Atlantic Provinces Pediatric Hematology Oncology Network

Réseau d'Oncologie et Hématologie Pédiatrique des Provinces Atlantiques 5850/5980

University Avenue, PO Box 9700, Halifax, NS, B3K 6R8

Guidelines on Vaccination in Pediatric Hematology and Oncology Patients

APPHON/ROHPPA supportive care guidelines are developed by Atlantic Provinces health professional specialists using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

Glossary:

Titer	Measure of antibodies in the blood to test the level of immunity
Protective titer	Level of antibodies in the blood correlating with protection against disease
Serology	Diagnostic examination of blood serum to measure antibodies to a particular antigen
Immunosuppressive therapy	Agents that lower the immune system
Chemotherapy	Drugs that treat cancer
Immunocompromised	Having an impaired immune system
Vaccine	Biological preparation that provides active acquired immunity to a particular disease
Immunization	The process by which an individual's immune system becomes fortified against an antigen

Abbreviations:

PHAC	Public Health Agency of Canada
NACI	National Advisory Committee on Immunization
dTap/DTaP	Diphtheria, Tetanus, Acellular Pertussis
Hib	*Haemophilus influenzae*
VZV	Varicella Zoster Virus
MMR	Measles, Mumps, Rubella
HepA	Hepatitis A
HepB	Hepatitis B
Flu	Influenza
Men	Meningococcal
CIG	Canadian Immunization Guide
HAV	Hepatitis A virus
ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
ALC	Absolute Lymphocyte Count
HI	Haemagglutination inhibition
PCV	Pneumococcal conjugate Vaccine
PP23	Pneumococcal Polysaccharide Vaccine
BCG	Bacillus Calmette-Guerin

Overview of Material

Guideline release date: 2019.

Print copies available through:

APPHON/ROHPPA
c/o IWK Health
Room K7132
5850/5980 University Avenue, PO Box 9700 Halifax, NS B3K 6R8

Electronic sources available through: www.apphon-rohppa.com

1. Summary

The following vaccine recommendations listed in Table 1 are based on the Canadian Immunization Guide (CIG) which incorporates recommendations from Health Canada's National Advisory Committee on Immunization (NACI). The CIG has guidance on immunization with specific vaccines, and a chapter on immunization of the immunocompromised host. The broad recommendations provided for Health Care Providers caring for children with cancer in this guideline are based on expert opinion of the Guideline Working Group.

Readers are encouraged to check the most recent recommendations. The expert panel of this guideline understand that this area is relatively novel and that evidence is evolving in regards to the risk vs benefit of providing vaccines to children with cancer. The guideline group also realizes that the nature of this research is difficult as vaccine preventable diseases vary based on location, and government funding. Several groups do recommend vaccine boosters based on the growing body of evidence that children treated for cancer do have some loss of immunity to vaccines. When more evidence becomes available the recommendations in this guideline may change.

APPHON/ROHPPA recommend, based on the existence of significant research gaps, that APPHON/ROHPPA and other institutions continue research to supply evidence to inform future decision-making on vaccination of children with cancer. Some identified research gaps are presented in Appendix A.

Table 1: Table of recommendations for immunization during and after the completion of cancer chemotherapy. This does NOT include the bone marrow transplant population (please see APPHON Transplantation (Hematopoietic Stem Cell Transplantation (HSCT)) Immunization Recommendations)

Vaccine	Recommendation
Hepatitis B	1. Insufficient evidence to recommend vaccinating immunosuppressed children with hepatitis B vaccine in North America during chemotherapy. 2. Hepatitis B serology is recommended for previously immunized children 3-6 months after completion of chemotherapy and at least 4 months after IVIG infusion; if non-immune then booster vaccination is recommended. 3. Immunization schedule: HBV vaccination may be initiated six months or more after chemotherapy OR when scheduled according to the provincial schedule (e.g. school-based vaccination in adolescents). a) If previously vaccinated and post treatment titer is non-immune, then give one HBV vaccine dose and check titer in one month. If titer non-immune, then give a complete HBV vaccine series. Check titer after a full series only in those children who are immunocompromised or are at ongoing risk of hepatitis B. b) If not previously vaccinated give full series. c) Give the appropriate number of doses based on age.
Hepatitis A	1. Insufficient evidence to recommend vaccinating immunosuppressed children with hepatitis A vaccine in North America during chemotherapy. 2. Pre or post exposure vaccination of immunosuppressed children with hepatitis A may be warranted under specific circumstances as it is for non- immunosuppressed children. 3. Insufficient evidence to recommend routine vaccination after the completion of therapy.

Vaccine	Recommendation
Diphtheria, Tetanus, Pertussis, Polio, *Haemophilus influenzae*	1. Insufficient evidence to recommend routine vaccination with diphtheria, tetanus, pertussis, polio and Hib during chemotherapy. 2. Children who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catchup schedule. 3. Children who received all doses of Hib-containing vaccines prior to chemotherapy may receive one additional dose six months after completion of chemotherapy (DTaP-IPV-Hib, according to age). 4. Children with asplenia, complement deficiency and certain other high-risk conditions (per NACI criteria) or who have received 22 Gy or higher of radiation to the spleen should receive the Hib vaccine, regardless of prior vaccine history. These children are also eligible for booster doses (see APPHON asplenia guideline).
Influenza vaccine	1. All children greater than 6 months of age should receive seasonal inactivated influenza vaccination during chemotherapy if their ALC is greater than 1 x 10^9/L based on influenza vaccine availability and disease epidemiology. 2. All children greater than 6 months of age who have completed chemotherapy should receive the annual seasonal influenza vaccine. Do not use live attenuated influenza vaccine for immunocompromised patients. 3. If possible, the influenza vaccine should be delayed for 6 months after anti-B cell antibody treatment (i.e. rituximab and blinatumomab).
Meningococcal vaccines	1. Insufficient evidence for vaccination of children on chemotherapy with any meningococcal vaccine. 2. Children who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catch- up schedule. Vaccination may be initiated six months or more after chemotherapy OR when scheduled according to the provincial schedule (e.g. school-based vaccination in adolescents). 3. Children with asplenia or splenic disorders including sickle cell disease or hemoglobinopathies, complement deficiency and certain other high-risk conditions (as per NACI criteria) or who have received 22 Gy or higher of radiation to the spleen should receive the ACYW and MenB vaccines, regardless of prior vaccine history. These children are also eligible for booster doses (see APPHON asplenia guideline).

Vaccine	Recommendation
Pneumococcal vaccine	1. Insufficient evidence for vaccination of children during chemotherapy with any pneumococcal vaccine. 2. Children who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catch-up schedule. Children considered immunocompromised should receive all doses of vaccines (not reduced dose schedules). 3. One dose of 20-valent conjugate pneumococcal vaccine (Pneu-C-20 or Pneu-C-21) is recommended for all children 6 months after the end of therapy. 4. Children with asplenia, complement deficiency and certain other high-risk conditions (as per NACI criteria) or who have received 22 Gy or higher of radiation to the spleen should receive pneumococcal vaccines, regardless of prior vaccine history. These children are also eligible for booster doses (see APPHON asplenia guideline).
Varicella vaccine (Note: live attenuated)	1. Varicella vaccine is not recommended during chemotherapy. Vaccination and evaluation of titers is affected by recent receipt of IVIG (Titers should be delayed to 4 months in recipients of IVIG). Once deemed immunocompetent, approximately 6 months after completion of therapy and when ALC is at least 1 x 10^9/L: • Children who are fully vaccinated prior to diagnosis should have titers measured and if non-immune receive full vaccination schedule and post vaccine titers at least one month after the last dose to ensure immunity. • Children who are partially vaccinated prior to diagnosis should complete the series and have titers at least one month after the last dose to check immunity. If non-immune give one more dose if eligible (e.g. Immunocompetent). • Children who are not vaccinated prior to diagnosis should receive all age-appropriate doses and post vaccine titers at least one month after the last dose to ensure immunity. The combined MMR-V vaccine can be used in children less than 13 years of age. Children 13 years of age and older are given varicella and MMR vaccines as separate injections at different injection sites. Post-exposure varicella vaccines may be considered in certain situations.

Vaccine	Recommendation
Measles, mumps and rubella vaccine(s) (Note: live attenuated)	1. Measles, mumps and rubella vaccine is not recommended during chemotherapy. • Vaccination and evaluation of titers is affected by recent receipt of IVIG (titers should be delayed to 4 months in recipients of IVIG). Once deemed immunocompetent, and approximately 6 months after completion of therapy: • Children who are fully vaccinated prior to diagnosis should have titers measured and if non-immune receive full vaccination schedule and post vaccine titers at least one month after last dose to ensure immunity. • Children who are partially vaccinated prior to diagnosis should complete the series and have titers at least one month after the last dose to check immunity. • Children who are not vaccinated prior to diagnosis should receive all age appropriate doses and post vaccine titers at least one month after the last dose to check immunity. If non-immune give one more dose, if eligible. (e.g. Immunocompetent). The combined MMR-V vaccine can be used in children less than 13 years of age. Children 13 years of age and older are given varicella and MMR vaccines as separate injections at different injection sites. Post-exposure measles vaccines may be considered in certain situations.
Human Papilloma Virus (HPV) vaccine (Note: Both male and female subjects.)	1. Insufficient evidence is available to recommend HPV vaccine during chemotherapy. 2. The full schedule of 3 doses of vaccine should be given rather than a reduced 2 or one dose schedule to all children who receive cancer treatment. 3. Children/adolescents who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catch-up schedule starting at least 6 months after chemotherapy. 4. Vaccination may be initiated six months or more after chemotherapy OR when scheduled in school. 5. A single dose of HPV vaccine is recommended for children/adolescents who are previously vaccinated with the reduced 2 doses schedule of HPV vaccine, 6 months after the end of chemotherapy.
Rotavirus vaccine (Note: live attenuated)	1. Rotavirus vaccine is not recommended during chemotherapy. 2. Rotavirus vaccine is not recommended after the first year of life.

NOTES:

1. Refer to provincial immunization schedule for timing and number of routine vaccines.
2. Measurement of B cell response is recommended in patients who receive B cell depleting therapies (e.g., Blinatumomab and Rituximab) 6-9 months after B cell depletion. Immunization should not start until severe B cell lymphopenia resolves.
3. Patients who receive greater than 22 Gy of radiation to the spleen should receive vaccinations according to the APPHON asplenia guideline.

2. Introduction

2.1 Background

Cancer is the second major cause of death in children in developed countries. Survival rates have improved due to advances in chemotherapy, surgery, radiotherapy and supportive therapies through a multidisciplinary approach.

Surviving patients treated with intensive chemotherapy are at increased risk of infection due to prolonged myelosuppression. The immune system recovers after cancer treatment, but this may take up to 12 months. Vaccine efficacy in immune suppressed persons may be lower than in healthy people because of complete or partial loss of protective serum antibody titers, a depleted immune system and the coexistence of other defects of the immune system.

Children who complete cancer therapy and whose immune systems are recovered are not thought to be at any higher risk of serious infectious complications than the healthy population, except for those who do not have a functioning spleen.

Geographic location is also relevant in the consideration of which vaccines are beneficial to children with cancer and at what time point as due to herd vaccinations and improvements in safety of blood products the risk in certain areas for certain infections is lower. For example, the risk of contracting Hepatitis B from a blood transfusion in Canada is almost zero.

It is; therefore, felt that this guideline is important to help guide management of vaccination in children treated for cancer. This guideline is based on available evidence and on expert opinion where evidence is lacking.

Vaccination during chemotherapy:

The inactive vaccines based on toxoid, protein subunits, bacterial antigens, or immunogenic proteins obtained with recombinant technology are not contraindicated in principle during chemotherapy [Allen, 2007[1]]. This category includes vaccines for tetanus, diphtheria, pertussis, poliomyelitis, hepatitis A and B, influenza, *Haemophilus influenzae*, pneumococcus, meningococcus and human papilloma virus (HPV) [Klosky, 2009[2]]. The major drawback of administering these vaccinations during the chemotherapy program is the potentially suboptimal antibody response, resulting in reduced efficacy compared to a healthy child. The Canadian National Advisory committee on Immunization [NACI3] currently recommends that immunosuppressed children should receive any indicated inactivated vaccines at least 14 days prior to the initiation of immunosuppressive therapy and if this is not possible to delay until at

least 3 months after the cessation of treatment (Canadian Immunization Guide online 2019).

Currently the evidence supports that immunosuppressed children should not receive live vaccines (which include varicella, measles, mumps, rubella, typhoid, yellow fever and rotavirus) unless the risk outweighs the benefit. The NACI[3] recommends that all indicated live vaccines be given at least 4 weeks prior to the start of immunosuppressive therapy and if this is not possible to delay until at least 6 months after the cessation of treatment. (Canadian Immunization Guide online 2019).

Vaccination after chemotherapy:

Most authors found that chemotherapy is associated with the disappearance of vaccine-induced immunity in patients who had completed the vaccination schedule before starting chemotherapy[4,5,6,7]. The incidence of lack of protective antibody titers, measured 6–12 months after chemotherapy, varied according to the type of vaccine: it was higher for hepatitis B vaccine (HBV) (about 50% of patients, 72% in sarcoma patients[8,9]) but it was lower for measles, mumps, rubella (between 20% and 40%), and polio-diphtheria-tetanus (between 10% and 30%) [10,11,12,13,14,15,16,17]. Although there is no clear correlation between the wide variation in the preservation of vaccine immunity and the type of cancer, i.e., lymphoid versus myeloid versus solid tumor, the intensity of the chemotherapy regimen has been advocated by Ek et al[18] to explain the insufficient immune response to tetanus, diphtheria, and *Haemophilus influenzae* b vaccination after chemotherapy for high-risk acute lymphoblastic leukemia (ALL), because of a delayed immune recovery and a low number of memory B cells[14,19,18,20,21].

Therapy regimens that include agents such as alkylating agents, purine nucleoside analogs, or corticosteroids are immunosuppressive; they particularly have an effect on lymphocyte function which may influence immunity to vaccine antigens and responses to vaccines[5]. A recent study of immune reconstitution showed that the recovery of newly developed transitional B cells and naive B and T cells occurs rapidly, within months, whereas the recovery of memory B and T cells is slower and can be incomplete for up to 5 years. In contrast, plasmablast B cells were not affected by chemotherapy and were higher than normal in the first months of follow-up. Moreover, immunoglobulin levels normalized within weeks from the end of chemotherapy and, importantly, functional T responses to antigens such as Cytomegalovirus, Herpes simplex 1, VZV, Candida, Tetanus, and Diphtheria were normal either within or after one year from the end of chemotherapy. These findings would explain the reported good responses to booster administration despite a long-lasting deficit of B and T memory cells[16]. A study by Kosmidis et al.[22] suggests that humoral immunity (immunoglobulin levels) was depressed after the intensive phase of ALL treatment and improved after maintenance therapy whereas cellular immunity was normal after the intensive phase and remained abnormal for at least a year post-therapy.

These authors suggest that a higher CD4/CD8 ratio results in protection against infections[22]. Most authors agree that the interval time of 6–12 months is adequate to achieve a sufficient immune recovery that, in turn, has a key role in determining the response to vaccination[6,7,8,9,15,16,17,18,23,24,25], but some studies have shown good results after reimmunization with inactivated vaccines already at 3 months[26].

Considering the frequency of the loss of protective serum antibody levels after chemotherapy and the high rate of seroconversion reported with a booster or revaccination, it is not considered mandatory to measure antibody titers to decide the revaccination as well as routine checking of antibody titer response after vaccination. In patients who stopped the course of the vaccination schedule during chemotherapy, the indication is to resume the program starting from the suspended dose.

In conclusion, chemotherapy results in a reduction of serum antibody levels for vaccine-preventable disease while immunological memory seems to be preserved. Once immunological recovery is complete, the response to vaccination is generally good, allowing patients to be protected and to contribute to herd immunity.

Vaccines discussed in this guideline:

The vaccines discussed in this guideline address vaccine preventable diseases relevant in North America. As such, the following vaccines will be discussed: Hepatitis A, Hepatitis B, Diphtheria, Tetanus, Pertussis, Polio, *Haemophilus influenzae* type B, Influenza, Meningococcal ACYW, C and B, Pneumococcus, Varicella, Measles, Mumps, Rubella, Human Papilloma Virus, Rotavirus.

2.2 Scope and Purpose

The scope of this guideline is routine vaccination of children with cancer. The purpose of this guideline includes recommendations for health practitioners caring for children with cancer in the Atlantic Provinces to guide in vaccinating during and after cancer therapy is complete.

2.3 Target Population

This guideline is intended to provide recommendations for vaccination of children during and after treatment for cancer. This guideline does not provide recommendation for children who have undergone a hematopoietic stem cell transplant.

Target users:

The target audience of this guideline is the healthcare providers involved in the care of children with cancer in the Atlantic Provinces. This document is a general reference and is not intended to replace good clinical judgment.

2.4 Health Questions

1. Is there sufficient evidence to support vaccination during chemotherapy? If so, who should be vaccinated and with which vaccines?
2. Is there sufficient evidence to support vaccination after completion of chemotherapy? If so, which vaccinations should be given and when should they be scheduled?
3. Are vaccinations indicated for parents and other family members? If so, who should be vaccinated and when?

3. Methods

3.1 Literature Search Strategy

The NACI literature search was adopted for each vaccine discussed.

3.2 Guideline and Evidence Selection Criteria

The NACI recommendations were adopted.

3.3 Decision Process

The recommendations in this guideline are in alignment with the Canadian National Advisory Committee on Immunization that informs the Canadian Immunization Guide recommendations.

3.4 Results

The NACI guidelines were considered appropriate for adoption.

4. Close Contacts of Patients Undergoing Cancer Chemotherapy

- Up-to-date routine immunizations are recommended for household members and other close contacts of immunocompromised individuals, including health care workers. Non- immune close contacts of immunocompromised people should be immunized against all recommended vaccines according to the local schedule as appropriate for age.
- Vaccine viruses in MMR vaccine are not transmitted to contacts. Susceptible close contacts of immunocompromised people should receive herpes vaccine based on the contact's health or varicella-containing vaccine as appropriate for age and risk factors. If the vaccine recipient develops a varicella-like rash, the rash should be covered and the vaccines should avoid direct contact with the immunocompromised person for the duration of the rash. Secondary transmission from people with post-varicella vaccination varicella-like rashes is rare. For adult household contacts with no prior history of varicella infection or vaccination should be vaccinated.
- To minimize the risk of transmission of vaccine virus in infants who are close contacts with rotavirus, careful hand washing should be used after contact with the vaccinated infant, especially after handling feces (e.g., after changing a diaper), and before food preparation or direct contact with the immunocompromised person.
- Other live vaccines:
    - Annual influenza immunization with inactivated influenza vaccine is recommended for close contacts of immunocompromised persons. Because of the theoretical risk for transmission, recipients of live attenuated influenza vaccine should avoid close association with persons with severe immunocompromising conditions (e.g., bone marrow transplant recipients requiring isolation) for at least two weeks following vaccination.
    - Smallpox vaccine should not be administered to household contacts of an

immunocompromised person in a non-emergency situation. If vaccination is required in an outbreak situation, precautions should be taken for unvaccinated household and other close contacts.
    - Oral polio vaccine should not be administered to household contacts of an immunocompromised person.
    - Other live vaccines including typhoid, BCG and yellow fever are safe to be administered to household contacts of an immunocompromised person.
    - The health care provider should discuss immunization of close contacts of children on cancer chemotherapy with the oncology team and/or an infectious disease specialist

5. General Principles

- Accurate immunization records of each child must be obtained at diagnosis and kept up to date.
- At diagnosis, baseline immune status testing should include antibody titers of varicella, hepatitis B, hepatitis C, cytomegalovirus (CMV IgG), human immunodeficiency virus (HIV), and Epstein-Barr virus (EBV). Measurement of routine antibody titers (e.g., diphtheria, pertussis, tetanus) is not necessary.
- Monitor patients carefully for infection, making no assumptions about susceptibility or protection from vaccine-preventable illnesses. A history of childhood infection or previous vaccination may be irrelevant, as children immunized prior to or during therapy may lose or never have attained protective antibody titers.
- Vaccinate at the time when the maximum immune response can be anticipated. It is recommended that vaccination be withheld for at least until 3-6 months after the completion of intensive chemotherapy, and ideally, ANC and absolute lymphocyte counts are greater than 1 x 10^9cells/L and at least 4 months after IVIG infusion. Except the inactivated influenza vaccine which is recommended to be given during chemotherapy preferably when the child is not neutropenic.
- Continue routine immunization for non-immune household contacts of certain vaccines including some live vaccines (MMR, Varicella, influenza, rotavirus and shingles).
- For children who are immunosuppressed consider passive immunization for certain pathogens (including measles, hepatitis A, hepatitis B, and varicella) using specific hyperimmune pathogen specific serum globulin is a prophylactic option in some specific circumstances.
- Application of topical anesthetic creams (i.e., EMLA®, Ametop®) prior to immunizations is acceptable.
- Education of healthcare professionals on the importance of vaccination of children with cancer and education to patients and families of the benefits of vaccination should be conducted in all programs.
- For children who are immunocompromised and traveling, the recommendations to be vaccinated will vary with their individual risk of exposure and the severity of potential

infection. Consult a travel clinic for recommendations on vaccines required for travel as these vary based on the destination. Consult the Committee to Advise on Tropical Medicine and Travel (CATMAT) for immunocompromised children.

- Generally if vaccines cannot be given prior to initiation of immunosuppressive therapy, a period of at least 3 months should elapse after immunosuppressive drugs have been stopped before administration of inactivated vaccines and 6 months for live vaccines. The decision to give a vaccine during immunosuppression is based on risk of infection, immune response and risk of adverse effects of the vaccine (Canadian immunization guide online 2019).
- Corticosteroid therapy is not a contraindication to vaccine administration when steroid therapy is short-term (i.e., less than 14 days); or a low-to-moderate dose (less than 2 mg/kg/day for a child); or long-term, alternate-day treatment with short-acting preparations; or maintenance physiologic replacement therapy; or administered topically, inhaled, or locally injected (e.g., joint injection).
- Vaccine responses have been studied for various vaccines and are used as a surrogate for determination of immunity. Long term studies need to be conducted on the outcome of vaccinating children during and after chemotherapy in the reduction of vaccine preventable diseases.
- Subsequent routine booster doses will not be necessary if scheduled to be given within one year of the booster doses recommended in this guideline.
- Unless otherwise specified all vaccines are to be given in the doses recommended for healthy children.

6. Guidelines for the interval between administration of immune globulin (Ig) preparations or blood products and measles-mumps-rubella (MMR), measles-mumps-rubella-varicella (MMRV) or univalent varicella vaccine to maximize immunization effectiveness

1. Standard replacement doses of intravenous immune globulin (IVIG) – 8 months
2. Packed red blood cells – 5 months
3. Platelets – 7 months
4. Other – for all other immune globulin and blood products please refer to the Canadian Immunization Guide.

Note: Giving vaccines with shorter washout periods than the above may reduce the immune response to the measles component of the MMR vaccine and the impact on the varicella vaccine is unknown.

7. ***Supporting Evidence and Information for Recommendations***

Points that were considered in making the following recommendations for each vaccine include:

1. Serologic correlates of immunity?
2. Risk of infection and incidence and timing of risk.
3. Adverse effects of the vaccine.
4. Risk vs benefit for each vaccine especially where evidence is lacking.
5. Cost of vaccines to the families, where relevant.

7.1 Hepatitis B

1. Insufficient evidence to recommend vaccinating immunosuppressed children with hepatitis B vaccine in North America during chemotherapy.
2. Hepatitis B serology is recommended for previously immunized children 3-6 months after completion of chemotherapy and at least 4 months after IVIG infusion; if non-immune then booster vaccination is recommended.
3. Immunization schedule: HBV vaccination may be initiated six months or more after chemotherapy OR when scheduled according to the provincial schedule (e.g. school-based vaccination in adolescents).
    - 3.1 If previously vaccinated and post treatment titer is non-immune then give one HBV vaccine dose and check titer in one month. If titer non- immune then give a complete HBV vaccine series. Check titer after a full series only in those children who are immunocompromised or are at ongoing risk of hepatitis B.
    - 3.2 If not previously vaccinated give full series. Give the appropriate number of doses based on age.

Discussion:

Several authors have assessed the efficacy of vaccination for hepatitis B virus (HBV) early after the diagnosis of pediatric malignancy[27,28,29,30,31,32]. This measure is generally adopted in countries with high prevalence of HBV infection, in which vaccination is not compulsory due to limited health resources. These studies showed that vaccination of seronegative patients for HBV in the early phase of chemotherapy reduces the risk of contracting hepatitis B and confers protection to immune-compromised patients, although at a lower rate than in healthy populations or in patients off-therapy.

A study conducted in the Maritimes identified that (17/19 or 89%) of immunosuppressed children vaccinated during chemotherapy do not respond adequately to the hepatitis B vaccine giving a false sense of protection[33,34]. Based on the evidence for lack of vaccine response and the low risk of contracting Hepatitis B in Canada from blood transfusions (1 in 1.7 million units or 0.6/million donations 95%CI:0.30-1.19) [Canadian Blood Services35] and since passive immune-prophylaxis is equally effective in preventing acute hepatitis, the expert panel of this guideline is not recommending vaccinating during immunosuppressive therapy.

The expert panel of this guideline does encourage more studies to be conducted to determine if vaccinating at birth provides protection during cancer treatment.

7.2 Hepatitis A

1. Insufficient evidence to recommend vaccinating immunosuppressed children with hepatitis A vaccine in North America during chemotherapy.
2. Pre or post exposure vaccination of immunosuppressed children with hepatitis A may be warranted under specific circumstances as it is for non-immunosuppressed children.
3. Insufficient evidence to recommend routine vaccination after the completion of therapy.

Discussion:

Two studies by Koksal et al.[27,28], have assessed the efficacy of vaccination for hepatitis A virus (HAV) early after the diagnosis of pediatric malignancy. This measure is generally adopted in countries with high prevalence of HAV infection, in which vaccination is not compulsory due to limited health resources. These studies showed that vaccination of seronegative patients for HAV in the early phase of chemotherapy reduces the risk of contracting hepatitis A and confers protection to immune-compromised patients, although at a lower rate than in healthy populations or in patients off-therapy.

The expert panel are not recommending that immunosuppressed children receive hepatitis A vaccine during or after the end of therapy unless travelling to an area with high incidence of HAV since passive immune-prophylaxis is equally effective in preventing acute hepatitis. The expert panel of this guideline do not recommend routine vaccination with hepatitis A of children with cancer unless pre and/or post exposure vaccination is indicated as in the general population.

7.3 Diphtheria, Tetanus, Pertussis, Polio, Haemophilus influenzae

1. Insufficient evidence to recommend routine vaccination with diphtheria, tetanus, pertussis, polio and Hib during chemotherapy.
2. Children who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catchup schedule.
3. Children who received all doses of Hib-containing vaccines prior to chemotherapy may receive one additional dose six months after completion of chemotherapy (DTaP-IPV-Hib, according to age).
4. Children with asplenia, complement deficiency and certain other high-risk conditions (per NACI criteria) or who have received 22 Gy or higher of radiation to the spleen should receive the Hib vaccine, regardless of prior vaccine history. These children are also eligible for booster doses (see APPHON asplenia guideline).

Discussion:

For poliomyelitis, tetanus, diphtheria, pertussis and Hib, limited data are available on vaccination during chemotherapy; [20,36,37,38,39,40]. These vaccinations are compulsory or highly recommended worldwide and most patients are expected to have completed (3 doses) or almost completed (2 doses) the primary vaccination schedule before pediatric malignancy is diagnosed. The need for maintaining during chemotherapy a protective level of serum antibodies for poliomyelitis and diphtheria is in part attenuated by the protection afforded by herd immunity, given the high percentage of protective antibody titers present in the healthy population.

For tetanus, policies for the management of the at-risk wound, such as washing of the wound, the use of antibiotics, and passive immunoprophylaxis, are effective preventive measures that reduce the need for active immunization while the patient is on chemotherapy. For pertussis, active immunization has been shown to be feasible in HIV patients, although the response was lower than in children not immune-compromised; no reports are available for pediatric cancer patients[41].

The expert panel of this guideline recommends consultation with infectious disease in the case of an outbreak of pertussis.
The expert panel of this guideline agrees that children with hematologic malignancies regardless of prior history of Hib vaccination should receive a booster dose. The expert panel of this guideline recommends children not fully vaccinated prior to the start of chemotherapy continue 6 months after the completion of chemotherapy. It is not recommended at this time that children fully vaccinated prior to the start of chemotherapy receive a booster dose of these vaccines unless high risk i.e., hyposplenia patients.

7.4 Influenza Vaccine

1. All children greater than 6 months of age should receive seasonal inactivated influenza vaccination during chemotherapy if their ALC is greater than 1×10^9/L based on influenza vaccine availability and disease epidemiology.
2. All children greater than 6 months of age who have completed chemotherapy should receive the annual seasonal influenza vaccine. Do not use live attenuated influenza vaccine for immunocompromised patients

If possible, the influenza vaccine should be delayed for 6 months after anti-B cell antibody treatment (i.e. rituximab and blinatumomab).

Discussion:

Influenza has a significant impact on pediatric cancer patients receiving chemotherapy because it causes frequent respiratory tract infections, possibly severe complications including frequent complication by bacteremia[42] requiring hospitalization, delays in chemotherapy administration and even death. Several authors have shown that vaccination for influenza may generate immune responses also in children receiving chemotherapy, although at lower rates than in healthy children or children off-chemotherapy.

In patients receiving current chemotherapy for high-risk leukemia and lymphoma patients receiving rituximab, a profound reduction of B-cell lymphocyte number and function has been reported, potentially affecting immune response to influenza vaccination during the maintenance phase [43]. Further studies looking at clinical outcomes of children vaccinated with the influenza vaccine during different time points of chemotherapy should provide direction on the optimal timing of this vaccine in this population.

Live attenuated influenza vaccine is not recommended in the immune-compromised host. Two studies have been published looking at the safety of the live vaccine in children with cancer. Halasa et al.[44], showed a moderate increase in hemagglutination inhibition (HI) in 20 mildly immunocompromised children receiving or who had received chemotherapy in the previous 3 months; no serious vaccine related adverse events were reported in this small sample. The same eligibility criteria were used in the study by Carr et al.[45], of 52 children half received either the live attenuated influenza vaccine or an inactivated vaccine. No serious adverse events were reported.

The adverse effects of the inactivated vaccine in all listed studies were minimal. Considering the possible protection of the vaccine to children with cancer and the risk of serious adverse events are low the expert panel of this guideline recommended all children 6 months of age who are receiving chemotherapy receive the inactivated influenza vaccine yearly in the fall and to all children yearly who have completed chemotherapy.

7.5 Meningococcal Vaccine:

1. Insufficient evidence for vaccination of children on chemotherapy with any meningococcal vaccine.
2. Children who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catch- up schedule. Vaccination may be initiated six months or more after chemotherapy OR when scheduled according to the provincial schedule (e.g. school-based vaccination in adolescents)
3. Children with asplenia or splenic disorders including sickle cell disease or hemoglobinopathies, complement deficiency and certain other high risk conditions (as per NACI criteria) or who have received 22 Gy or higher of radiation to the spleen should receive the ACYW and MenB vaccines, regardless of prior vaccine history. These children are also eligible for booster doses (see APPHON asplenia guideline).

Discussion:

Invasive infections by capsulated bacteria may represent severe complications during chemotherapy [8,9]. There is limited experience on the use of vaccinations for Meningococcus. Effective prevention remains based on prompt antibiotic treatment of febrile at-risk patients and isolation measures to prevent contact especially during periods of severe neutropenia.

The expert panel of this guideline recommends that meningococcal vaccine not be given during

chemotherapy and a dose of meningococcal ACYW given after the end of chemotherapy. In regards to meningococcal B vaccine the expert panel of this guideline recommends it to be given to all children with asplenia and complement deficiency. For all others as this vaccine currently is not provided by the local government free of charge it is felt that the decision to vaccinate should be determined by the family as the risk for meningococcal B is not higher in children who have received cancer therapy.

7.6 Pneumococcal Vaccine

1. Insufficient evidence for vaccination of children during chemotherapy with any pneumococcal vaccine.
2. Children who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catch- up schedule. Children considered immunocompromised should receive all doses of vaccines (not reduced dose schedules).
3. One dose of 20-valent conjugate pneumococcal vaccine (Pneu-C-20 or Pneu-C-21) is recommended for all children 6 months after the end of therapy.

Children with asplenia, complement deficiency and certain other high risk conditions (as per NACI criteria) or who have received 22 Gy or higher of radiation to the spleen should receive pneumococcal vaccines, regardless of prior vaccine history. These children are also eligible for booster doses (see APPHON asplenia guideline).

Discussion:

Invasive infections by encapsulated bacteria may cause severe complications during chemotherapy, especially in leukemic patients in whom an impairment of pneumococcal immunity has been reported[25,46,47]. There is limited experience on the use of vaccinations for Pneumococcus in children being treated for cancer.
Since the protection provided by the vaccine during chemotherapy is uncertain and the presence of decrease quality of life to the patient due to pain at reaction site and admission to hospital for treatment of cellulitis and the low incidence of invasive pneumococcal infection due to prompt management of febrile neutropenic episodes, the expert panel of this guideline do not recommend vaccination with pneumococcal vaccines during chemotherapy. The expert panel recommend effective prevention based on prompt antibiotic treatment of febrile at-risk patients and isolation measures to prevent contact especially during periods of severe neutropenia.

The expert panel of this guideline recommends that pneumococcal vaccine not be given during chemotherapy and catch-up doses be given after the end of chemotherapy.

7.7 Varicella Vaccine

*If an outbreak occurs, the varicella vaccine may be given as early as 3 months after the end of chemotherapy if the T-cell function of the child is considered normal and in consultation with

pediatric infectious disease specialist or a pediatric hematology/oncologist.

1. Varicella vaccine is not recommended during chemotherapy.

Vaccination and evaluation of titers is affected by recent receipt of IVIG (titers should be delayed to 4 months in recipients of IVIG).

Once deemed immunocompetent, approximately 6 months after completion of therapy and when ALC is at least 1 x 109/L:

- Children who are fully vaccinated prior to diagnosis should have titers measured and if non-immune receive full vaccination schedule and post vaccine titers at least one month after the last dose to ensure immunity.
- Children who are partially vaccinated prior to diagnosis should complete the series and have titers at least one month after the last dose to check immunity. If non-immune give one more dose if eligible (e.g. Immunocompetent).
- Children who are not vaccinated prior to diagnosis should receive all age-appropriate doses and post vaccine titers at least one month after the last dose to ensure immunity.

The combined MMR-V vaccine can be used in children less than 13 years of age. Children 13 years of age and older are given varicella and MMR vaccines as separate injections at different injection sites.

Post-exposure varicella vaccines may be considered in certain situations.

Discussion:

Luthy et al.[48] reviewed several studies performed over the last thirty years to evaluate the safety and efficacy of live attenuated varicella zoster virus (VZV) vaccine administered to children with acute lymphoblastic leukemia during maintenance therapy[48]. Overall, vaccination for VZV resulted in effective seroprotection with no impact on the risk of leukemia relapse compared to unimmunized controls[48]. The rate of failure to protect from varicella was 10–13% and the development of herpes zoster was 1–3%. A more recent study conducted by Cakir et al.[12], supports the rate of failure of the vaccine upwards of 25% in children vaccinated during maintenance. Another study conducted by Emir et al.[49], reports a 25% vaccine failure rate in children with lymphoma and solid tumors.

The major drawback of giving a live vaccine during chemotherapy is the need for withdrawal of chemotherapy for 2 weeks, the occurrence of a vaccine disease has been reported in up to 20% of the patients[48] although the two more recent studies reviewed for this guideline report a 2-7% risk of disease from the vaccine. The patients who incur vaccine caused infection consequently need isolation, and the potential risk of developing a varicella-like illness[48]. If vaccination is considered necessary a lymphocyte count > 0.7–1.0 × 10^9 /L and a platelet count > 100 × 10^9 /L in patients in remission for at least 12 months are considered safe and effective to vaccinate leukemic patients while receiving chemotherapy for VZV[41]. Vaccination is not recommended during profound leukopenia (neutrophils < 0.5 × 109 /L, lymphocytes < 0.7 × 10^9 /L) or during full-dose steroid therapy (>7 days with ≥2 mg/kg/day of prednisone or

≥0.4 mg/kg/day of dexamethasone) alone or combined with other immunosuppressive drugs. VZV vaccination during induction chemotherapy for acute leukemia remains associated with the risk to cause fatal, disseminated disease by the live-attenuated strain due to the heavy immunosuppression of the patients[50,51]. The risk of mortality of varicella significantly decreased over the last 20 years with the introduction of acyclovir and, more recently, of other effective agents such as foscarnet and cidofovir[13,52]. Taken altogether, the potential side effects must be weighed against the real benefits in any decision to vaccinate for varicella seronegative leukemia patients while they are on therapy[13,52,53].

Given the lower risk of mortality of varicella infection for patients on maintenance therapy for acute lymphoblastic leukemia, the overall low risk of varicella infection in general and the availability of effective antiviral drugs, the expert panel suggests that postponing vaccination for VZV until after completion of chemotherapy is an equally safe option. It is generally considered safe to revaccinate with live vaccines 6 months after the end of chemotherapy as this believed to be the interval associated with immune recovery.

7.8 Measles, mumps and rubella vaccine(s):

*If an outbreak occurs, the MMR vaccine may be given as early as 3 months after the end of chemotherapy if the T-cell function of the child is considered normal and in consultation with pediatric infectious disease specialist or a pediatric hematologist/oncologist.

1. Measles, mumps and rubella vaccine is not recommended during chemotherapy.
    - Vaccination and evaluation of titers is affected by recent receipt of IVIG (titers should be delayed to 4 months in recipients of IVIG).

Once deemed immunocompetent, and approximately 6 months after completion of therapy:

- Children who are fully vaccinated prior to diagnosis should have titers measured and if non-immune, receive full vaccination schedule and post vaccine titers at least one month after last dose to ensure immunity.
- Children who are partially vaccinated prior to diagnosis should complete the series and have titers at least one month after the last dose to check immunity.
- Children who are not vaccinated prior to diagnosis should receive all age-appropriate doses and post vaccine titers at least one month after the last dose to check immunity. If non-immune, give one more dose, if eligible (e.g., immunocompetent).

The combined MMR-V vaccine can be used in children less than 13 years of age. Children 13 years of age and older are given varicella and MMR vaccines as separate injections at different injection sites.

Post-exposure measles vaccines may be considered in certain situations.

Discussion:

The use of live-virus vaccines for is usually not indicated for patients on chemotherapy because they are at higher risk of disease by the vaccine strain[41]. Thus, the use of these vaccinations is not recommended by the expert panel of this guideline during chemotherapy. In case of measles epidemic, considering the high morbidity and the potential for mortality in immunocompromised patients, the panel of experts suggests that the risk/benefit ratio of vaccination is individually assessed for each patient; evidence of an adequate CD4+ count may assist in the decision[41]. Consult infectious disease for these patients.

Data shows that a significant number of children have reduced immunity to measles 58%, mumps 47% and rubella 26% after the end of therapy[54,55,56,57], 27%, 47% and 19% of the patients were seronegative after the end of therapy in all children with cancer. All children should have vaccine titers drawn after the end of therapy. All those non-immune children should receive a booster or start revaccination at 6 months after the end of therapy.

7.9 Human Papilloma Virus (HPV) Vaccine (For both male and female subjects):

1. Insufficient evidence is available to recommend HPV vaccine during chemotherapy.
2. The full schedule of 3 doses of vaccine should be given rather than a reduced 2 or one dose schedule to all children who receive cancer treatment.
3. Children/adolescents who did not receive all dose(s) recommended prior to the start of immunosuppression should complete their vaccination based on a catch-up schedule starting at least 6 months after chemotherapy.
4. Vaccination may be initiated six months or more after chemotherapy OR when scheduled in school.
5. A single dose of HPV vaccine is recommended for children/adolescents who are previously vaccinated with the reduced 2 doses schedule of HPV vaccine, 6 months after the end of chemotherapy.

Discussion:

Not enough evidence is available to recommend HPV vaccine during chemotherapy. A few reports are suggestive of higher risk for HPV in the childhood cancer survivor population. Children treated for lymphoma, those who received pelvic radiation and those who have undergone a bone marrow transplant have been identified as high risk[2]. As the vaccine is well tolerated the expert panel of this guideline recommend a booster does of HPV vaccine 6 months after the end of therapy for children who received 2 doses prior to the start of chemotherapy.

The expert panel of this guideline recommends the HPV vaccine be given to both male and female patients based on provincial practices.

7.10 Rotavirus Vaccine:

1. Rotavirus vaccine is not recommended during chemotherapy.

2. Rotavirus vaccine is not recommended after the first year of life.

Discussion:

Due to the lack of data on the use of rotavirus vaccine during chemotherapy the expert panel of this guideline does not currently recommend the use of this vaccine for children treated for cancer.

Appendix A – Research Gap Summary

1) Schedule of booster vaccine doses after completion of chemotherapy:
   - What is the optimal schedule of booster doses of each vaccine after the completion of cancer therapy?
   - Should inactivated and live vaccines be given on a different schedule?
2) Should vaccine titers be monitored?
   - Which vaccine titers should be monitored?
   - When should the titers be monitored?
   - How frequently should the titers be monitored?
3) Should children receiving cancer therapy be vaccinated?
   - If vaccines indicated during cancer treatment, which vaccines and when in treatment should they be given?
4) Protective titers:
   - What is the level of antibodies required to provide protection against infection in children treated for cancer?
5) Longitudinal studies:
   - There is a need for more longitudinal studies looking at risk of death in non-vaccinated vs. vaccinated persons during and after cancer therapy.
6) Compliance with recommendations:
   - Determine break points of where recommendations are not followed.

Appendix B – Organizational Barriers and Cost Implications

Potential organizational barriers/cost implications to applying the recommendations found in this guideline include:

- Inability to obtain vaccines.
- Costs of some vaccines.

Patient/family preferences:

- Religious or other objection to vaccines.
- Issues with adherence.

Appendix C – Key Review Criteria for Monitoring and/or Audit Purposes

Key review criteria for monitoring/audit include:

- Number of children with vaccine preventable diseases.
- Extent of adherence to guideline recommendations.

Appendix D – Membership Lists

Guideline prepared by Tamara MacDonald, PharmD.

Internal reviewers:

Bruce Crooks, MD
(Oncology) Annette
Flanders RN (Oncology)

Expert panel:

Joanne Langley, MD (ID)
Beata Derfalvi, MD (Immunology)

External review was completed by various Health Care Professionals from the Atlantic Provinces.

References:

1. Allen UD. Immunization for children with cancer. Pediatr Blood Cancer 2007;49(7):1102-08.
2. Klosky JL, Gamble HL, Spunt SL, et al. Human Papillomavirus (HPV) Vaccination in Survivors of Childhood Cancer. Cancer. 2009;115(24):5627-36.
3. National Advisory Committee on Immunization (NACI): The Canadian Immunization Guide 2016. http://www.phac-aspc.gc.ca/publicat/cig-gci/index-eng.php (last accessed June 8th 2016).
4. Rubin LG, Levin MJ, Ljungman P, et al. 2013 IDSA Clinical Practice Guideline for Vaccination of the Immunocompromised Host. Clinical Infectious Disease 2014;58(3):309-18.
5. Patel SR, Chisholm JC, Heath PT. Vaccination in Children Treated with Standard-Dose Cancer Therapy or Hematopoietic Stem Cell Transplantation. Pediatr Clin N Am 2008;55:169-186
6. Esposito S, Cecinati V, Scicchitano B, et al. Impact of influenza-like illness and effectiveness of influenza vaccination in oncohematological children who have completed cancer therapy. Vaccine 2010;28:1558-1565.
7. Esposito S, Cecinati V, Brescia L, et al. Vaccination in children with cancer. Vaccine 2010;28:3278-84.
8. Yu JW, Borkowski A, Danzig L, et al. Immune response to conjugated meningococcal C vaccine in pediatric oncology patients. Pediatr Blood Cancer 2007;49(7):918-23.
9. Yu J, Chou AJ, Lennox A, et al. Loss of Antibody Titers and Effectiveness of Revaccination in Post-Chemptherapy Pediatric Sarcoma Patients. Pediatr Blood Cancer 2007;49:656-660.
10. Nilsson A, De Milito A, Engstrom P, et al. Current Chemotherapy Protocols for Childhood Acute lymphoblastic Leukemia Induce Loss of Humoral Immunity to Viral Vaccination Antigens. Pediatrics 2002;109:1-6.
11. Cheng FWT, Leung TF, Chan PKS, et al. Recovery of Humoral and Cellular Immunities to Vaccine-Preventable Infectious Diseases in Pediatric Oncology Patients. Pediatric Hematology and Oncology 2010;27:195-204.
12. Cakir FB, Timur C, Yoruk A, et al. Seroconversion Status After Single Dose and Double Doses of Varicella Vaccination in Children With Leukemia. Pediatric Hematology and Oncology 2012;29:191-194.
13. Caniza MA, Hunger SP, Schrauder A, et al. The Controversy of Varicella Vaccination in Children With Acute Lymphoblastic Leukemia. Pediatr Blood Cancer 2012;58:12-16.
14. Van Tilburg CM, Sanders EAM, Rovers MM, et al. Loss of antibodies and response to re-vaccination in children after treatment for acute lymphocytic leukemia: a systematic review. Leukemia 2006;20:1717-1722.
15. Cheng FWT, Leung TF, Chan PKS, et al. Humoral Immune Response after Post-Chemotherapy Booster Diphtheria-Tetanus-Pertussis Vaccine in Pediatric Oncology Patients. Pediatr Blood Cancer 2009; 52:248-253.
16. Zignol M, Peracchi M, Tridello G, et al. Assessment of humoral immunity to poliomyelitis, tetanus, hepatitis B, measles, rubella, and mumps in children after chemotherapy. Cancer 2004;101(3):635-641.
17. Ruggiero A, Battista A, Coccia P, et al. How to Manage Vaccinations in Children With Cancer. Pediatr Blood Cancer 2011;57:1104-1108.

18. Ek R, Mellander L, Andersson B, et al. Immune Reconstitution After Childhood Acute Lymphblastic Leukemia Is Most Severely Affected in the High Risk Group. Pediatr Blood Cancer 2005;44:461-468.
19. Brodtman DH, Rosenthal DW, REdner A, et al. Immunodeficiency in children with acute lymphoblastic leukemia after completion of modern affressive chemotherapeutic regimens. The Journal of Pediatrics 2005;654-661.
20. Ek T, Mellander L, Hahn-Zoric M, et al. Intensive Treatment for Childhood Acute Lymphoblastic Leukemia Reduces Immune Responses to Diphtheria, Tetanus, and Haemophilus influenza Type b. J Pediatr Hematol Oncol 2004;26:727-733.
21. Van Tilburg CM, Bierings MB, Berbers GAM, et al. Impact of Treatment Reduction for Childhood Acute Lymphoblastic Leukemia on Serum Immunoglobulins and Antibodies Against Vaccine-Preventable Diseases. Pediatr Blood Cancer 2012;58:701-707.
22. Kosmidis S, Baka M, Bouhoutsou D, et al. Longitudinal Assessment of Immunological Status and Rate of Immune Recovery Following Treatment in Children With ALL. Pediatr Blood Cancer 2008;50:528-32.
23. Van Tibburg CM, van Gent R, Bierings MB, et al. Immune reconstitution in children following chemotherapy for haematological malignancies: a long-term follow-up. British Journal of Haematology 2010;152:201-210.
24. Shetty AK, Winter MA. Immunization of Children Receiving Immunosuppressive Therapy for Cancer of Hematopoietic Stem Cell Transplantation. The Ochsner Journal 2012;12:228-243.
25. Lehrnbecher T, Schubert R, Allwinn R, et al. Revaccination of children after completion of standard chemotherapy for acute lymphoblastic leukaemia : a pilot study comparing different schedules. British Journal of Haematology 2011;152:754-757.
26. Patel SR, Ortin M, Cohen BJ, et al. Revaccination of Children after Completion of Standard Chemotherapy for Acute Leukemia 2007;44:635-642.
27. Koksal Y, Varan A, Aydin B, et al. Comparison of accelerated and rapid schedules for monovalent Hepatitis B and combined Hepatitis A/B vaccines in children with cancer. Pediatric Hematology and Oncology 2007;24:587-94.
28. Koksal Y, Yalcin B, Aydin B, et al. Immunogenicity of Hepatitis A vaccine in children with cancer. Pediatric Hematology and Oncology 2006;23:619-24.
29. Yetgin S, Tavil B, Aytac S, et al. Unexpected protection from infection by two booster hepatitis B virus vaccination in children with acute lymphoblastic leukemia. Leukemia Research 2007;31:493-96.
30. Ghosh N, Mannan MA, Monjur F, et al. Escalated regimen of hepatitis B vaccine in childhood hematological malignancies while on chemotherapy 2010;41(3):555-61.
31. Bayton B, Gunes AM, Gunay U. Efficacy of Primary Hepatitis B Immunization in Children with Acute Lymphoblastic Leukemia. Indian Pediatrics 2008;45:265-70.
32. Tavil B, Cetin M, Tuncer M, et al. The rate of hepatitis B and C virus infections and the importance of HBV vaccination in children with acute lymphoblastic leukemia. Hepatology Research 2007;37:498-502.
33. MacDonald T, Price V, MacDonald N. Is it Safe to Immunize Children Receiving Chemotherapy? Pediatric Academic Societies, Vancouver, May 2-6, 2014.

34. MacDonald T, Price V, MacDonald N. Is Immunizing Children Receiving Chemotherapy with the Hepatitis B Vaccine Providing a False Sense of Protection? Pediatric Academic Societies, Vancouver, May 2-6, 2014.
35. Canadian Blood Services
36. Kwon HJ, Lee JW, Chung NG et al. Assessment of Serologic Immunity to Diphtheria-Tetanus-Pertussis After Treatment of Korean Pediatric Hematology and Oncology Patients. J Korean Med Sci 2012;27:78-83.
37. Paulides M, Stohr W, Laws HJ, et al. Antibody levels against tetanus and diphtheria after polychemotherapy for childhood sarcoma: A report from the late effects surveillance system. Vaccine 2011;29:1565-1568.
38. Calaminus G, Hense B, Groeger M, et al. Diphtheria(D) and Tetanus (T) Antibody Values in Children with Acute Lymphoblastic Leukaemia (ALL) after Treatment According to Co-ALL 05/92. Kin Padiatr 2007;219:355-360.
39. Januszkiewicz-Lewandowska D, Gowin E, Bocian J, et al. Vaccine-Derived Immunity in Children with Cancer-Analysis of Anti-Tetanus and Anti-diphtheria Antibodies Changes After Completion of Antineoplastic Therapy. Pediatr Blood Cancer 2015;62:2108-2113.
40. Ek T, Mellander L, Hahn-Zoric M, et al. Avidity of Tetanus and Hib antibodies after childhood acute lymphoblastic leukaemia- implications for vaccination strategies. Acta Paediatrica 2006;95:701-706.
41. Cesaro S, Giacchino M, Fioredda F, et al. Guidelines on Vaccinations in Paediatric Haematology and Oncology Patients. Biomed Research International 2014; 2314-2324.
42. Tasian SK, Park JR, Martin FT, et al. Influenza-associated morbidity in children with cancer. Pediatric Blood and Cancer 2008;50(5):983-987.
43. Kersun LS, Reilly AF, Coffin SE, et al. Protecting Pediatric Oncology Patients From Influenza. The Oncologist 2013;18:204-211.
44. Halasa N, Englund JA, Nachman S, et al. Safety of live attenuated influenza vaccine in mild to moderately immunocompromised children with cancer. Vaccine 2011;29:4110-15.
45. Carr S, Allison KJ, Van De Velde LA, Zhang K, et al. Safety and Immunogenicity of Live Attenuated and Inactivated Influenza Vaccines in Children with Cancer. The Journal of Infectious Disease 2011;204:1475-82.
46. Meisel R, Toschkle AM, Heiligensetzer C, et al. Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukemia. British Journal of Haematology 2007;137:457-460.
47. Lehrnbecher T, Schubert R, Behl M, et al. Impaired pneumococcal immunity in children after treatment for acute lymphoblastic leukaemia. British Journal of Haematology 2009; 147:700-705.
48. Luthy KE, Tiedeman ME, Beckstrand RL, et al. Safety of live-virus vaccines for children with immune deficiency. J Am Acad Nurse Pract 2006;18(10):494-503.
49. Emir S, Buyukpamukcu M, Koseoglu V, et al. Varicella vaccination in children with lymphoma and solid tumours. Postgrad Med J 2006;82:760-62.
50. Schrauder A, Henke-Gendo C, Seidemann K, et al. Varicella vaccination in a child with acute lymphoblastic leukaemia. The Lancet 2007;369(9568):1232.
51. Grote V, Von Kries R, Springer W, et al. Varicella-related deaths in children and adolescents-Germany 2003-2004. Acta Paediatric. 2008;97(2):187-192.

52. Kamboj M, Sepkowitz KA. Risk of transmission associated with live attenuated vaccines given to healthy persons caring for or residing with an immunocompromised patient. Infection Control and Hospital Epidemiology 2007;28(6):701-707.
53. Cheuk DK, Chiang AK, Lee TL, et al. Vaccines for prophylaxis of viral infections in patients with hematological malignancies. Cochrane Database of Systematic Reviews 2011;3.
54. Koochakzadeh L, Khosravi MH, Pourakbari B, et al. Assessment of Immune Response following Immunization with DTP/Td and MMR Vaccines in Children Treated for Acute Lymphoblatic Leukemia. Pediatric Hematology and Oncology 2014;31;656-663.
55. Aytac S, Yalcin SS, Cetin M, et al. Measles, mumps, and rubella antibody status and response to immunization in children after therapy for acute lymphoblastic leukemia. Pediatric Hematology and Oncology 2010;27;333-43.
56. Zengin E and Sarger N. Humoral Immunity to Diphtheria, Tetanus, Measles, and Hemophilus Influenzae Type b in Children With Acute Lymphoblastic Leukemia and Response to Re-Vaccination. Pediatr Blood Cancer 2009;53:967-972.
57. Bochennek K, Allwinn R, Langer R, et al. Differential loss of humoral immunity against measles, mumps, rubella and varicella-zoster virus in children treated for cancer. Vaccine 2014;32:3357-61.