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SHORT REPORT

Immunization practices in acute lymphocytic leukemia and post-hematopoietic stem cell transplant in Canadian Pediatric Hematology/Oncology centers

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ABSTRACT

There are no Canadian immunization guidelines for children treated for malignancy. Guidelines do exist for patients who underwent hematopoietic stem cell transplant (HSCT), but they provide broad timeframes for initiating vaccination; there is no standard schedule. The optimal approach to immunization in these populations is unclear. We sought to describe immunization practices at Canadian Pediatric Hematology/Oncology centers. A 43-item online questionnaire was distributed to the 16 programs in the C^{17} research network of pediatric hematology/oncology centers to capture information on timing and criteria for immunization of patients with acute lymphocytic leukemia (ALL) and those who have undergone HSCT. At each center, 1–2 physicians or pharmacists completed the survey to reflect center-wide immunization practices. Responses were received from 11/16 (69%) programs; 11 respondents reported on practices for patients with ALL and 9 reported on practices for patients who are post-HSCT. In 5/11 ALL programs (45%) re-immunization is recommended routinely after chemotherapy, starting 3–6 months post-chemotherapy. In HSCT programs, timing of pneumococcal conjugate vaccination (PCV) varied from 3 months post-HSCT (4 programs) to 12 months post-HSCT (4 programs). Live vaccines were administered 24 months post-HSCT in 8/9 programs. All HSCT programs considered graft-versus-host-disease and 7 considered discontinuation of immunosuppression in immunization decisions. Pediatric hematology/oncology programs were divided in regards to re-immunization of patients with ALL post-chemotherapy. After HSCT, timing of PCV administration varied, with 4 programs initiating immunization later than Canadian guidelines recommend (3–9 months post-HSCT). These findings suggest a need to standardize immunization practices in these populations.

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Introduction

Children treated with chemotherapy for malignancy and/or who undergo hematopoietic stem cell transplant (HSCT) for malignant or non-malignant conditions appear to have persistent deficits in their immune function lasting months to years after chemotherapy or HSCT.[1,2] These children are at high risk of complications from vaccine-preventable infections such as pneumococcal infection,[3,4] which underscores the importance of immunization in these populations.

In children with acute lymphocytic leukemia (ALL), reduced antibody titers to specific vaccine antigens (e.g., tetanus, measles) have been observed after completion of the 2–3 year course of chemotherapy treatment, suggesting waning of immunity to vaccines received before diagnosis.[1,5,6] These findings have contributed to recommendations in the United Kingdom and Australia to administer booster immunizations, including diphtheria-tetanus-acellular pertussis (DTaP/Tdap), inactivated polio (IPV) and measles-mumps-rubella (MMR) vaccines starting 6 months after chemotherapy (Table 1).[7,8] In contrast, a recent Infectious Disease Society of America (IDSA) guideline made no recommendations regarding booster vaccinations, citing insufficient evidence for the need of such an approach.[9] In Canada, there are no specific recommendations regarding re-immunization of children with ALL.[10]

After autologous or allogeneic HSCT, the Canadian National Advisory Committee on Immunization (NACI) recommends immunization with 13-valent pneumococcal conjugate vaccine (PCV13) starting 3–9 months post-HSCT, with trivalent inactivated influenza vaccine beginning 4 to 6 months post-transplant and with other inactivated vaccines [e.g., DTaP-IPV, *Haemophilus influenzae* type b (Hib), meningococcal conjugate serogroups ACWY (MenC-ACWY), hepatitis B vaccine] starting 6–12 months post-HSCT (Table 1).[10] Live attenuated vaccines (e.g., MMR, varicella) can be administered after 24 months in patients without chronic graft-vs.-host disease (GVHD) and off immunosuppressive therapy for at least

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Table 1. Comparison of guidelines for immunization after ALL chemotherapy and post-HSCT.

Organization	NACI[10]	ATAGI[7]	EBMT[11]	RCPCH[8]	IDSA[9]
Country/Region	Canada	Australia	Europe	United Kingdom	United States
Immunization after ALL chemotherapy					
Vaccines recommended	No specific recommendation	DTaP or Tdap IPV MMR Hepatitis B HPV PCV13* Varicella	N/A	DTaP or Tdap IPV MMR Hib MenC-C	Routine immunizations only
Timing of immunization after chemotherapy	Not specified	6 months	N/A	6 months	3 months
Timing of initiation of immunization after HSCT					
Pneumococcal conjugate vaccine	3–9 months	6 months	3–6 months	15 months	3 months or later
Other inactivated vaccines†	6–12 months	6 months	6–12 months	12–18 months	3–6 months or later
Live vaccines‡	24 months	24 months	24 months	18–24 months	24 months

ALL, acute lymphocytic leukemia; ATAGI, Australian Technical Advisory Group on Immunization; EBMT, European Group of Blood and Marrow Transplantation; HSCT, hematopoietic stem cell transplant; IDSA, Infectious Disease Society of America; NACI, National Advisory Committee on Immunization; RCPCH, Royal College of Paediatrics and Child Health; DTaP, diphtheria-tetanus-acellular pertussis vaccine; Hib, *Haemophilus influenzae* type b conjugate vaccine; IPV, inactivated polio vaccine; MenC-C, meningococcal conjugate serogroup C vaccine; MMR, measles, mumps, rubella vaccine; PCV13, 13-valent pneumococcal conjugate vaccine.

* If previous age-appropriate dose not received.

† Includes tetanus, diphtheria, pertussis, *Haemophilus influenzae* type b, inactivated polio, hepatitis A, hepatitis B, human papillomavirus, quadrivalent meningococcal conjugate, meningococcal conjugate serogroup C vaccines.

‡ Includes measles, mumps, rubella, varicella.

3 months. Guidelines regarding the recommended timeframes for initiating vaccination vary between Canada, Australia, the US and Europe,[7,9-11] suggesting that uncertainty exists about the best time to initiate immunization to prevent early infections and achieve long-term protection.

Due to the controversy regarding booster immunization in patients with ALL and the lack of consistency in immunization guidelines for patients who are post-HSCT, there may be significant variation in practice between pediatric hematology/oncology and HSCT centers. We sought to describe current immunization practices for children with ALL and those who have undergone HSCT at pediatric hematology/oncology and HSCT centers in Canada.

Results

Responses were received from 11/16 (69%) programs (12/17 centers) in the C[17] group, representing the largest centers in Canada, and including all 6 programs that perform HSCT. Three programs that did not provide a response to the survey are among the smallest 5 programs in the C[17] network. Eight respondents provided information on immunization practices in ALL and post-HSCT, 3 provided information on practices in ALL only and one respondent provided information on practices post-HSCT only. Characteristics of respondents and the patient populations in their programs are described in Table 2. Seven of 11 (64%) programs had a local practice guideline for immunization of children with ALL and 8/9 (89%) programs had local immunization guidelines for children post-HSCT (3 programs follow patients who received their transplants at other centers). Vaccines were administered at primary care, public health and hematology/oncology clinics, with respondents from 8/11 (73%) ALL programs and 6/9 (67%) HSCT programs reporting that immunizations are delivered at more than one type of clinic.

Immunization practices in ALL

During intensive phases of chemotherapy, no program recommended routine immunizations and only 1/11 (9%) programs recommended influenza immunization. During maintenance chemotherapy, immunization is recommended in 3/11 programs with the following vaccines: trivalent inactivated influenza, PCV13 and meningococcal conjugate vaccine (MenC serogroup C and MenC-ACWY). In addition, hepatitis B vaccine and DTaP-containing vaccines are recommended by physicians in 2 programs, and in one program 23-valent pneumococcal polysaccharide vaccine (PPV23) is also recommended.

After chemotherapy, re-immunization is recommended in 5/11 (45%) programs, 3 of which are the same programs that recommend vaccination during maintenance therapy. Re-immunization is recommended either routinely (4 programs) or based on antibody titers (1 program). The recommended vaccines include DTaP, hepatitis B, meningococcal conjugate (MenC-C or MenC-ACWY), MMR and varicella. Four programs also recommend PCV13. In a sixth program, practice varies by physician, with some offering re-immunization while others do not. The timing of administration of immunizations after chemotherapy is shown in Table 3. In two programs, physicians consider patient age in decisions regarding restarting immunizations and in one program, immunologic markers are used to determine when to restart immunization: absolute lymphocyte count $\geq 1000/mm^3$, CD4+ T cell count $\geq 200/mm^3$ (Table 4).

Antibody titers are measured after chemotherapy "always" or "often" in 4/11 (36%) programs, "sometimes" or "rarely" in 3 programs, and "never" in 4 programs. Booster immunizations were routinely recommended after chemotherapy in 4/6 programs in which antibody titers were monitored at least "sometimes." In all centers where

Table 2. Characteristics of Survey Respondents and their Oncology or HSCT Programs.

	n	%
Position (N = 12)		
Division Head/Chief	2	17
Attending Physician*	9	75
Other	1	8
Time in current position		
<10 years	6	50
≥10 years	6	50
Immunization practice guideline		
ALL	7/11	64
Post-HSCT	8/9	89
ALL Programs (N = 11)		
New patients per year		
<10	1	9
10–24	6	55
≥25	4	36
Programs performing HSCT (N = 6)	6	67
Autologous HSCT performed per year		
<10	2	33
≥10	4	67
Allogeneic HSCT performed per year		
<10	1	17
10–19	3	50
≥20	2	33
Number of patients followed long-term post-HSCT (N = 9)		
1–19	4	44
20–29	2	22
≥30	3	33
Where immunizations are administered†	ALL n (%)	HSCT n (%)
Hematology/Oncology/HSCT clinic	4 (36)	4 (44)
Public Health clinic	4 (36)	2 (22)
Primary care physician	6 (55)	4 (44)

ALL, acute lymphocytic leukemia; HSCT, hematopoietic stem cell transplant.
* Fully licensed subspecialist.
† Locations where ≥25% of patients receive their vaccines, by program.

titers are measured at least sometimes, testing includes: varicella, hepatitis B and measles serology. Three programs also measure mumps and rubella antibodies, and 2 measure diphtheria and tetanus antibodies.

Immunization practices post-HSCT

In all programs, patients who have undergone HSCT receive the full primary immunization series followed by booster doses. The timing of administration of immunizations after HSCT is shown in Table 3. Other than the time since transplant, clinical features that influence initiation of immunization include chronic GVHD, discontinuation of immunosuppression, and type of transplant (allogeneic versus autologous) (Table 4). In one program patient age is considered in decisions regarding timing of initiation of inactivated vaccines, and in 2 programs different diphtheria-tetanus-pertussis-containing vaccines are used depending on the child's age (DTaP in children <7 years of age and Tdap in children ≥7 years of age). No programs consider patient age as a factor in timing of live vaccines. Physicians in 2/9 (22%) programs use one or more immunologic markers to guide immunization recommendations including: absolute lymphocyte count ≥1000/mm^3, CD4+ T cell count ≥200/mm^3 and antibody titers to hepatitis B and measles, mumps, rubella and varicella. In 4/9 programs, serologic responses to vaccination are measured "sometimes," "often" or "always," while in 5 programs responses are never measured. No significant differences in timing of initiation of immunization were noted between programs that measure serologic responses that those that do not.

Safety monitoring

Systems are in place to track adverse events following immunization (AEFI) in patients with ALL and those who are post-HSCT at 2 centers, and at a third center AEFI are monitored in patients immunized post-HSCT only. For three ALL programs and one HSCT program, the respondent was unsure if AEFI were monitored. At two of the centers that track AEFI, at least 40% of recommended vaccines are administered in the hematology/oncology or HSCT clinic. At the third center that tracks AEFI over 75% of vaccines are administered by primary care physicians. At 3/7 centers that do not track AEFI, vaccines are also regularly administered in hematology/oncology or HSCT clinics.

Discussion

In this survey of 69% of pediatric oncology programs and all programs performing pediatric HSCT in Canada, immunizations practices varied substantially. For patients who completed therapy for ALL, re-immunization practices were split: in 5 programs re-immunization with 4–5 vaccines is routinely recommended, while in 5 programs no additional vaccines are

Table 3. Timing of Earliest Administration of Immunizations after Chemotherapy or HSCT by Program.

	3 months n (%)	6 months n (%)	9 months n (%)	12 months n (%)	24 months n (%)	Not specified n (%)
ALL (N = 11)						
Inactivated vaccines*	4 (36)	6 (55)	—	—	—	1 (9)
Live attenuated vaccines	3 (27)	3 (27)	—	4 (36)	—	1 (9)
Post-HSCT (N = 9)						
Pneumococcal conjugate vaccine	4 (44)	1 (11)	—	4 (44)	—	—
Other inactivated vaccines†	—	3 (33)	1 (11)	5 (56)	—	—
Live attenuated vaccines‡	—	—	—	1 (11)	8 (89)	

ALL, acute lymphocytic leukemia; HSCT, hematopoietic stem cell transplant
* Excludes inactivated influenza vaccines.
† Excluding PCV13 and inactivated influenza vaccines, but including tetanus-diphtheria-acellular pertussis, *Haemophilus influenzae* type b, inactivated polio, hepatitis AB, hepatitis B, human papillomavirus, quadrivalent meningococcal conjugate, meningococcal serogroup C conjugate vaccines.
‡ Measles, mumps, rubella, varicella.

Table 4. Criteria Used by Physicians to Determine When to Administer or Recommend Vaccines after ALL chemotherapy or HSCT.

	Inactivated vaccines n (%)	Live vaccines n (%)
ALL (N = 11 programs)		
Age	2 (18)	2 (18)
Immunization history	3 (27)	6 (55)
Disease risk category*	1 (9)	1 (9)
Immunologic markers or titers	3 (27)	4 (36)
None other than interval since chemotherapy completed	6 (55)	3 (27)
Post-HSCT (N=9 programs)		
Age	1 (11)	0 (0)
Type of transplant†	2 (22)	3 (33)
Presence of GVHD	7 (78)	9 (100)
Discontinuation of immunosuppression	7 (78)	7 (78)
Treatment with monoclonal antibodies	5 (56)	6 (67)
Immunologic markers	2 (22)	1 (11)
None other than time from transplant	1 (11)	0 (0)

ALL, acute lymphocytic leukemia; GVHD, graft-versus-host disease; HSCT, hematopoietic stem cell transplant.
*Standard risk, high risk, very high risk.
†Allogeneic vs. autologous.

recommended. Among HSCT programs, the most notable difference was the variation in timing of PCV13; in 4 programs immunization is started 3 months post-HSCT while in 4 programs immunization is delayed until 12 months post-HSCT. Measurement of serologic responses to vaccines was variable for both populations.

Immunization practices for patients with ALL varied widely, reflecting the lack of evidence-based national guidelines. A recent survey of members of the American Society of Pediatric Hematology and Oncology (which included some Canadian members) similarly found that 42% of care providers always or often recommend re-immunization while 40% rarely or never recommend re-immunization.[12] In our study, immunization practices in 5/11 pediatric hematology/oncology programs were consistent with recommendations in the UK and Australia in routinely recommending DTaP-containing vaccines, meningococcal conjugate vaccine, hepatitis B, pneumococcal conjugate vaccine, MMR and varicella vaccine.[7,8,13] In 5/11 programs, no additional vaccines are recommended, a practice that is more consistent with the IDSA guideline.[9] These findings highlight the controversy that exists regarding the role of re-immunization in the management of children with ALL who have completed chemotherapy.

Previous studies suggest that adherence to existing guidelines for immunization after HSCT is suboptimal and could leave patients vulnerable to vaccine-preventable infections.[14-16] In one survey from the United States, Canada and Australia, adherence to the Centers for Disease Control and Prevention's immunization recommendations after HSCT ranged from 22–93% for each vaccine with many centers administering fewer than the recommended number of vaccine doses.[15] In our study, adherence to NACI guidelines was 100% for timing of initiation of inactivated vaccines other than PCV13 (6–12 months post-HSCT).[10] However, NACI recommendations for timing of PCV13 immunization (3–9 months post-HSCT) were followed by only 5/9 (56%) programs. The Australian, European and IDSA guidelines similarly recommend PCV13 immunization starting 6 months and 3–6 months post-HSCT, respectively.[7,9,11] Reasons for delaying PCV13 could represent concerns about the effectiveness or safety of early immunization, as the evidence supporting these guidelines is based on small studies.[17,18]

In 8/9 HSCT programs live attenuated vaccines are recommended at 24 months post-HSCT, and all programs consider immunosuppressive medications and/or the presence of chronic GVHD in making immunization recommendations, practices that are consistent with NACI guidelines. In contrast, NACI guidelines also recommend measuring serology after MMR vaccination to verify immune status, but most programs (5/9; 56%) reported that they never measure antibody levels after immunization.

Administration of vaccinations is delegated to a range of providers across the centers, including primary care, public health and hematology/oncology clinics, with most respondents reporting that immunizations are delivered at more than one type of clinic. Although not assessed in this study, this diffusion of responsibility for immunizations among different healthcare provider groups raises concern about the potential for fractured delivery of immunization services and missed immunization opportunities. Greater involvement of vaccine experts in managing these patients may lead to improvements in care.

This study had limitations. There was a degree of response bias. The individuals who reported on immunization practices for patients with ALL were either involved in the Canadian Immunization Research Network (CIRN) themselves or were identified by colleagues who were CIRN investigators and therefore, they likely had greater interest and experience in immunization than most oncologists. In contrast, 3/5 non-responding programs do not have representation in CIRN and they were mostly small programs. This survey also focused on center-wide immunization practices and may not necessarily reflect the practices of individual physicians. For these reasons, the results may not be generalizable to all pediatric hematology/oncology programs in Canada or elsewhere. However, the similarity between our findings regarding re-immunization of patients with ALL, and those of Sulieman et al[12] who surveyed individual physicians, suggests that our findings are likely to be representative of practices in North America. The key strength of the study is that it describes immunization practices from all centers performing HSCT and 70% of ALL programs, including the largest centers in Canada, and thus represents the institutional policies that apply to the large majority of these patients.

This survey demonstrates that institutional immunization practices vary markedly across Canadian pediatric hematology/oncology and HSCT programs, mirroring the variability in immunization guidelines and practices in different countries. Prospective studies comparing the immunogenicity and safety of different immunization schedules are urgently needed to better define the role of booster immunization in children with ALL and the optimal timing of immunization after HSCT. Due to the small numbers of patients with these conditions, such studies need to be multi-centered, preferably through existing research networks, such as the C[17] network, CIRN and the Children's Oncology Group. Such studies would support the

standardization of immunization guidelines for these patients in Canada and abroad.

Methods

Study design and Subjects

A 43-item self-administered online questionnaire was distributed between October and December 2014 to the 16 pediatric hematology/oncology and HSCT programs in Canada (representing 17 pediatric centers). All centers are members of the C^{17} research network, a collaborative network for multi-disciplinary and multi-center studies in pediatric hematology, oncology and HSCT. The questionnaire was sent via email to oncologists, HSCT specialists, infectious diseases specialists and clinical pharmacists with expertise in immunization in these populations. One to 2 individuals at each center were asked to complete the survey on behalf of their colleagues.

The survey was distributed to individuals identified by the study team as having immunization expertise and/or to pediatric hematology/oncology program heads who were asked to forward the survey to the appropriate individual(s) at their center. For four programs, the survey was only distributed to the program head. Survey reminders were sent via email approximately one month after the first mailing. Participants indicated their consent on the survey introductory page in order to proceed to the survey. This study received ethical approval from the IWK Health Centre Research Ethics Board.

Survey instrument and validation

The questionnaire was developed based on published surveys and existing immunization guidelines (see Supplemental Content).[10,12,14-16] Six co-authors (SH, VP, APH, LS, DT, WV) reviewed the questionnaire for face validity and comprehensibility, and the questionnaire was piloted among 4 physicians and 1 clinical pharmacist at 4 centers. Responses were analyzed for consistency, comments were reviewed, and the survey was modified to improve comprehensibility. The final questionnaire included questions regarding the respondent's current position and location, as well as detailed questions regarding timing of initiation of inactivated and live attenuated vaccines after chemotherapy or HSCT, the criteria used to determine when to initiate immunizations, use of serologic testing, whether additional booster doses of vaccines are given after chemotherapy for ALL and if systems are in place to track AEFI.

Statistical analysis

The questionnaire was distributed using Remark Web Survey® software. Statistical analysis was descriptive and was conducted using SAS version 9.3 (SAS Institute, Cary, NC).

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All authors report having no conflicts to declare.

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