, 2011</i>	prospective cohort	Hematologic malignancies: 1. Vaccinated 2. Unvaccinated	62 41	AS03A-adjuvanted H1N1 vaccine x 1 dose	<ul style="list-style-type: none"> 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
<i>de Lavallade, 2011</i>	prospective cohort	1. Hematological (B-cell malignancies, CML, and ASCT recipients) 2. Healthy controls	97 25	AS03A-adjuvanted H1N1v vaccine x 1 dose + trivalent seasonal influenza vaccine x 1 dose	<ul style="list-style-type: none"> 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

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					respectively rated as severe
<i>Louergue, 2011</i>	prospective cohort	1. Breast – docetaxel 2. Prostate – docetaxel	13 12	Trivalent inactivated influenza vaccine x 1 dose	<ul style="list-style-type: none"> 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
<i>Mackay, 2011</i>	prospective cohort	1. Hematologic malignancies 2. Solid tumours	26 20	pH1N1 vaccine x 1 dose	<ul style="list-style-type: none"> Seroconversion: 50% vs. 27% (solid vs. hematologic; p=.11) Seroconversion: 45% vs. 19% (solid vs. hematologic; p=.06); addition of rituximab resulted in failure to convert (p=.05) Highest titres: mid-cycle immunization in pts w/solid tumours and start of cycle for hematological pts Immunization was well tolerated
<i>Sasson, 2011</i>	prospective cohort	Palliative care patients	13	Trivalent influenza vaccine Vaxigrip x 1 dose	<ul style="list-style-type: none"> Seroconversion: 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
<i>Stadtmauer, 2011</i>	randomized controlled trial	Multiple myeloma	21	1. Influenza-primed autologous T-cell product (HSCT) 2. Nonspecifically primed autologous T-cell product (HSCT)	<ul style="list-style-type: none"> Seroconversion: influenza-primed autologous T-cell product group more likely to respond to influenza vaccine (P=.001) No differences in the global quantitative recovery of T-cell and B-cell subsets or in global T-cell and B-cell function
<i>Chadha, 2011</i>	prospective cohort	Prostate cancer	35	Trivalent influenza vaccine (Fluzone) x 1 dose	<ul style="list-style-type: none"> Serological response (against any strain): 80% Effect of vitamin D: baseline 25-D3 level associated with response (p=.045) and all upper quartile 25-D3 patients responded (p=.034)
<i>Mulder, 2011</i>	case control	1. mRCC - sunitinib 2. mRCC - sorafenib 3. mRCC - no CT 4. Healthy controls	16 6 7 11	Seasonal influenza inactivated vaccine x 1 dose	<ul style="list-style-type: none"> Seroconversion: 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
<i>Bedognetti, 2011</i>	case control	1. Non-Hodgkin lymphoma – post rituximab 2. controls	31 34	Trivalent seasonal influenza vaccine x 1 dose	<ul style="list-style-type: none"> 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
<i>Meerveld-Eggink, 2011</i>	randomized controlled trial	1. Breast cancer – FEC chemotherapy 2. Healthy controls	38 21	Influenza vaccine administered either early (day 4 of chemo; n=20) or late (day 16 of chemo; n=18)	<ul style="list-style-type: none"> 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) Subgroup analysis performed in 2017 reported that there was a broad serum antibody response to the influenza virus vaccine in patients treated with chemotherapy for breast cancer
<i>Avetisyan, 2008</i>	comparative study	1. Healthy volunteers 2. Allo-SCT patients	18 14	Inactivated trivalent 2005/2006 influenza vaccine x 1 dose	<ul style="list-style-type: none"> 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 there is no GVHD or ongoing immunosuppression

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Ljungman, 2005	open, randomized	Hematologic malignancies (N=59 receiving active CT against malignancy)	36 34	1. one-dose vaccine 2. two-doses vaccine <i>minimum of 1 week between immunization and the next scheduled CT course</i>	<ul style="list-style-type: none"> Response rates: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> H1/N: 1 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
Machado, 2005	prospective cohort	Hematologic malignancies: 1. < 6 months post-BMT, not eligible for immunization 2. ≥ 6 months post-BMT	134 43	Trivalent seasonal influenza vaccine x 1 dose	<ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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
Earle, 2003	retrospective cohort	1. Stage IV colorectal cancer patients who received seasonal influenza vaccine 2. Stage IV colorectal cancer patients who were not immunized	626 951	Seasonal influenza vaccine	<ul style="list-style-type: none"> 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
Nordoy, 2002	controlled clinical trial	1. Solid tumours or malignant lymphoma; mild-moderate immunosuppressive CT 2. Healthy controls	35 38	Trivalent inactivated seasonal influenza vaccine x 1 dose + 23-valent polysaccharide pneumococcal vaccine	<ul style="list-style-type: none"> 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 2019^{49,51-53,85-106}

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
<i>Doganis, 2018</i>	prospective cohort	Patients with leukemia (48), lymphoma (5), and solid tumours (22); median age = 8.8 years	75	Inactivated trivalent seasonal vaccine	<ul style="list-style-type: none"> Protective rates after vaccination = 79% H1N1, 75% H3N2, 59% influenza B Seroconversion rates = 54% H1N1, 44% H3N2, 43% influenza B Variables that correlated with a higher post-vaccination seroprotective titer: ALC >1000/mm³ for H1N1, age >9 years, or solid tumors for H3N2 and B strains Variables that correlated with a significantly higher seroconversion rate: solid tumours and prevaccination HAI_≥40 Variables that correlated significantly with higher post-vaccination GMTs: GMTs before vaccination, high ALC at the vaccination time, and solid tumours for H1N1; GMTs before vaccination and solid tumours were also significant factors for higher post-vaccination GMTs for H3N2 and influenza B
<i>Sykes, 2017</i>	retrospective cohort	patients with acute leukemia treated on the TOTALXVI protocol; median age = 6 years	498	2011-12, 2012-13, and 2013-14 inactivated trivalent seasonal vaccines	<ul style="list-style-type: none"> 354/498 were vaccinated (71.1%) and 98 were given a booster dose (19.7%) No difference in overall rates of influenza between vaccinated and unvaccinated patients overall or in any season No difference in rates of influenza between patients who received 1 dose vs. 2 doses of vaccine No difference in time to first influenza infection in vaccinated vs. unvaccinated patients
<i>de la Fuente Garcia, 2017</i>	retrospective cohort	Children treated for ALL between 2000-2012; median age = 4.1 years	60	Booster dose of inactivated conjugated Haemophilus influenza B given at least 3 months after the end of CT	<ul style="list-style-type: none"> Seroprotection rate at the end of CT = 20% Seroprotection rate after booster dose administered = 92% During the previous influenza season, 18 mothers (40.0%), 19 fathers (42.2%), and 16 siblings (35.6%) had received the seasonal influenza vaccine
<i>Choi, 2016</i>	prospective cohort	Patients receiving CT for solid tumours (76) and hematologic malignancies (183) were studied over 2 years	259	2012-13 trivalent inactivated influenza (N=112) vaccine and 2013-14 quadrivalent inactivated influenza vaccine (N=147)	<ul style="list-style-type: none"> Seroresponse rate = 62% (98/157) Median ALC at vaccination was higher in seroresponders than nonresponders (854 cells/mm³ vs. 602 cells/mm³, p< 0.036) Patients with an ALC <1,000 cells/mm³ at time of vaccination were twice as likely to be serononresponders (OR = 2.4, 95% CI 1.1-5.0; p<0.02) 31/259 (12%) of patients developed influenza: 31/31 had fever at presentation, 8/31 required hospitalization, and 25/31 had CT delays
<i>Hakim, 2016</i>	randomized open-label trial	Children and young adults (3-21 years) with leukemia (27), solid tumours (17), or HIV (41)	85	Two doses of high-dose (HD) TIV vs. two doses of standard-dose (SD) TIV; doses administered 21 days apart	<ul style="list-style-type: none"> Leukemia patients receiving HD TIV had significantly greater increase in HAI titers to B antigen versus leukemia patients receiving SD TIV Solid tumour patients receiving HD TIV had significantly greater increase in HAI titers to H1 antigen versus solid tumour patients receiving SD TIV No differences in seroconversion or seroprotection rates between HD TIV and SD TIV in all groups No significant difference in reactogenicity events in recipients of HD TIV (54% after dose 1, 38% after dose 2) versus SD TIV (40% after dose 1, 20% after dose 2)
<i>Kotecha, 2016</i>	prospective cohort	Children with hematologic and solid tumours aged 6 months-18 years receiving or within 4 weeks of completion of CT	100	2010-11 trivalent inactivated vaccine: A/Perth/16/2009, A/California/7/2009, and B/Brisbane/60/2008	<ul style="list-style-type: none"> Seroprotection rates = 55% H3N2, 61% H1N1, 41% B strain Seroconversion rates = 43% H3N2, 43% H1N1, 33% B strain Significant response observed for H3N2 (Geometric Mean Fold Increase = 4.56, 95% CI 3.19–6.52, p< 0.01) and H1N1 (GMFI = 4.44, 95% CI 3.19–6.19, p< 0.01) Children with solid tumors significantly more likely to serorespond to each vaccine strain compared to children with hematologic malignancies

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					<ul style="list-style-type: none"> ○ H3N2: OR=7.39, 95% CI 2.42–22.53, p< 0.01 ○ H1N1: OR=2.90, 95% CI 1.02–8.23, p=0.045 ○ B strain: OR=3.75, 95% CI 1.25–11.24, p= 0.02 <ul style="list-style-type: none"> • Children with solid tumours significantly more likely to undergo complete seroconversion to all three strains (OR=6.03, 95% CI 1.56–23.29, p< 0.01) compared to children with hematological malignancies
<i>Ottóffy G, 2014</i>	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	<ul style="list-style-type: none"> • 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% • Seroresponse 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
<i>McManus M, 2014</i>	randomized, double-blind, phase I safety trial	ALL (80% on maintenance therapy)	34 16	1. High-dose TIV (60 µg) 2. Standard-dose TIV (15 µg)	<ul style="list-style-type: none"> • 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
<i>Dotan A, 2014</i>	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	<ul style="list-style-type: none"> • 57 total episodes; 13/57 (22.8%) were influenza A/H1N1 positive • 2/13 (15%) H1N1-positive episodes were previously immunized versus 14/44 (32%) 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)
<i>Goossen GM, 2013</i>	meta-analysis (Cochrane Review)	Pediatric malignancies	770	<ul style="list-style-type: none"> • 9 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 4 studies, responses to influenza vaccine were assessed in 236 children on CT compared with responses in 142 healthy children • Immune responses in children receiving CT were consistently weaker (four-fold rise of 38% to 65%) than in those children who had completed CT (50% to 86%) and in healthy children (53% to 89%) • Adverse events included mild local reactions and low grade fever; no persistent or life-threatening effects reported • <i>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</i> 	
<i>Leahy TR, 2013</i>	prospective cohort	ALL	45	<p>Patients received 2 doses of the inactivated split-virion AS03-adjuvanted vaccine.</p> <p>Serological response measured before each vaccine dose (days 0 & 28) and 3 months after the second dose.</p>	<ul style="list-style-type: none"> • 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 (0.5 ml) in univariate analyses, and a trend towards significance (p=0.07) in multivariate analyses. • Factors including age, gender, lymphocyte count, treatment phase and

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					<ul style="list-style-type: none"> 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 ($p=0.001$).
<i>Mavinkurve-Groothuis AM, 2013</i>	prospective cohort	Children with hematologic malignancies (20) or solid tumours (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)	<ul style="list-style-type: none"> 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/mm³.
<i>Karras NA, 2012</i>	randomized trial	Vaccine-naïve patients >60 days post- allogeneic HSCT	33 32	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	<ul style="list-style-type: none"> 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
<i>Kersun LS, 2012</i>	prospective cohort	ALL	177	Inactivated trivalent influenza vaccine x dose in repeat vaccinees and x 2 doses in vaccine-naïve patients	<ul style="list-style-type: none"> 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.
<i>Wong-Chew RM, 2012</i>	prospective cohort	AML, solid tumours, or lymphoma	56	Inactivated trivalent seasonal vaccine	<ul style="list-style-type: none"> 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 ($p=0.11$)
<i>Shahin K, 2012</i>	prospective cohort	Patients receiving CT for solid tumours	20	AS03-adjuvanted or nonadjuvanted monovalent vaccine x 2 doses at day 0 and 21; most often administered on day 1 of CT	<ul style="list-style-type: none"> Seroprotection: 90% Seroconversion: 65% 8.8-fold increase in GMT from pre- to post-vaccine
<i>Hakim H, 2012</i>	prospective observation	Solid and hematological, receiving CT	37	2009 H1N1 influenza monovalent vaccine x 1 or 2 doses (age dependent)	<ul style="list-style-type: none"> 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

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					tumour patients after the last dose <ul style="list-style-type: none"> No significant differences in seroconversion or seroprotection rates between patients who received one dose versus two doses
<i>Carr S, 2011</i>	randomized trial	Solid and hematological, receiving or received CT or RT within last 3 months	28 27	1. LAIV x 1 or 2 doses 2. TIV x 1 or 2 doses	<ul style="list-style-type: none"> 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)
<i>Yen TY, 2011</i>	prospective cohort	Solid and hematological, receiving CT	25	2009 H1N1 influenza monovalent vaccine x 1 or 2 doses (age dependent)	<ul style="list-style-type: none"> Seroprotection: 52% pre-vaccine; 72% post-vaccine (p=.24) Sero-response: 32% post-vaccine; greater in pts without pre-vaccine seroprotective titer than those with (50% vs. 15%, p=.07) and greater in those with lymphocyte counts >1,500/μl (p=.008) GMT: increased post-immunization in patients <10 yrs receiving two immunizations (21.4 to 60.6; p=.025)
<i>Cheng FW, 2011</i>	prospective cohort	Patients receiving CT or completed ≤12 mos	12	Haemagglutinin of influenza A/California/07/2009 (H1N1)-like virus x 2	<ul style="list-style-type: none"> Seroprotection: 58% after 1st dose (7/12 patients); 100% after 2nd dose Seroconversion: 41% after 1st dose; 75% after 2nd dose
<i>Bate J, 2010</i>	prospective cohort	Solid and hematological	54	2009 H1N1 influenza monovalent AS03(B)-adjuvanted vaccine x 2 doses, days 0 and 21	<ul style="list-style-type: none"> Seroconversion: 44.4% of patients <ul style="list-style-type: none"> 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
<i>Bektas O, 2007</i>	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	<ul style="list-style-type: none"> 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%
<i>Matsuzaki A, 2005</i>	controlled clinical trial	Pediatric malignancies	44	2 doses of influenza vaccine 2-4 weeks apart	<ul style="list-style-type: none"> 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. 90% (p=.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 administration of CT (p=.003); H3N2= administration Of CT (p=.008); influenza B= low WBC count (p=.03) and low IgG (p=.030)
<i>Chisholm J, 2005</i>	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	<ul style="list-style-type: none"> Following immunization: <ul style="list-style-type: none"> 25/64 patients (38%) were protected against all three viruses, representing a full response Protective responses to one or two viral strains were seen in 12/64 (19%) patients 27 (41%) patients showed no protective response to

Author, Year	Study Type	Disease Site and Comparisons	N	Immunization Details	Results and Recommendations
					<p>immunization, including 5 patients who remained fully susceptible to all 3 viruses following immunization</p> <ul style="list-style-type: none"> Estimated increases in percentage protected against each viral subtype following immunization were: <ul style="list-style-type: none"> H1N1: 29% (95% CI 17–42%, p<.0001) H3N2: 22% (95% CI 10–33%, p=.0002) Influenza B: 43% (95% CI 29–57%, p<.0001) N= 27 patients transfused with blood and/or platelets during the study: <ul style="list-style-type: none"> N=10 (38%) showed no response N=6 (23%) showed a protective response to 1-2 viral subunits 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	controlled clinical trial	<ol style="list-style-type: none"> ALL in 1st remission, maintenance CT, completed last delayed intensification at least 4 weeks earlier Healthy controls 	20 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	<ul style="list-style-type: none"> 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
Hseih YC, 2002	controlled clinical trial	<ol style="list-style-type: none"> Pts with ALL in maintenance stage; received 6-mercaptopurine + methotrexate, and reinduction with vincristine + prednisolone Pts with asthma Healthy controls previously unvaccinated 	25 30 10	TIV x 2 doses for children younger than 8 yrs, 1 dose for children older than 8 yrs	<ul style="list-style-type: none"> group 1 developed significant antibody titers to H3N2 antigen 4 weeks after the 2nd immunization Seroconversion rates after 2 doses of vaccine were 57.1 to 84.6% and seroresponse rates were between 24 and 60% in group 1 Compared to group 2, group 1 had less seroconversion and lower seroresponse rates to H1N1 Seroconversion and seroresponse 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 seroresponse 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.

Table 3. Literature Search Strategy

#	Searches	Results
1	exp Neoplasms/	3202004
2	exp Carcinoma/	619508
3	"cancer".ab.	1288550
4	"cancer".ti.	891915
5	"tumor".ab.	979611
6	"tumor".ti.	252083
7	"tumour".ab.	182414
8	"tumour".ti.	45207
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	3842038
10	exp Influenza A virus/	41950
11	"influenza A virus".ab.	8188
12	"influenza A virus".ti.	4606
13	exp Influenza B virus/	3968
14	"influenza B virus".ab.	1110
15	"influenza B virus".ti.	491
16	10 or 11 or 12 or 13 or 14 or 15	45279
17	exp Immunization/	168940
18	"immunization".ab.	74590
19	"immunization".ti.	26522
20	17 or 18 or 19	216149
21	9 and 16 and 20	136
22	limit 21 to (english language and yr=2018-Current)	5
23	16 or 20	256001
24	9 and 23	28253
25	limit 24 to (english language and yr=2018-Current)	1323
26	exp Influenza, Human/	46887
27	9 and 26	931
28	influenza.ab.	69227
29	influenza.ti.	66005
30	26 or 28 or 29	97488
31	9 and 20 and 30	517
32	limit 31 to (english language and yr=2018-Current)	26
33	exp Vaccination/	80935
34	vaccination.ab.	97752
35	vaccination.ti.	47608
36	20 or 33 or 34 or 35	273214
37	9 and 30 and 36	863
38	limit 37 to (english language and yr=2018-Current)	71