Hematopoietic Stem Cell Transplantation (HSCT) of Children with Cancer: Immunization Recommendations

***** Immunizations for the HSCT population should only commence after consultation with the pediatric oncology physician. *****

It is known that differences are present between children who undergo allogeneic versus autologous HSCT in regards to immunization responses, but not enough evidence is available to recommend different vaccination schedules. For the purposes of simplicity, APPHON (in accordance with the American Society for Blood and Marrow Transplantation guideline 2009) is recommending the same schedule for both allogeneic and autologous HSCT patients.

Pre-Transplantation:

- If possible, all appropriate vaccines should be administered 10-14 days prior to implementation of ablative or immunosuppressive therapy if this can be achieved without delaying therapy. In allogeneic HSCT, consider administration of appropriate vaccines to the donor (at least) 10-14 days before bone marrow harvesting.
- All household and other close contacts should also be immunized if not previously immunized or immune with influenza, meningococcal, pneumococcal, MMR, varicella, pertussis.

Post-Transplantation:

- The inactivated influenza vaccine may be given as early as 6 months after HSCT.
- The pneumococcal conjugate (Prevnar) vaccines may be given as early as 6 months after HSCT. In the case of a patient who is on active chemotherapy, including antibody directed myelosuppressive therapy, a consult to Pediatric Infectious Disease Specialist may be sent to review appropriate timing of Prevnar.
- All other vaccines should start no earlier than 12 months post HSCT or at least 3 months after stopping all chronic GVHD therapy, if greater than 1-year post transplant including high dose steroids (equivalent to 2 mg/kg/day prednisone or 20 mg prednisone/day if less than 10 kg for 2 weeks or longer) OR active chemotherapy including antibody directed myelosuppressive therapy.
- All household and other close contacts should also be immunized if not immunized prior to transplant.

***CAR T-cell Therapy*:**

- The role of vaccination following CAR T-cell therapy remains unclear. Until further evidence is available, no specific recommendations can be made and the advisability of vaccinations needs to be evaluated for each individual based on the history of infections and cell assessments of cellular and humoral immunity[1].
- Vaccinations are generally not given unless patients experience loss of B-cell aplasia, normalization of IgG and IgM levels and do not receive regular IVIG infusions as efficacy of vaccinations in

populations without B-cells is unclear with the exception of the seasonal flu-vaccine (non-live formulation) and the SARS-CoV-2 vaccine.

- Evidence suggests that long-lived plasma cells can still produce antigen-specific IgG to previously administered vaccines.

[1] Hill et al., "How I prevent infections in patients receiving CD19-targeted chimeric antigen receptor T cells for B-cell malignancies". Blood. 2020 Aug 20;136(8):925-935. doi: 10.1182/blood.2019004000.

This guidance document is an APPHON consensus document that included experts from Infectious Disease, Immunology and Oncology.

This document follows the recommendations put forth by the National Advisory Committee for Immunization in Canada. Refer to the *Canadian Immunization Guide* www.phac-aspc.gc.ca/publicat/cig-gci/p01-10-eng.php

This document does not replace good clinical care.

Routine Immunizations									
	6 months after HSCT	**7 months after HSCT**	**8 months after HSCT**	**12 months after HSCT**	**14 months after HSCT**	**16 months after HSCT**	**24 months after HSCT**	**27 months after HSCT**	**36 months after HSCT**
Influenza (Inactivated)	**X**		Live influenza vaccine is contraindicated for HSCT patients for at least 24 months post-HSCT and until deemed immunocompetent by the transplant physician.						
Pneu-C 20[1,2,3]	**X**	**X**	**X**						
DTaP-IPV-Hib				**X**	**X**	**X** (for children less than 7 years of age)	**X**		TAT serology If low, give a booster dose
MenC-ACYW				**X**					
(For asplenia) MenC-ACYW + Men B				**X**		**X**			
Hepatitis B				**X**	**X**		**X**		Serology for anti-HBs
HPV				**X**	**X**		**X**		
MMRV (combined vaccine)							**X**	**X** At least 3 months after 1st dose	IgG for measles and rubella AND varicella

See detailed recommendations on following pages.

INFLUENZA (Inactivated)								
	6 months after HSCT	**7 months after HSCT**	**8 months after HSCT**	**12 months after HSCT**	**14 months after HSCT**	**24 months after HSCT**	**27 months after HSCT**	**36 months after HSCT**
Influenza (Inactivated)	**X**[(a)]	Live influenza vaccine is contraindicated for HSCT patients less than 24 months post-HSCT and until deemed immunocompetent by the transplant physician.						

INFLUENZA

Annual seasonal administration starting before HSCT. Inactivated influenza vaccine must be administered at least two weeks prior to transplant conditioning or mobilization chemotherapy.

(a) Inactivated Influenza vaccine may be administered as early as four months post-transplant in outbreak situations with approval of oncologist. If administered less than six months post-transplant (i.e., 4 – 6 months), a 2nd dose may be administered four weeks later if there is ongoing circulation of virus in the community.

Children younger than nine years of age receiving influenza vaccine for the first-time post-transplantation require two doses administered at least four weeks apart.

Transplant recipients should receive the influenza vaccine yearly.

Annual influenza vaccine is strongly recommended for close contacts of pre- and post-transplant recipients (e.g., family members, household contacts, etc.). Either inactivated or live influenza vaccines may be administered to close contacts.

Note: Individuals who have received FluMist® should avoid close association with individuals with severe immunocompromising conditions (e.g., bone marrow transplants recipients requiring protective isolation) for at least two weeks following immunization.

Immunity screening after immunization is not recommended.

PNEUMOCOCCAL								
	6 months after HSCT	**7 months after HSCT**	**8 months after HSCT**	**12 months after HSCT**	**14 months after HSCT**	**24 months after HSCT**	**27 months after HSCT**	**36 months after HSCT**
Pneu-C 20	**X**	**X**	**X**		**X**		**X**	

PNEUMOCOCCAL

The minimum interval between Pneu-C20 doses is four weeks.

Children who have previously received at least one dose of Pneu-C13 or C15 will need to complete the series with Pneu-C20 with an additional dose of Pneu-C20 given with a minimum interval of 4 weeks.

Pneumococcal titer should be monitored one month after the 3rd dose. If non-immune consult the pediatric immunologist.

DTaP-IPV-HIB									
	6 months after HSCT	7 months after HSCT	8 months after HSCT	12 months after HSCT	14 months after HSCT	16 months after HSCT	24 months after HSCT	27 months after HSCT	36 months after HSCT
DTaP-IPV-Hib				**X**	**X**	**X**[(a)]	**X**		TAT serology. If low, give a booster dose[(b)]

DTaP-IPV-HIB

(a) Children younger than seven years of age should receive a 3rd dose 4-8 weeks following the 2nd dose. The minimum interval between each of the first three doses is four weeks and between the 3rd and 4th dose is six months.

Screen for tetanus antitoxin (TAT) after immunization at three years post-transplant. If the patient is on intravenous immune globulin (IVIG), serology should be delayed until three months after the completion of IVIG therapy.

(b) If TAT results indicate not immune for tetanus (< 0.1 IU/mL), administer a booster dose of DTaP-IPV/Hib. Ordering booster dose (if needed) should be done in consultation with the immunologist.

Note: Off-license use of DTaP-IPV/Hib – The higher dose of Diphtheria and Pertussis recommended by APPHON as immunity with lower doses in this population deemed suboptimal.

The immunization recommendations for the general population should be followed long term (i.e., after the TAT assessment and recommendations at three years).

Immunity screening for diphtheria, pertussis, polio and Hib is not recommended.

MENINGOCOCCAL								
	6 months after HSCT	7 months after HSCT	8 months after HSCT	12 months after HSCT	14 months after HSCT	24 months after HSCT	27 months after HSCT	36 months after HSCT
MenC-ACYW				**X**				

MENINGOCOCCAL

All children should receive a dose of Men-C-ACYW after HSCT.

Children younger than two years of age should receive Menveo® (not Menactra® or Nimenrix®) vaccine. Immunity screening after immunization is not recommended.

MENINGOCOCCAL (For Asplenia and Hyposplenia ONLY)

	6 months after HSCT	7 months after HSCT	8 months after HSCT	12 months after HSCT	16 months after HSCT	24 months after HSCT	27 months after HSCT	36 months after HSCT
MenC-ACYW (+ Men B)				**X**	**(X)**			

MENINGOCOCCAL

Children with asplenia or hyposplenia should receive 2 doses of Men-C-ACYW and 2 doses of Men B vaccine at least 8 weeks apart.

Children younger than two years of age should receive Menveo® (not Menactra® or Nimenrix®) vaccine and if Men B vaccine is indicated, Bexsero® should be used (not Trumenba®)

Immunity screening after immunization is not recommended.

Hepatitis B (HBVD)

	6 months after HSCT	7 months after HSCT	8 months after HSCT	12 months after HSCT	14 months after HSCT	24 months after HSCT	27 months after HSCT	36 months after HSCT
Hepatitis B				**X**	**X**	**X**		Serology for anti-HBs[(a)]

HEPATITIS B

Administer at double the dose used in the routine 3-dose schedule.

(a) If patient is on IVIG, serology should be delayed until 4 to 6 months after the completion of IVIG therapy.

*If antibody levels are suboptimal, a repeat HBV series is indicated. Recommending the 2nd series is the responsibility of the immunologist.

HPV

	6 months after HSCT	7 months after HSCT	8 months after HSCT	12 months after HSCT	14 months after HSCT	24 months after HSCT	27 months after HSCT	36 months after HSCT
HPV				**X**	**X**	**X**		

HUMAN PAPILLOMAVIRUS – Girls and Boys 12 years of age or older (regardless of previous immunization)

The minimum interval between dose 1 and dose 2 is four weeks and between dose 2 and dose 3 is twelve weeks.

Patients younger than 12 years of age may wait for HPV vaccination as part of school programs.
Immunity screening after immunization is not recommended.

MEASLES, MUMPS, RUBELLA, VARICELLA								
	6 months after HSCT	**7 months after HSCT**	**8 months after HSCT**	**12 months after HSCT**	**14 months after HSCT**	**24 months after HSCT**	**27 months after HSCT**	**36 months after HSCT**
MMR-V Combined vaccine						**X**[(a)]	**X**[(a)] At least 3 months after 1st dose	IgG for measles and rubella AND varicella after 2nd dose

MEASLES, MUMPS, RUBELLA and Varicella (MMR-V combined vaccine)

(a) If active chronic GVHD, live vaccines are contraindicated. A live vaccine may be administered after all immunosuppressive drugs have been discontinued for at least three months and the child is deemed immunocompetent by the immunologist for allogeneic patients and oncologist for autologous. Children on maintenance chemotherapy or immunomodulator therapy should not receive live vaccines until 3 months off therapy.

IVIG: Interval between IVIG and a live vaccine is dependent upon the dose of IVIG used and ranges between eight and eleven months. Refer to the *Canadian Immunization Guide* https://www.canada.ca/en/public-health/services/publications/healthy-living/canadian-immunization-guide-part-1-key-immunization-information.html?page=11 per discretion of the immunologist/oncologist.

Measles and rubella IgG level at 36 months (in case of delayed immunization with live vaccines, IgG level should be determined at least one month after the 2nd MMR).

If after two doses of MMR vaccine, measles IgG is negative or indeterminate consider non-immune to measles – no further doses of vaccine should be administered. If patient is exposed to measles in the future, prophylactic IG within six days of exposure should be provided.

Ordering booster dose (if needed) is the responsibility of the immunologist.

Even if the patient has previously developed shingles or chickenpox (pre or post-transplant), varicella vaccine should be administered.

All individuals with HSCT who have not received varicella vaccination post-transplant should be considered susceptible in case of exposure to VZV and should be offered VZIG.

Antiviral medications should be discontinued at least 24 hours before receipt of varicella-containing vaccines and should not be restarted until at least 14 days after vaccination.

MMRV combined vaccine can be administered in children 12 years and less and the separate MMR and Varicella vaccine should be administered to the children 13 years and older.

APPENDIX

- COVID vaccine schedule can start as early as 3 months post HSCT. See provincial guidelines for direction especially in regards to additional dose for immunocompromised patients.
    - Nova Scotia: https://www.nshealth.ca/coronavirusvaccine
    - Prince Edward Island: https://www.princeedwardisland.ca/en/topic/covid-19-vaccines
    - New Brunswick: https://www2.gnb.ca/content/gnb/en/corporate/promo/covid-19/nb-vaccine.html
- If questions about other vaccinations please contact IWK
- Ideally, absolute neutrophil counts and absolute lymphocyte counts should be greater than 1 x 10^9 cells/L
- Application of topical anesthetic creams (i.e., EMLA®, Ametop®) prior to immunizations is acceptable
- In presence of platelet level less than 20 x 10^9/L, bleeding disorder or patient receiving anticoagulant therapy it is recommended to use a small gauge needle (23 gauge or smaller) and apply firm pressure to the injection site for ≥ 2 minutes.