A. Introduction

Children with malignancies have an increased risk of severe outcomes from vaccine-preventable infections because their immune system may be compromised by the underlying primary disease, antineoplastic treatment, or both.\textsuperscript{1,2,3}

Limited data are available regarding the effects of vaccination on immunocompromised hosts, particularly children with malignancies. Consequently, information used to support decision making is generally extrapolated from the available data on healthy children or expert opinions. The purpose of this review is to support pediatric oncologists or family physicians that treat children with cancer by providing recommendations derived from recent literature regarding vaccination during and after the treatment therapy for childhood cancer.
A. References


B. The Immune System in Children with Cancer

The immune response to vaccination occurs through the cell-mediated and humoral immune response mechanism. To establish the best strategies for the immunization of children with cancer it is essential to have an understanding of the changes in the immune systems of these patients.  

Most children with cancer are immunocompromised. Although the cancer itself may cause a variable degree of immunosuppression, the main cause of immunosuppression in children with cancer is cytotoxic antineoplastic therapy.  

Both cellular and humoral immune responses may be suppressed by malignancies. In children, hematopoietic malignancies may impair cellular immunity through prolonged myelosuppression, particularly in the form of granulocytopenia; they may also have an adverse influence on lymphocyte function and natural killer (NK) cells.  

Currently, there is only conflicting information available regarding the effect of malignancies on humoral immunity. Some studies show that in patients with vaccine-preventable infections, the total immunoglobulin concentrations, as well as the specific antibody concentrations, are normal at the time of diagnosis. This suggests that the cancer itself is likely to have a relatively small effect on the adaptive immune system of cancer patients.
In patients with acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), the aberrant differentiation and proliferation of malignantly transformed lymphoid and myeloid progenitors could have an effect on the adaptive immune system and may impair antibody responses to vaccine antigens. However, Ercan et al. recently reported that ALL itself does not produce any suppressive effect on the antibody titers acquired by previous immunization.

The age of children at the time they are diagnosed with cancer influences their ability to produce protective antibodies against bacterial and viral vaccines. Infants diagnosed with and treated for malignancies before the age of 1 year will receive immunosuppression before their immune systems have developed the capacity to maximally respond to some vaccines. Because of this, infants and young children can have a significant loss of antibody titers acquired by previous vaccination and can develop more immune defects, which can persist up to the first year after the completion of chemotherapy.

Chemotherapy has been proven to be the main contributor to the impairment of the immune system in cancer-affected children. Differences in the duration of chemotherapy, treatment intensity, and the chemotherapeutic agents used (e.g., purine analogs, which cause a marked depletion of CD4+ T cells, or glucocorticoids, which cause a profound lympholysis) may explain the variability of the immune imbalance noted among cancer-affected children.

For example, treatment regimens for ALL are targeted at lymphoid cells and can adversely influence lymphocyte function, while the chemotherapy used to treat early-stage Wilms tumors (actinomycin and vincristine) is not particularly immunosuppressive.

Although some reports indicate that patients with hematopoietic malignancies have a higher risk for immune deficiency than those with solid tumors, solid tumor patients may still experience immune defects comparable to those seen in leukemia patients. This may be partially explained by the increased use of high-intensity chemotherapy regimens in the treatment of
solid tumors, probably because of the high-intensity chemotherapeutic regimens used for solid tumors.\textsuperscript{5}

With regard to humoral immunity, chemotherapeutic agents used to treat childhood cancer may result in a quantitative and qualitative deficit in the immunoglobulin concentrations of children affected by malignancies. Kantar et al. studied immunosuppression following cancer treatment in children with leukemia and solid tumors. They found that only the patients with leukemia had significantly low levels of IgA and IgM at the completion of cancer therapy, and these levels returned to normal values within 6 months, while the Ig G and IgG levels were normal both at the time of the completion of chemotherapy and 6 months later.\textsuperscript{7} These findings were consistent with those of other studies which reported, the total serum Ig concentrations were often reduced during the chemotherapy program but were returned to normal within 3–6 months after the completion of antiblastic therapy.\textsuperscript{1,5,11,12}

Some studies have demonstrated that the recovery of normal cellular immunity values after the completion of chemotherapy takes longer than that of humoral immunity, however, available data regarding the time required for the reconstitution of B and T lymphocytes and natural killer NK cells are conflicting.\textsuperscript{13,14,15}

The total B-cell population is usually completely restored, both quantitatively and functionally, 6–12 months after the completion of chemotherapy. It has been demonstrated that CD4+ lymphocyte regeneration is not completed within 6 months of treatment for childhood ALL, and the recovery begins at 1 year after completion of chemotherapy. CD8+ cells begin to regenerate 3 months to 1 year after the completion of chemotherapy and return to normal values after 1 year or longer. The population of NK cells returns to its normal size within 6 months, however, it has been demonstrated that the NK cell count in children with cancer are comparable to the levels found in healthy children soon after the cessation of therapy.\textsuperscript{1,5,11} Considering the variability in the available data, the precise time of reconstitution of the
immune system in children after chemotherapy remains unclear. Nevertheless, the reconstitution of the immune system occurs between 3–12 months after the completion of chemotherapy, so these children could receive the necessary vaccines during this period.

With regard to the appropriate immunization strategy, the following questions for physicians arise regarding the correct strategy for immunization:

1) What are the contraindicated and relatively contraindicated vaccines?
2) What are the vaccines that are not contraindicated and what is the best time to administer vaccinations to children with cancer?
3) Should children be revaccinated after the completion of chemotherapy, should the regular vaccination schedule be continued, and should any booster vaccine doses be administered?

B.1 What are the contraindicated and relatively contraindicated vaccines?

Live viral vaccines are contraindicated in children with cancer. The oral polio, yellow fever, oral typhoid, and live attenuated intranasal influenza vaccines are also contraindicated in these children.

Vaccines against measles, mumps, rubella, and varicella are relatively contraindicated. Live bacterial vaccines (e.g., bacille Calmette-Guerin and the oral typhoid vaccine) should be avoided in children with malignancies. Overall, the administration of live vaccines should be deferred until immune function has returned to normal.\textsuperscript{16,17,18}
B.1.1 Measles, Mumps, and Rubella

The measles, mumps, and rubella (MMR) vaccine is a live vaccine that is relatively contraindicated in immunocompromised patients. Children undergoing chemotherapy, including non-intensive antiblastic therapy, should not receive live vaccines.\textsuperscript{16} The recommendations regarding the best timing for the administration of live vaccines are conflicting. MMR vaccines could be administered for an interval of at least 3 months after immunosuppressive chemotherapy has been discontinued. It has also been demonstrated that the administration of live vaccines including MMR should be delayed for 6–12 months after immunosuppressive therapy is complete.\textsuperscript{19,20} Based on these considerations, it is not possible to make a definitive recommendation for the administration of all live vaccines, however, in our opinion, administering the MMR vaccine 6 months after the discontinuation of chemotherapy is a good strategy for immunizing children with cancer.

B.1.2 Varicella Vaccine

Immunocompromised children have an increased risk of developing severe illnesses, including disseminated diseases, pneumonia, encephalitis, and varicella,\textsuperscript{21} and there are some preventive and therapeutic strategies to prevent and treat varicella in children with cancer. Siblings and susceptible household members should be vaccinated and the risk of vaccine transmission from siblings to the cancer patients is small. All cancer patients without a history of varicella or immunization against varicella should receive post-exposure prophylaxis with VariZIG within 96 hours. If VariZIG is not available, IVIg or acyclovir prophylaxis (80 mg·kg\textsuperscript{-1}·day\textsuperscript{-1}; 4 times/day for 7 days) may be used.\textsuperscript{22,23}

The varicella vaccine is relatively contraindicated and the American Academy of Pediatrics and the current Canadian guidelines suggest that immunization should be considered for susceptible children with ALL who
have a lymphocyte count greater than 0.7–1.2 \times 10^9/L and a platelet count greater than 100 \times 10^9/L, 12 months after the end of antiblastic therapy. In a recent paper Schrauder et al. confirmed these data and recommended that in seronegative children with ALL who are in complete remission for at least 12 months, VZZ vaccination should not be undertaken unless at least 9 months have elapsed after the end of immunosuppressive treatment (including maintenance therapy) and not before a lymphocyte count of 1–5 \times 10^9/L has been ascertained.

If needed (during periods of varicella epidemics), children with can be vaccinated during maintenance chemotherapy, provided the treatment is discontinued for at least 1 week before to 1 week after the immunization with a minimum interval of 4 weeks after pulse treatment with steroids.\textsuperscript{24} In a previous study, ALL patients continuing maintenance therapy with 6-mercaptopurine and methotrexate were safely immunized and developed a satisfactory titer of antibodies to VZV, however, patients receiving complete therapeutic (induction) regimens developed unacceptable vaccine-related complications.\textsuperscript{25} It has been demonstrated that the better approach for these patients is that the vaccination be administered in 2 doses at an interval of 1–3 months, instead of a single dose, in order to achieve greater immunogenicity.\textsuperscript{24,26}

In children with solid tumors, the varicella vaccine is well tolerated even if it is administered soon after chemotherapy has been discontinued. Children with cancer have exhibited good immune responses to the vaccination, without vaccine-related side effects.\textsuperscript{27} Notably, it has been commonly found in all studies on the varicella vaccine in children with cancer that vaccine-related complications are mild and comparable to those noted in healthy children.
B.2 What are the vaccines that are not contraindicated and what is the best time to administer vaccinations to children with cancer?

B.2.1 Vaccines against diphtheria, tetanus, a cellular pertussis, inactivated polio, and haemophilus influenzae type B

Non-live vaccines can be administered to children with cancer during chemotherapy. Many studies have evaluated the antibody responses to non-live vaccines administered during chemotherapy (especially during the maintenance phase of chemotherapy for ALL) and it has been demonstrated that the immune responses are usually impaired. Nevertheless, the current recommendations for children with cancer in cancer-affected children, non-live vaccines should be administered according to the routine schedule for childhood immunization, within 3–6 months of the completion of antiblastic therapy, when immune reconstitution is complete.  

B.3 Vaccination against other encapsulated organisms

B.3.1 Meningococcal Vaccine

The American Academy of Pediatrics recommends that the quadrivalent meningococcal polysaccharide vaccine or the quadrivalent conjugate vaccine be administered to high-risk individuals (starting at the age of 2 years).  

Cancer patients have an increased risk for meningococcal disease. Patients with Hodgkin lymphoma (HL) are known to be at an increased risk for serious bacterial infections with encapsulated organism.  

There are currently no standard recommendations regarding the meningococcal C conjugate vaccine for immunosuppressed patients secondary to chemotherapy. In contrast to live viral vaccines, which are contraindicated in immunosuppressed individuals, the meningococcal C conjugate vaccine may be
administered because it contains purified, non-viable bacterial components. We found only 1 paper on the use of meningococcal vaccines in children with cancer. Yu et al. examined the response of children with ALL to the meningococcal C conjugate vaccine administered during or after maintenance chemotherapy and after bone marrow transplantation. The authors concluded that vaccination with the meningococcal type C conjugate vaccine was safe, however, it was only effective in 40–50% of the patients. Therefore, vaccine-induced responses in children on maintenance chemotherapy should be monitored. Vaccination is improved in patients with B lymphocyte counts less than 0.260 × 10/L and in those who have been finished with maintenance chemotherapy for more than 3 months.

In children with cancer, the meningococcal C conjugate vaccine could be considered safe and effective if administered until reconstitution of immune system in children with cancer, not earlier than 3–6 months after the completion of chemotherapy.31

B.3.2 Pneumococcal Vaccine

Children with cancer are susceptible to serious bacterial infections with encapsulated organisms.29 Children with HL are at a high risk for developing invasive pneumococcal disease.30,32 Although limited data are available on the use of the pneumococcal vaccine in immunosuppressed patients, it may be presumed that children with HL should be in the high-priority group for receiving pneumococcal vaccination.

Children with cancer should receive pneumococcal immunization at the time of the immune system’s recovery (3–6 months after the completion of ant blastic therapy). The following information on the administration of pneumococcal vaccine can be derived from healthy children: infants younger than 2 years should receive the conjugate vaccine according to the regular schedule, while children who are older than 5 years but younger than 9 years
may receive either the 7-valent vaccine or the 23-valent vaccine, and children older than 9 years may receive the 7-valent vaccine. For children older than 2 years but younger than 5 years, the schedule should be based on data recorded for children with sickle cell disease.\textsuperscript{13}

B.3.3 Vaccines against hepatitis B and hepatitis A

In countries with a high or intermediate risk of HBV infection, this infection is one of the major causes of morbidity in children with malignancies. The incidence of HBV infection in patients with cancer should be reduced because this infection can result in a high incidence of chronic HBV carriers and chronic liver disease, altered pharmacokinetics of certain antineoplastic agents that are metabolized by the liver, and a delay in the chemotherapy schedule.\textsuperscript{34} Since the 1990s, many countries (e.g., Italy in 1990 and Poland in 1995) have mandated nationwide immunization against hepatitis B for all newborns. Because of this mandate, more children with neoplasms have a protective level of anti-HBV antibodies and are therefore safeguarded against HBV infection.\textsuperscript{35} In countries that do not have a national program of immunization against HBV infection, particularly developing countries, the risk of this viral infection is elevated.

The use of the HBV vaccine is recommended and, in some cases, necessary (particularly in developing countries) for children with cancer. Some studies have demonstrated that the use of this vaccine is safe and a good immune response can be achieved even if the vaccine is administered during maintenance therapy in children with ALL and other malignancies.\textsuperscript{36,37,38} Very limited data are available regarding vaccination against the hepatitis A virus (HAV) in children with cancer. Only 2 papers describe the safety and effectiveness of the hepatitis A vaccine in children with malignancies. These studies reported that children receiving chemotherapy showed good antibody responses to the vaccine and suggest that the approach to vaccination against
HAV in children receiving chemotherapy should be selected with a view to preventing both the development of HAV infection and a delay in the treatment of primary disease due to HAV. 39,40

B.4 Should children be revaccinated after the completion of chemotherapy, should the regular vaccination schedule be adopted, and should any booster vaccine doses be administered?

These questions cannot be adequately answered because the available relevant data are controversial and offer conflicting information. Opinions on the best vaccination strategy for children with cancer after the completion of chemotherapy vary drastically depending on the experience of each research group. Three possible strategies have been reported:

1) A booster vaccine dose is administered if needed after an evaluation provides evidence of low protective antibody titers.
2) Revaccination without assessing the residual immunity.
3) Continuing the regular childhood immunization schedule is adopted.

Zignol et al. support the first strategy in the list. They evaluated the serum titers of antibodies for tetanus, polio, diphtheria, HBV, measles, mumps, and rubella after chemotherapy in 192 children with solid tumors or leukemia. They found that chemotherapy reduced the overall protective serum antibody titers in 52% of the patients, mostly in children with HBV (46%), followed by those with rubella, mumps, and measles (approximately 25%). The administration of a booster dose at 12 months after the completion of chemotherapy is a simple and cost-effective way to restore humoral immunity against most vaccine-preventable diseases.7

Fioredda et al. evaluated the titers of antibodies for HBV and tetanus in 70 children who were treated for leukemia, at a median of 12 months after the
completion of chemotherapy. They observed protective antibody titers comparable to those in healthy children 85% of the patients. They recommend the regular childhood vaccination schedule be continued depending on the patient’s age.\textsuperscript{41} Laws et al. dispute these findings because in their experience, the loss of protective antibodies after the end of chemotherapy is considerable in children with cancer, and revaccination at the earliest opportunity appears to be the best strategy for these patients.\textsuperscript{42}

The recommendations of Von der Hardt et al. are similar to those of Zignol et al. Von der Hardt et al. measured the serum titers of antibodies against the diphtheria and tetanus toxins and against poliomyelitis virus serotypes 1–3 at various times after the completion of chemotherapy (0–15 months after chemotherapy for diphtheria and tetanus and at 0–18 months after the cessation of chemotherapy for poliomyelitis) in 75 children with malignancies. Overall, the titers of antibodies against diphtheria, tetanus, and polio were deficient by 62%, 18%, and 75%, respectively. When the lack of protective antibodies was discovered, booster immunization was recommended.\textsuperscript{42}

Patel et al. and Reinhardt et al. support the strategy of revaccinating children after the completion of chemotherapy. Patel et al. defended the utility of revaccination, arguing that this strategy is practical and desirable for achieving higher levels of protective titers against vaccine-preventable disease in children who have recently completed a treatment program for leukemia. In addition, they found that 1 year after vaccination, the titers of antibodies against vaccine-preventable diseases remained protective in all patients.\textsuperscript{48}

Reinhardt et al. found markedly reduced and undetectable levels of specific antibodies against measles, mumps, poliomyelitis, diphtheria, tetanus and \textit{H. influenzae} type B in 139 children with malignancies. However, the original antibody titers were, in most cases, restored by the revaccination that these authors proposed. It seems to be reasonable to make use of the option to revaccinate children with malignancies.
Brodtman et al. and their colleagues recommend that pediatricians and oncologists periodically monitor humoral immunity in children with cancer after chemotherapy is finished and should revaccinate these children as needed to ensure sustained immunoprotection.  

Yu et al. adopted the same strategy of revaccination used by Reinhardt et al., analyzing sarcoma patients exclusively. They found that most of the children who had undergone chemotherapy for solid tumors (71.2%) no longer possessed detectable titers of antibodies against most vaccine-preventable diseases. This finding suggested that children with cancer may need to be revaccinated against vaccine-preventable diseases after chemotherapy.

B. References


C. Conclusions

Available data on immunization in immunocompromised patients, particularly children with cancer, are limited and often provide conflicting information. Despite the conflicting information, the following can be concluded after a careful review of the available data: we have concluded the following:

1) Children with cancer experience vaccine-related side effects comparable to those seen in healthy children.
2) In laboratory assessment of residual immunity general screening for immune response is not recommended for children with cancer after chemotherapy is complete. From a pragmatic point of view, most children will require 1 or more vaccines, and few laboratories are able to perform the necessary assays. The use of a specific concentration may not be helpful because the protective antibody titers are not clearly established, and the titers reported in studies on healthy children may not be applicable to children with cancer.

3) In children with cancer, the minimum duration required for reconstitution of the immune system and for achieving an acceptable immune response after vaccination is 3 months after the completion of chemotherapy.

4) Live and bacterial vaccines are contraindicated, varicella and MMR vaccines are relatively contraindicated, and non-live vaccines can be administered even during chemotherapy for childhood cancer.

5) Compared to older patients, those aged less than 1 year, especially those who have not completed the primary vaccination schedule, are less protected against vaccine antigens and should therefore be followed up more carefully.

6) The optimum approach to immunization in children with cancer is still being debated. The 3 approaches under debate are the use of booster vaccine doses, revaccination, or the continuation of the regular vaccination schedule.