



Atlantic Provinces Pediatric Hematology Oncology Network
Réseau d'Oncologie et Hématologie Pédiatrique des Provinces Atlantiques

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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.

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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:	<i>Haemophilus Influenzae</i>
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:	Hemagglutination inhibition
PCV:	Pneumococcal conjugate Vaccine
PP23:	Pneumococcal Polysaccharide Vaccine
BCG:	Bacillus Calmette-Guerin

Overview of Material

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Print copies available through:

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1. Summary

The following vaccine recommendations listed in Table 1 are based on the NACI guidelines available at <http://www.phac-aspc.gc.ca>. 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 for immunization from Canada's National Advisory Committee on Immunization (NACI) <http://www.phac-aspc.gc.ca>. 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 disease vary based on location, availability of serum vaccine testing and government funding. Several groups do recommend vaccine boosters based on the growing body of evidence that children treated for cancer do have sufficient 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	<ol style="list-style-type: none"> 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; 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 in school. <ol style="list-style-type: none"> 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. b) If not previously vaccinated give full series. c) Give the appropriate number of doses based on age.
Hepatitis A	<ol style="list-style-type: none"> 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.
Diphtheria, Tetanus, Pertussis, Polio, <i>Haemophilus influenzae</i> :	<ol style="list-style-type: none"> 1. Insufficient evidence to recommend routine vaccination with diphtheria, tetanus, pertussis, polio and Hib during chemotherapy. 2. One dose of a <i>Haemophilus influenzae</i>-containing vaccine is recommended for patients over 5 years of age with hematologic malignancies regardless of prior history of Hib vaccination, and at least 1 year after any previous dose. 3. For children who did not receive all dose(s) recommended prior to the start of immunosuppression they should continue where they stopped based on a catch-up schedule. 4. Children who received all doses of Hib-containing vaccines prior to immunosuppression may receive one additional dose six months after completion of chemotherapy.
Influenza vaccine:	<ol style="list-style-type: none"> 1. All children greater than 6 months of age should receive seasonal inactivated influenza vaccination during chemotherapy if their ALC is greater than $1 \times 10^9/L$ 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

Vaccine	Recommendation
	<ol style="list-style-type: none"> 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:	<ol style="list-style-type: none"> 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 continue where they stopped based on a catch-up schedule. Vaccination may be initiated six months or more after chemotherapy OR when scheduled in school. 3. Children with asplenia, complement deficiency and certain other high risk conditions should be considered for ACYW and MenB vaccines. These children are also eligible for booster doses (see NACI).
Pneumococcal vaccine:	<ol style="list-style-type: none"> 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 continue where they stopped based on a catch-up schedule. Children considered immunocompromised should receive all doses of vaccines (not reduced dose schedules). 3. One dose of 13-valent conjugate pneumococcal vaccine (Pneu-C-13) is recommended for all children 6 months after the end of therapy. 4. Children greater than 2 years should also receive a dose of polysaccharide pneumococcal vaccine (Pneu-23) not earlier than 8 weeks after the dose of Pneu-C-13.
Varicella vaccine (Note: live attenuated):	<ol style="list-style-type: none"> 1. Varicella vaccine is not recommended during chemotherapy. 2. Titers should be drawn on all patients 3-6 months after the end of therapy. 3. Varicella vaccine is recommended for seronegative children 6 months after the end of chemotherapy when ALC is at least $1 \times 10^9/L$. <ol style="list-style-type: none"> a) If received 2 doses prior to therapy give one booster dose. b) If partially vaccinated prior to therapy give 2 doses at least 1 month apart. <p>Give varicella as univalent vaccine and not as MMRV combined vaccine. In time of outbreak contact specialist for timing of varicella vaccine.</p>
Measles, mumps and rubella vaccine(s): (Note: live attenuated)	<ol style="list-style-type: none"> 1. Measles, mumps and rubella vaccine is not recommended during chemotherapy. 2. Titers should be drawn on all patients 3-6 months after the end of therapy. 3. Measles, mumps and rubella vaccine is recommended for seronegative children 6 months after the end of chemotherapy. <ol style="list-style-type: none"> a) If received 2 doses prior to therapy give one booster dose. b) If partially vaccinated prior to therapy give 2 doses at least 1 month apart. <p>Give MMR separate vaccine from varicella and not as MMRV combined vaccine. In time of outbreak contact specialist for timing of MMR vaccine.</p>

Vaccine	Recommendation
Human Papilloma Virus (HPV) vaccine (Note: Both male and female subjects.)	<ol style="list-style-type: none"> 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 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 continue where they stopped 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)	<ol style="list-style-type: none"> 1. Rotavirus vaccine is not recommended during chemotherapy. 2. Rotavirus vaccine is not recommended after the first year of life.

NOTE: Refer to provincial immunization schedule for timing and number of routine vaccines.

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, 2007¹]. This category includes vaccines for tetanus, diphtheria, pertussis, poliomyelitis, hepatitis A and B, influenza, *Haemophilus*, pneumococcus, meningococcus and human papilloma virus (HPV) [Klosky, 2009²]. 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 NACI³ 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 al¹⁸ 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 vaccines⁵. 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 cells¹⁶. 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 infections²². 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 months²⁶.

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 1×10^9 cells/L. 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; 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 in school.

4. 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.
5. If not previously vaccinated give full series.
6. 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 are 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 Koksai 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. One dose of a *Haemophilus influenzae*-containing vaccine is recommended for patients over 5 years of age with hematologic malignancies regardless of prior history of Hib vaccination, and at least 1 year after any previous dose.
3. For children who did not receive all dose(s) recommended prior to the start of immunosuppression they should continue where they stopped based on a catch-up schedule.
4. Children who received all doses of Hib-containing vaccines prior to immunosuppression may receive one additional dose six months after completion of chemotherapy.

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 patients⁴¹.

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 does not feel the risk of polio, hemophilus influenzae; diphtheria, tetanus and pertussis are significant in children treated for cancer who have exceeded the age for routine vaccination. 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 hyposplenism 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 $1 \times 10^9/L$ 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 bacteremia⁴² 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 phase⁴³. 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 had received chemotherapy in the previous 3 months, no serious vaccine related adverse events were reported. The same eligibility criteria was used in the study by Carr et al.⁴⁵, of 52 children half received the live influenza vaccine and the other half the inactivated vaccine. No serious adverse events were reported and higher HI was seen in the children who received the inactivated influenza vaccine. Since the evidence for efficacy of the live influenza vaccine in mildly immunocompromised children suggests that although the vaccine may be safe, its efficacy is no better than the established inactivated vaccine.

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 continue where they stopped based on a catch-up schedule. Vaccination may be initiated six months or more after chemotherapy OR when scheduled in school.

Children with asplenia, complement deficiency and certain other high risk conditions should be considered for ACYW and MenB vaccines. These children are also eligible for booster doses (see NACI).

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 continue where they stopped based on a catch-up schedule. Children considered immunocompromised should receive all doses of vaccines (not reduced dose schedules).
3. One dose of 13-valent conjugate pneumococcal vaccine (Pneu-C-13) is recommended for all children 6 months after the end of therapy.

4. Children greater than 2 years should also receive a dose of polysaccharide pneumococcal vaccine (Pneu-23) not earlier than 8 weeks after the dose of Pneu-C-13.

Discussion:

Invasive infections by capsulated bacteria may represent 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. Local data shows that a significant number of children receiving cancer treatment incur moderate to severe local reactions (10% 9/89) to the pneumococcal polysaccharide vaccine (PPV-23)^{33,34}.

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 PCV or PPV 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

1. Varicella vaccine is not recommended during chemotherapy.
2. Titers should be drawn on all patients 3-6 months after the end of therapy.
3. Varicella vaccine is recommended for seronegative children 6 months* after the end of chemotherapy when ALC is at least $1 \times 10^9/L$.
 - a) If received 2 doses prior to therapy give one booster dose.
 - b) If partially vaccinated prior to therapy give 2 doses at least 1 month apart.

*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.

Note: MMR and V is available as a combined vaccine MMRV but should be given as the separate MMR and univalent varicella vaccine to maximize response in the post chemotherapy patient.

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 therapy⁴⁸. Overall, vaccination for VZV resulted in effective seroprotection with no impact on the risk of leukemia relapse compared to unimmunized controls⁴⁸. 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 patients⁴⁸ 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 illness⁴⁸. If vaccination is considered necessary a lymphocyte count $> 0.7\text{--}1.0 \times 10^9 /\text{L}$ and a platelet count $> 100 \times 10^9 /\text{L}$ in patients in remission for at least 12 months are considered safe and effective to vaccinate leukemic patients while receiving chemotherapy for VZV⁴¹. Vaccination is not recommended during profound leukopenia (neutrophils $< 0.5 \times 10^9 /\text{L}$, lymphocytes $< 0.7 \times 10^9 /\text{L}$) 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):

1. Measles, mumps and rubella vaccine is not recommended during chemotherapy.
2. Titers should be drawn on all patients 3-6 months after the end of therapy.
3. Measles, mumps and rubella vaccine is recommended for seronegative children 6 months* after the end of chemotherapy.
 - a) If received 2 doses prior to therapy give one booster dose.
 - b) If partially vaccinated prior to therapy give 2 doses at least 1 month apart.

*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 hematology/oncologist.

Note: MMR and V is available as a combined vaccine MMRV but should be given as the separate MMR and univalent varicella vaccine to maximize response in the post chemotherapy patient.

Discussion:

The use of attenuated-virus vaccination for measles mumps-rubella is usually not indicated for patients on chemotherapy because they are at higher risk of fever or vaccine disease by vaccine strain⁴¹. 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 decision⁴¹. 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 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 continue where they stopped 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 risk². 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)

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Expert panel:

Joanne Langley, MD (ID)

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

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