VACCINATING CHILDREN AFTER CHEMOTHERAPY FOR ACUTE LYMPHOBLASTIC LEUKEMIA: A Canadian Immunization Research Network Study

Research Protocol

Study number: **SI02**

Protocol Date: **14 June 2017**

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1. Background and rationale

1.1 Acute Lymphoblastic Leukemia

Acute leukemias are the most common malignancies in children, accounting for 32% of all cancers in children <15 years of age. Acute lymphoblastic leukemia (ALL) accounts for 80% of childhood leukemia. The annual incidence of ALL is approximately 5 per 100,000 population, peaking at 9 per 100,000 among children 1 to 4 years of age.[1] With current chemotherapy protocols the prognosis is excellent with 5-year survival of over 85%.

1.1.1 Chemotherapy regimens and their immunosuppressive effects

At diagnosis, children are stratified as standard, high or very high risk, depending on clinical and genetic features. The clinical features that predict high risk ALL are: male sex, age <1 year or ≥10 years at diagnosis, presenting peripheral white blood cell (WBC) count ≥50 $x10^9$/l. Treatment consists of multiple phases of multi-drug systemic and intrathecal chemotherapy: induction, consolidation, interim maintenance, delayed intensification and maintenance therapy. Total treatment course is approximately 2 years for girls and 3 years for boys. Most pediatric oncology centres in Canada use the treatment protocols developed by the Children's Oncology Group (COG). Three centres use the protocols developed by the Dana-Farber Cancer Institute (DFCI) ALL Consortium.[2] Examples of standard and high risk COG and DFCI ALL protocols are shown in Tables 1 and 2.

Table 1. COG ALL chemotherapy protocol (AALL0932)

	Induction	Consolidation	Interim Maintenance I/II	Delayed Intensification	Maintenance
SR-ALL	5 weeks	4 weeks	8 weeks	8 weeks	to complete 2-3 years total therapy
	Vincristine, Dexamethasone, Pegaspargase; IT Methotrexate & Cytarabine	Vincristine, Mercaptopurine; IT Methotrexate	Vincristine, Methotrexate; IT Methotrexate	Dexamethasone, Vincristine, Doxorubicin, Pegaspargase, Cyclophosphamide Thioguanine, Cytarabine; IT Methotrexate	Vincristine, Dexamethasone, Mercaptopurine, Methotrexate; IT methotrexate
HR-ALL	5 weeks	8 weeks	9 weeks	8 weeks	to complete 2-3 years total therapy
	As above + Daunorubicin	As above + Cyclophosphamide, Cytarabine, Pegaspargase	As above with high dose Methotrexate + Leucovorin	As above	As above with Prednisone instead of Dexamethasone

SR, standard risk; HR, high risk; IT, intrathecal

Multi-drug chemotherapy leads to profound bone marrow suppression as well as specific impairment of innate, cell-mediated and humoral immune responses. Consequently, infection is the most common cause of treatment-related mortality, with a cumulative risk of 3%.[3-5]

Table 2. DFCI ALL treatment protocol 95-01.[2]

	Induction	CNS therapy	Intensification	Continuation
SR-ALL	4 weeks	3 weeks	30 weeks	Until 24 months continuous remission
	Vincristine, Prednisone, Doxorubicin Asparaginase; IT Cytarabine, IT Methotrexate, IT Hydrocortisone	IT Methotrexate & Cytarabine +/- cranial radiation	Vincristine, Prednisome Methotrexate 6-Mercaptopurine Asparaginase	Vincristine, Prednisome Methotrexate 6-Mercaptopurine
HR-ALL	4 weeks	3 weeks	30 weeks	Until 24 months continuous remission
	As above +/- Dexrazoxane	As above + cranial radiation for all	As above + Doxorubicin +/- Dexrazoxane	As above

Furthermore, while neutrophil counts return to normal after each cycle of chemotherapy, recovery of lymphocytes is much slower. Recovery of B lymphocytes has been observed to occur during maintenance chemotherapy, but T lymphocyte counts, particularly CD4+ T cells, remain low for over 6 months after chemotherapy.[6-8] Lymphocyte proliferation responses to mitogens and specific antigens may remain abnormal for 12 months or longer post-chemotherapy.[8, 9] Various risk factors for delayed immune reconstitution have been reported, including younger age, older age, and high-risk ALL.[6-8] Children with delayed recovery of adaptive immune function may remain at increased risk of invasive infections long after they have returned to school and other community activities where their risk of exposure is high.

1.2 Vaccine-preventable infections and waning vaccine-induced immunity

ALL disproportionately affects children under 5 years of age, most of whom have not completed their preschool immunizations at the time of diagnosis.[1] These children are at high risk of complications from vaccine-preventable infections such as measles, varicella-zoster, and *Streptococcus pneumoniae*.[10-13] Measles can be particularly severe in children with cancer, with 80% of patients suffering complications such as pneumonitis, and mortality of up to 70%.[12] Children with ALL who are non-immune to varicella are at high risk of disseminated disease leading to pneumonitis and hepatitis.[10] Among children and adults with leukemia, the risk of invasive pneumococcal disease (IPD) has been reported to be 10 to 12-fold higher than in the general population.[13, 14] Additionally, vaccine failures leading to invasive infections, such as *Haemophilus influenzae* type b (Hib), have been reported in fully immunized children with ALL who were later found to have decreased titres to multiple vaccines.[15, 16] Herd protection may mitigate the risk of vaccine-preventable infection associated with waning vaccine immunity. There has been a recent resurgence of vaccine-preventable infections, such as measles and pertussis related to decreased vaccine coverage and/or inadequate duration of vaccine-induced protection among healthy children.[17, 18] While overall vaccine coverage rates in Canada have been stable over the past decade, coverage for several vaccines is below the 90-95% level needed for reliable herd protection.[19, 20] Additionally, vaccine coverage is not uniform; areas with

large numbers of underimmunized children can be more susceptible to disease outbreaks.[21] Outbreaks have also occurred in communities with high vaccine coverage, for example in Quebec in 2011 where over 700 cases of measles occurred in a community with >90% measles vaccine coverage.[22] Children with ALL typically return to school and community activities while they are on maintenance therapy, which puts them at risk of exposure to infectious diseases. The failure of herd protection in these cases underscores the importance of ensuring optimal immunization of children with ALL.

There is increasing evidence that antibody titres to vaccine antigens decrease over time in children who were fully vaccinated prior to chemotherapy.[23-26] A systematic review found that 25-35% of patients who had completed chemotherapy had antibody levels to tetanus and diphtheria that were below protective levels and 70% were susceptible to pertussis.[26] Among 80 children with ALL treated between 2001 and 2010, approximately 30% of those who were seropositive to measles and 17% who were seropositive for varicella at diagnosis subsequently lost immunity to those antigens.[25] In another study of 100 ALL patients who were a mean of 2 years post-chemotherapy, only 42-86% had protective titres to routine childhood vaccines including Hib, hepatitis B, diphtheria and rubella, compared to 96-100% of healthy controls.[23] Seventy-three percent of subjects had non-protective titres to ≥2 antigens. Studies conducted prior to the introduction of universal infant pneumococcal conjugate vaccination (PCV) reported that pneumococcal antibody concentrations were significantly lower in children with ALL who were 3-6 months post-chemotherapy compared to age-matched healthy controls.[27, 28] No published studies have evaluated the impact of infant PCV immunization on pneumococcal titres post-chemotherapy.

1.3 Vaccination post-chemotherapy

Responses to booster immunizations given after chemotherapy are variable, with poorer responses observed in children with high-risk versus standard-risk ALL in some studies.[24, 26, 29] In one study of 46 children with ALL ages 1 to 18 years who were ≥6 months post-chemotherapy, immunization with one dose of combined diphtheria-tetanus-pertussis-polio-Hib vaccine (DTaP-IPV-Hib), followed one month later by measles-mumps-rubella (MMR) and meningococcal serogroup C conjugate vaccine (MenC-C) resulted in significant increases in antibody titres with over 90% of subjects achieving protective levels and/or achieving a ≥4-fold increase in titres.[29] At one year post-immunization there was evidence of long-term protection against tetanus and measles in all patients tested. Other studies similarly reported good short-term responses to DT, Hib and MMR vaccination, but long-term responses were not measured.[24, 30] No published studies have assessed the impact of PCV13 booster immunization on pneumococcal titres, but one study of 10-valent pneumococcal conjugate vaccine (PCV10) administered to children with ALL on chemotherapy found that 60% achieved titres >0.35 μg/ml (WHO standard for protection [31]) to 7/10 PCV serotypes.[32] These studies must rely on assessment of serologic correlates of protection because vaccine efficacy cannot be evaluated due to the low incidence of most vaccine-preventable infections in this small patient population.

Guidelines in the United Kingdom and Australia recommend booster doses of routine vaccines such as DTaP, IPV, Hib, MMR and MenC-C for all patients with leukemia starting 6 months

after chemotherapy, but compliance with guidelines appears to be suboptimal.[33-35] The Australian guidelines also recommend administering one dose of PCV13 at least 6 months after completion of chemotherapy in patients not previously immunized followed by 23-valent pneumococcal polysaccharide vaccine (PPV23). However, a recent guideline by the Infectious Disease Society of America (IDSA) made no recommendations regarding booster vaccinations, citing insufficient evidence of the benefit of such an approach.[4]

In Canada, there is no standard of care for immunization of children after chemotherapy for ALL. The National Advisory Committee on Immunization (NACI) recommends one dose of PCV13 followed by PPV23 in patients at high risk of IPD, including those with malignancies.[36]

1.3.1 Immunization Practices in Canada

To better understand immunization practices for patients with ALL at Canadian pediatric oncology centres, we conducted a survey of the 16 centres in the C[17] group of pediatric oncology and bone marrow transplant centres in Canada. The survey was launched in October 2014. The results revealed wide variability in practices among the 10 centres responded. Four centres routinely provide immunizations after chemotherapy and at a fifth centre antibody titres are routinely measured and booster doses are recommended for patients with low titres. At one centre, the respondent remarked that his/her personal practice was to routinely measure titres and offer booster vaccinations but his/her colleagues' practices varied. Four centres administer PCV13 and one administers PPV23 to children who have completed chemotherapy. Centres initiate immunization with inactivated vaccines either 3 or 6 months post-chemotherapy (at 4 and 6 centres, respectively), while live-attenuated vaccines are administered 3, 6 or 12 months post-chemotherapy across the ten participating centres. Respondents at only two centres reported that AEFI are monitored in patients with ALL, while three respondents were unsure.

1.4 Vaccine safety

Studies of vaccine safety in immunocompromised patients have primarily focused on live attenuated vaccines (e.g., MMR, varicella).[4, 37, 38] One study demonstrated a similar risk of herpes zoster after varicella immunization, compared to natural infection, in children with ALL on maintenance chemotherapy.[38] There is one report of death in a child with ALL after varicella immunization, although that child was receiving chemotherapy.[39] One study of 39 children immunized with PCV10 while on chemotherapy for ALL reported local reactions in 73% and systemic symptoms in 41%, most frequently diarrhea. Only one patient experienced fever.[32] The systemic symptoms were considered to be most likely chemotherapy-related. The risk of adverse events following immunization (AEFI) with inactivated vaccines is assumed to be similar in immunocompromised children compared to healthy children, but the data supporting this assumption are limited.[4] Further data on the frequency, severity and impact of AEFI in children with ALL are needed.

1.5 Rationale

NACI has identified vaccine safety and effectiveness in immunocompromised individuals as a research priority for vaccines recently introduced in Canada (e.g., PCV13).[36] Among

physicians caring for pediatric ALL patients, there is currently a lack of empirical scientific evidence to guide immunization practices, which has likely contributed to the variation in practices observed in our survey. Although universal PCV immunization programs have been in place for a decade or more in many developed countries, there is a paucity of literature evaluating these vaccines in children with ALL. Infants have been immunized routinely with PCV in Canada since at least 2006, and the 13-valent vaccine has been available since 2010. Most children completing chemotherapy for ALL would have been immunized in infancy with PCV7, but many would never have received a dose of PCV13 or PPV23, which is not routinely administered to healthy children. Due to waning humoral immune responses, children who received PCV13 prior to diagnosis with ALL may also benefit from an additional dose of PCV13, and from PPV23 immunization. It is unclear whether children with ALL are receiving all recommended immunizations and whether they would benefit from additional booster doses of other vaccines such as tetanus-diphtheria-pertussis-containing vaccines (i.e., DTaP) after they complete chemotherapy.

This study will be the first multi-centre study of vaccination in ALL survivors in Canada and among the largest prospective vaccination studies to date in this population. It will provide critical information to identify children with ALL who may be at greater risk for vaccine-preventable infections due to low antibody titres, and will assess immunogenicity and safety of PCV13 and DTaP-IPV-Hib in this population. The study results will support the development of immunization recommendations for children with ALL. This study will also test a methodology to assess vaccine immunogenicity and safety in a high-risk population that, if successful, will be expanded to other groups of immunocompromised children and adults, such as patients who received bone marrow transplants, have primary immunodeficiency or are on high dose steroids.

This study will be led by the Special Immunization Clinic (SIC) network as part of the Public Health Agency of Canada/Canadian Institutes for Health Research (PHAC/CIHR)-funded Canadian Immunization Research Network (CIRN), in collaboration with pediatric oncologists at the study sites. The SIC network, originally part of the PHAC/CIHR Influenza Research Network (PCIRN), was established in 2013 at 13 tertiary care centres across Canada to provide expertise in the clinical care of patients with prior AEFI and potential contraindications to immunization. SIC investigators employ a standard approach to patient assessment, vaccination and follow-up. De-nominalized data are transferred to a central database with patient consent. The network was designed as both a clinical service and a platform for research studies. Thus, the SIC Network is uniquely positioned to lead this study.

2. Objectives

- To identify risk factors for low baseline antibody titres to pneumococcal serotypes, tetanus, pertussis toxin, and varicella in previously immunized children diagnosed with ALL at ≥1 year of age who completed chemotherapy within 6-12 months, as compared to immunocompetent age-matched controls.
- To assess short and long-term immune responses to PCV13 followed by PPV23 in children immunized 6-12 months after completing chemotherapy for ALL.

- To assess short and long-term immune responses to a DTaP-IPV-Hib booster in children immunized 6-12 months after completing chemotherapy for ALL.
- To estimate the frequency of medically-attended AEFI in children immunized after completing treatment for ALL.

3. Methods

3.1 Study design

This will be a prospective multi-centre open-label clinical trial at 10 pediatric centres that are members of the SIC network and the C[17] council which is comprised of the heads of the 16 pediatric oncology and blood and marrow transplantation programs in Canada. Each participating site is run by a Site Investigator in conjunction with a nurse coordinator (SIC nurse). The coordinating site will be the Canadian Center for Vaccinology at the IWK Health Centre, Halifax, NS.

Children who were diagnosed with ALL at ≥1 year of age, are within 3-12 months of completing chemotherapy, and have not received immunizations other than influenza since completing chemotherapy will be eligible. As most centres initiate immunization at 6 months post-chemotherapy, children will be enrolled and immunized at the 6-month visit, where possible. Children can be enrolled as late as 12 months post-chemotherapy if they meet all other eligibility criteria. All participants will undergo a clinical assessment, and immunologic and serologic testing for pneumococcus, tetanus, pertussis and varicella. They will then be immunized with PCV13, DTaP-IPV-Hib, regardless of immunization history [unless PPV23 was received within the prior 12 months (see section 3.2.1)]. Other routine vaccines required as per provincial and centre-specific immunization policies will also be administered. Pneumococcal polysaccharide vaccine (PPV23) will be administered approximately 2 months after PCV13. Repeat serologic testing will be conducted at 2-3 months and 12-15 months after DTaP-IPV-Hib and PCV13 immunization to assess short and long-term immune responses.

Study visits and bloodwork will be coordinated with routine blood draws wherever possible. Baseline antibody titres will be compared to age-matched immunocompetent controls. Vaccine responses will be compared to healthy vaccine recipients in published clinical trials. Multivariable analysis will be conducted to identify predictors of low baseline antibody titres after chemotherapy and poor immune responses to vaccination.

Adverse events following immunization will be captured through standardized telephone interviews conducted by the SIC nurse coordinator on days 8-10 and 30-33 post-immunization. Severity of AEFI will be classified as outlined in section 5.3 and a formal causality assessment based on a published algorithm (e.g., [40]) will be conducted for all events of moderate impact or greater (see section 5.3.1 for definitions).

3.2 Subjects, recruitment and consent

3.2.1 Cases

Inclusion criteria

- Diagnosed with standard risk, high risk or very high risk ALL
- Age at diagnosis: ≥1 year of age (age at enrollment: ≥3 years)
- Completed chemotherapy 3 to 12 months prior to enrollment
- No evidence of ALL relapse or secondary malignancy
- No known primary immunodeficiency
- No receipt of pneumococcal or tetanus-containing vaccines since completing chemotherapy
- No history of allergy to any component of PCV13
- Caregiver and/or participant is English or French-speaking and able to provide written informed consent

Exclusion criteria

- Infantile ALL
- Evidence of disease relapse or secondary malignancy
- History of underlying primary immunodeficiency
- Transplant recipient
- Received intravenous immunoglobulin (IVIG) within past 9 months or other blood products within the prior 3 months.
- Children who received PPV23 within 12 months of enrollment will not be eligible to receive PCV13 or PPV23. These children can still participate in the baseline evaluation, receive DTaP-Hib-IPV vaccine, and have tetanus and pertussis serology measured at 2 and 12-15 months post-immunization.

3.2.2 Controls:

Inclusion criteria

- Children 3-18 years of age, age-matched to cases
- Caregiver and/or participant is English or French-speaking and able to provide written informed consent

Exclusion criteria

- History of primary or secondary immunodeficiency including aplastic anemia, malignancy, nephrotic syndrome, malabsorption or severe malnutrition
- Immunosuppressive therapy within 3 months of enrollment (excluding inhaled corticosteroids)
- Received intravenous immunoglobulin (IVIG) within past 9 months or other blood products within the prior 3 months.

3.2.3 Recruitment and Consent

The oncologists and/or clinic nurses will identify potentially eligible subjects with ALL.

Caregivers of eligible patients will then be approached to participate in the study during routine outpatient visits to the pediatric oncology clinic. The consent form will be reviewed with caregivers by a research nurse, oncologist or oncology clinic nurse. Participants' and caregivers' questions will be answered and written informed consent will be obtained.

Children 3-18 years of age who are not immunocompromised will be recruited as controls from among children requiring venous blood draws in the outpatient laboratory, siblings of participants with ALL, prior study participants who have consented to future contact, and other methods depending on the study site. Caregivers of potentially eligible children will be approached by study staff in the outpatient laboratory or clinic, or contacted by the study team via telephone, email or mail and invited to participate. As above, written informed consent will be obtained after the consent form is reviewed and the participants' and caregivers' questions have been answered. Controls will be frequency age-matched to cases to ensure that the age distribution of cases and controls is similar. Three participating sites will be responsible for recruiting approximately 75 control subjects. The coordinating site will conduct the age-matching of controls to cases.

4. Study Plan

4.1 Timeline

July–December 2014: Protocol development (pending final results of an institutional survey of immunization practices at pediatric oncology and HSCT centres)
January 2015–April 2015: External scientific review, finalize protocol
May – June 2015: Finalize REB documents, REB submission
November 2015–August 2017: Patient recruitment/enrollment (22 months)
April 2017–January 2018: Recruitment of control subjects
August 2018: Patient follow-up completed
December 2017–January 2019: Laboratory analysis; data analysis, presentation of preliminary results, manuscript preparation
January–March 2019: Final data analysis
March–May 2019: Complete final manuscripts, presentations

4.2 Visit procedures

The study will involve three clinic visits (with the option for a separate screening visit before visit 1) and four follow up telephone calls. Visits and blood draws will be coordinated with regular follow up visits in the oncology clinic wherever possible. Procedures are summarized in Table 3.

Table 3. Schedule of Study Activities

Procedures for patients	Visit 1	Follow up Phone call 8-10 days post V1	Follow up Phone call 30-33 days post	Visit 2 2 months Post V1†	Follow up Phone call 8-10 days post V2	Follow up Phone call 30-33 days post V2	Visit 3 12-15 months post V1

			V1				
Informed Consent	X*						
Past Medical History	X*						
Current Health Status	X*						
Medications	X*						
Review of Immunization Records	X*						
Vital signs	X						
Immune Markers (CBC, qIgs, T and B subsets)	X						
Vaccine serologies	X			X			X
PCV13 and DTaP Immunization	X						
PPV23 immunization				X			
Phone Call (adverse events)		X	X		X	X	

qIgs: quantitative immunoglobulins; *Maybe be conducted as part of a screening visit at 3-5 months post-treatment. †Visit can occur up to 3 months post-immunization.

Visit 1 (Baseline assessment):
After providing informed consent, participants with ALL will undergo a standardized health evaluation, including review of past medical history, current health status, and medications, and vital signs as part of routine clinical care. Immunization records will be obtained from the participant's vaccination card, medical chart, family physician or public health. Varicella serology results at time of ALL diagnosis (measured as part of routine care) will be obtained from the medical record. The above activities can be completed as part of a separate screening visit at 3-5 months post-treatment, with visit 1 then scheduled at 6 months post-treatment to collect bloodwork and administer immunizations.

Baseline laboratory evaluation will include complete blood count, quantitative serum immunoglobulins (IgA, IgG, IgM), peripheral blood T and B cell subsets and antibody titres to the following vaccine antigens: tetanus toxoid, pertussis toxin (PT), varicella, and pneumococcal serotype-specific IgG. If serum immunoglobulins, T and B cell subsets or antibody titres were measured within one month prior to enrollment, those results can be obtained as baseline results, in lieu of repeating the testing.

Participants will be immunized with PCV13, DTaP-IPV-Hib (If DTaP-IPV-Hib is not available, DTaP-IPV and Hib may be administered separately) in addition to the "catch-up" vaccines

required according to the schedule currently followed at their centre. Vaccines will be administered in the SIC or oncology clinic, where possible, but may be administered by the primary care physician or public health. Vaccines must administered within two months of the baseline assessment and within 12 months of completing chemotherapy. The SIC nurse will obtain vaccination details from the vaccine provider within 7 days of the vaccination visit.

Telephone follow-up for AEFI:
A study nurse will contact caregivers (or participants where appropriate) by telephone on days 8-10 and 30-33 after each immunization to elicit local and systemic symptoms and their severity using a standard questionnaire.

Visit 2 (2 months post-immunization)
Serologic responses will be measured to tetanus, PT and pneumococcus. PPV23 will be administered. If necessary, this visit can be delayed to 3 months post-immunization.

Visit 3 (12-15 months after visit 1):
Serologic responses will be measured to tetanus, PT and pneumococcus.

Blood sampling will be coordinated with routine blood draws, which are conducted at most follow up visits.

Controls:
Past medical history will be reviewed for any excluding conditions and once informed consent has been obtained, immunization records will be obtained as described above. Serum will be collected to measure "baseline" antibody titres to tetanus, PT, varicella, and pneumococcal serotypes, based on the vaccinations received. There will be no further follow-up of controls.

4.3 Obtaining, Handling, Storage, Shipment of Specimens

Whole blood (up to 15 ml for visit 1 and 5ml for visits 2 and 3) will be collected by venipuncture. Specimens will be labelled with the participant's study number and the date the sample was drawn. Samples will be processed on-site for complete blood cell count and differential, quantitative IgG, IgA and IgM levels and T and B lymphocyte subsets.

4.3.1 Immunologic assessment

Quantitative immunoglobulins
Up to 5 ml of whole blood will be collected for baseline quantitative measurement of total IgA, IgG and IgM levels. Samples will be processed at the local clinical laboratory according to standard procedures and denominalized results will be transferred to the coordinating centre. At some centres this testing is conducted as part of routine clinical care.

Lymphocyte subsets
Up to 5 ml of whole blood will be collected for baseline quantitative measurement of T, B and NK lymphocyte subsets. Samples will be processed for flow cytometry at the local laboratory according to standard procedures and denominalized results will be transferred to the coordinating centre.

4.3.2 Serologic testing

Up to 5 mL of whole blood will be collected in a serum separator tube by venipuncture. After collection, blood will be kept at room temperature for 30 minutes to clot. Blood will then be centrifuged for 10 minutes at approximately 2500 RPM. Serum will be separated, aliquoted and frozen at -20°C in the local clinical or research laboratory.

Samples will be batch shipped on dry ice to the Canadian Center for Vaccinology's research laboratory at the IWK Health Centre in Halifax, NS approximately every 3-6 months where they will be stored at -80°C until they are processed locally and/or shipped to other laboratories as below.

Tetanus, pertussis toxoid and varicella IgG measurement will be conducted at the Canadian Center for Vaccinology laboratory using validated enzyme immunoassays.

Pneumococcal serotype-specific IgG levels to vaccine serotypes will be measured at McGill University Health Centre.

4.4 Modifying/Discontinuing Planned Vaccination/Treatment

4.4.1 Temporary Contraindications

Prior to immunization, possible contraindications to vaccination will be reviewed. If temporary contraindications are present, vaccination will be postponed and re-attempted within the allowable time frame for enrolment (up to 12 months post-chemotherapy).

Temporary contraindications to vaccination are as follows:

- An acute illness with or without fever (temperature > 38.0ºC).

4.4.2 Definite Contraindications

Subject has a known hypersensitivity to any component of the vaccine.

4.5 Clinical Supplies

As per policies at each study site. Where additional supplies are needed above what is considered routine clinical care, the costs will be covered in the study budget.

4.6 Products

Only licensed vaccines will be administered to participants including: PCV13 (Prevnar®13, Pfizer Canada, Inc.), PPV23 (Pneumovax® 23, Merck Canada Inc., or Pneumo 23®, sanofi pasteur Ltd.) and DTaP-IPV-Hib (Pediacel®, sanofi pasteur Ltd, or Infanrix®-IPV/Hib, GlaxoSmithKline Inc).

4.6.1 PCV13

This vaccine will be administered according to NACI guidelines for children at high risk of IPD, with the exception that all participants will receive a dose of PCV13, regardless of whether they

have previously received a dose of PCV13 after 12 months of age and prior to inititation of chemotherapy. This practice is already conducted routinely at four Canadian pediatric oncology sites, based on our recent survey. However, as per NACI guidelines, if a participant received PPV23 within 12 months of enrolment, they will not be eligible to receive PCV13.

4.6.2 PPV23

This vaccine will be administered according to NACI guidelines for children at high risk of IPD. Children who have previously received PPV23 will not be reimmunized.

4.6.3 DTaP-IPV-Hib

This formulation of diphtheria-tetanus-pertussis vaccine is licensed for children up to 7 years of age due to the increased risk of local reactions in older children and adolescents from the higher doses of diphtheria toxoid and acellular pertussis antigens. Administration of this vaccine to all participants regardless of age would be in keeping with current guidelines in the UK and Australia for patients who have completed chemotherapy for ALL. Additionally, based on our survey, the majority of pediatric centres administer DTaP-IPV-Hib to all bone marrow transplant recipients regardless of age due to evidence of improved vaccine responses in this population, in keeping with current IDSA guidelines.[4] The administration of the Hib component is consistent with NACI guidelines for patients with hematologic malignancies.

If DTaP-IPV-Hib is not available, DTaP-IPV plus Hib vaccine may be given.

5. Surveillance, Monitoring and Assessment

5.1 Immunologic Status

Immunologic status will be assessed by quantitative measurement of total IgA, IgG and IgM and by assessment of T, B and NK lymphocyte subsets, as available at the local laboratory. At a minimum the following will be assessed on all patients:

- total white blood cell count, total lymphocyte count, total and percentages of: total T cells (CD3+), , CD4+ T cells, CD8+ T cells, CD4/CD8 ratio, B cells (CD19+), and NK cells (CD56+/CD16+).

Where available, in addition to the above, an expanded panel of cell surface markers will be measured to determine total and percentages of the following subpopulations:

- memory T cells (CD3+/CD4+/CD45RO+)
- naïve T cells (CD3+/CD4+/CD45RA+)
- regulatory T cells (CD3+/CD4+/CD25+)
- activated T cells (CD3+/CD4+/HLA-DR+)
- memory B cells (CD19+/CD27+)
- unswitched B cells (CD19+/sIgD+)

5.2 Immune Responses to Vaccines

Vaccine antigens to be tested include tetanus, pertussis toxoid, varicella and 14 pneumococcal vaccine serotypes (1, 3, 4, 5, 6B, 7F, 8, 9V, 9N, 12F, 14, 18C, 19F, 23F). Of the pneumococcal

serotypes tested, 10 are included in both PCV13 and PPV23 (1, 3, 4, 6B, 7F, 9V, 18C, 19F, 23F) and 3 are only included in PPV23 (8, 9N, 12F). Vaccine responses will be determined by measurement of GMT to vaccine antigens pre-vaccination, 2 months and 12-15 months post-vaccination, and calculating GMT ratios. An adequate vaccine response will be defined as GMT ratio ≥4 (post-vaccination/pre-vaccination). For pneumococcal serotypes, GMT ≥0.35 μg/ml is the World Health Organization accepted correlate of protection in clinical trials,[31] while GMT ≥0.50 μg/ml has been used in other studies of immunocompromised children.[27, 41] The proportion of participants with GMT at or above these thresholds at baseline, at 2 months post-PCV13, and at 12-15 months post-PCV13+PPV23 immunization will be reported for each serotype. Vaccine titres will also be reported as "seropositive" or "seronegative" for tetanus and varicella.

5.3 Adverse Events

5.3.1 Definitions

Adverse event following immunization (AEFI): Any untoward medical occurrence in a patient that is temporally associated with vaccination and not clearly attributable to another known cause [42].

Serious adverse event (SAE): The Public Health Agency of Canada defines a serious adverse event following immunization as any untoward medical occurrence that:

- Requires in-patient hospitalization or prolongation of existing hospitalization for >24 hours
- Results in permanent disability
- Is a congenital anomaly or birth defect
- Is fatal

High impact AEFI: event that results in hospitalization for 24hrs or less or medical supervision out of hospital or requires ≥3 physician assessments for AEFI and/or leads to disability >3 days (unable to perform daily activities, unable to go to work, unable to attend school).

Moderate impact AEFI: event that requires an unscheduled physician visit, including emergency department visit or new or change in medication or leads to 1-3 days of disability.

Low impact AEFI: event managed by immunization clinic staff, with telephone advice or during previously scheduled appointment, and/or resulting in <24 hours of disability.

5.3.2 Adverse Event Monitoring

A study nurse will contact caregivers by telephone on days 8-10 and 30-33 post-immunization to elicit local and systemic symptoms and their severity using a standard questionnaire. Patients with AEFI requiring medical attention will be reviewed by the site investigator according to SIC network protocols, including a causality assessment using a published algorithm.[40]

Decisions regarding reimmunization of patients who experience AEFI will be made by the SIC investigator in consultation with the oncologist, patient and their family.

5.3.3 Reporting of Serious Adverse Events

AEFI will be reported to public health authorities according to provincial and national guidelines. All SAEs will be reviewed by the principal investigator and discussed with co-investigators in a timely manner, as appropriate. AEFI will be reported to public health as per local guidelines. There will be no external safety monitoring board as all vaccines are currently approved for use in this population and will be provided per standard of care.

6. Data Management and analysis

6.1 Responsibility for the analysis

The Principal Investigator will take primary responsibility for the analysis. The analysis will be conducted by data analysts at the Canadian Center for Vaccinology (CCfV), IWK Health Centre.

6.2 Sample size and Power

Approximately 278 new cases of ALL are diagnosed annually in Canadian children <15 years of age.[1] We estimate that approximately 50-60% of children diagnosed with ALL will complete chemotherapy, and consent to participate in the study. We expect to recruit 75–80 children over the enrollment period. To ensure adequate power (>75%) to assess differences in vaccine responses according to treatment protocol, at least 30 subjects will be recruited from centres using DCFI protocols, with the remainder recruited from COG centres. Seventy-five age-matched control subjects will be recruited. If at least 60% of controls have protective antibody titres, a sample of at least 75 cases will give 77% power to detect a ≥20% absolute difference in the proportion of cases achieving seroprotection. This sample size will also give 90% power to detect a standardized difference in mean log titre of ≥0.53 between cases and controls.

Safety assessment: With a total sample size of 75 vaccinees, the probability of detecting at least one occurrence of an AEFI that occurs at a frequency of ≥2% in the population is 0.78 and the probability of detecting an AEFI that occurs at a frequency of ≥1% in the population is 0.53.

6.3 Variables

6.3.1 Outcomes

The primary outcomes are the proportion of participants with protective titres (≥0.35 μg/ml) to the PCV13 serotypes tested, at baseline (compared to age-matched controls), 2 months and 12-15 months post PCV13+PPV23.

Secondary outcomes include baseline GMTs and frequency of protective titres to varicella, pertussis toxin and tetanus among ALL patients versus controls, short-term (baseline to 2 months after vaccination) and long-term (baseline to 12-15 months) vaccine responses to DTaP, based on GMT ratios, the proportion of subjects with protective titres (e.g., tetanus, varicella) and/or the

proportion with an adequate immune response (defined as GMT ratio ≥4 at 2 and 12-15 months post-vaccination).

Safety assessment: The primary outcome is frequency of AEFI of moderate impact or greater (see definitions in section 5.3). The secondary outcomes are frequency of any AEFI and frequency of AEFI deemed to be causally associated with vaccination.

6.3.2 Independent variables

Demographics: Patient's month/year of birth, sex, province of residence

Medical history: Age at diagnosis of ALL, disease risk category (standard risk, high risk or very high risk), treatment protocol used, time to disease remission, total length of treatment, current disease status, vaccine-preventable infections (before and after re-immunization).

Immunization history: number of doses of each vaccine received prior to ALL diagnosis and while receiving chemotherapy, vaccine products received, age at immunization, type of vaccine provider, interval from last chemotherapy to immunization, and varicella serology results at ALL diagnosis.

Immunologic status: absolute lymphocyte count, total IgG level; total T cells, CD4+ T cells, CD8+ T cells, CD4/CD8 T cell ratio, memory and naïve T cells; total, memory and naïve B cells, NK cell counts.

6.4 Statistical Methods

Immune responses: Immune markers (see 5.2) will be compared to age-specific reference values. Baseline GMTs with 95% confidence intervals and proportion with protective titres at baseline will be reported for cases and controls, stratified by interval since last vaccination. Varicella titers will be compared pre-chemotherapy (i.e., at diagnosis) and post-chemotherapy and the proportion with loss of immunity will be reported. The proportion of subjects with GMT ratios ≥4 or protective titres at 2 and 12-15 months post-vaccination will be reported for pneumococcal vaccines (PCV13+PPV23) and DTaP-IPV-Hib, stratified by age, ALL treatment protocol (COG versus DFCI), interval from last chemotherapy to immunization, and ALL risk category. Vaccine responses will be compared to the expected responses in healthy children based on published clinical trials. Differences among categorical variables will be assessed by Pearson's χ^2 test or with Fisher exact test when expected cell sizes are <5. Independent predictors of low baseline GMTs to tetanus toxoid and pneumococcal serotypes and of an adequate immune response to PCV13+PPV23 vaccination and DTaP-IPV-Hib booster will be assessed using multivariable regression models.

Safety assessment: The frequency of low impact, moderate impact and high impact or serious AEFI will be reported by vaccine type, age and ALL risk category, and compared to the published frequencies in healthy children. The frequency of events deemed to be related to vaccination based on the causality algorithm will also be reported.

All statistical analyses will be conducted using SAS® version 9.4 (Cary, NC).

6.5 Data Management

Data management will be the responsibility of the data manager at the CCfV. Data will be stored on a secure server at the CCfV and all files will be password-protected. All source documents, including consent forms and copies of data collection forms, will be stored in a locked cabinet in a secure area at each study site. Source documents will be retained by site investigators for 10 years after study completion.

7. Ethical Considerations

This research protocol will be submitted to the Research Ethics Board (REB) at each participating site for ethical approval, along will all other necessary documents. At each site, the study will be initiated once approval from the local REB has been received.

This study will be conducted in accordance with the latest version of the Declaration of Helsinki, ICH Good Clinical Practice regulatory guidelines, and requirements regarding ethical committee review, and other statutes and regulations regarding the protection of the rights and welfare of subjects participating in the study.

7.1 Potential Harms and Benefits

Clinical assessments will be performed as per routine clinical care. Blood samples for this study will be collected in conjunction with routine blood draws for clinical care when possible and the minimum additional volume required to conduct the required tests will be collected (5 to 15 ml). There is the risk of discomfort related to venipuncture in some patients with ALL who would only require blood by fingerstick for their routine tests (e.g., CBC).

Participants with ALL may experience adverse events following PCV13, PPV23 or DTaP-IPV-Hib immunization. For most participants, administration of these vaccines will be consistent with NACI guidelines. Expected adverse events include local reactions, fever, headache, and malaise. In patients who have previously received a full infant series of PCV13 (2, 4 and 12 months) prior to chemotherapy, they may be at higher risk of developing a large local reaction at the injection site (pain, swelling, erythema ≥10 cm diameter). Such reactions can be managed with acetaminophen or non-steroidal anti-inflammatory agents. There is also a risk of large local reactions after DTaP-IPV-Hib in children ≥7 years of age. As discussed in section 4.6, the vaccine schedule proposed in this study is in keeping with current practice at some Canadian centres and in other jurisdictions. There is a small risk of unexpected adverse events. Participants will be monitored for adverse events as outlined above.

There will be direct benefits to participants with ALL. They may receive a more detailed clinical and immunological assessment than would be routinely conducted, and will receive close follow up after vaccination. In some cases they will receive additional vaccines that may not be routinely administered at all sites and which are expected to confer additional protection against

invasive pneumococcal disease, tetanus, diphtheria and pertussis. Their immunological and serological test results will be shared with site investigators who will discuss them with the primary oncologist, participant and family, as appropriate for clinical care. However, due to the need batch samples and to test pre and post-vaccination samples concurrently for some assays, results may not be available in a timely manner. The information learned from this study will support the development of immunization guidelines for patients with ALL that will lead to improvements in care. In this study, the benefits outweigh the potential harms.

For control participants, participation in this study involves minimal to low risk. Participants who already require venipuncture for another indication will only be asked to agree to have a small additional sample (3-10 ml) drawn for study purposes. The only risk is related to a breach of their confidential information which will be minimized by the measures outlined below. For participants undergoing venipuncture only for the purposes of this study, the potential harms include pain, bleeding, or bruising, fainting, and very rarely, infection. These discomforts are brief and transient. There will be no direct benefits to controls.

Individual results will not be routinely available to healthcare providers of controls as the clinical relevance of such results in immunocompetent children following the routine immunization schedule is uncertain. However, if the principal and/or site investigator determines that antibody titers are sufficiently low to raise concerns regarding an unidentified health problem in a participant, the results will be sent to the primary care provider with recommendation for follow up and/or referral for further evaluation.

7.2 Alternative treatments/management

As discussed above, there is no accepted standard of care for immunization of patients after chemotherapy for ALL and practices vary between centres. The alternative to PCV13 and PPV23 boosters would be no additional vaccination against pneumococcus and clinical assessment of febrile episodes and empiric antibiotics if serious bacterial infection is suspected. Alternatives to DTaP-IPV-Hib immunization would be to postpone immunization in children who are up to date for age or to administer Tdap or Tdap-IPV (with reduced diphtheria and pertussis antigens) for children ≥7 years of age. DTaP-IPV is an alternative in children <7 years of age who require a booster dose.

7.3 Informed Consent Process

The consent form will be reviewed with caregivers by the SIC nurse, research coordinator, the oncologist or oncology clinic nurse. All participants/controls or their primary caregiver will be asked to consent to the following: permit study staff to access the patient's chart and contact other healthcare providers as necessary to retrieve immunization records and other clinical information, collection of additional blood for serology, transfer specimens and clinical data to the coordinating centre in Halifax (CCfV) and to send serum specimens to McGill University for pneumococcal serotype-specific IgG testing (if necessary). Some participants (ALL and controls) will also be asked to consent to venipuncture for study bloodwork, if venipuncture is not required for routine blood work. Consent will also be sought to allow future contact for participation in other studies.

In addition to the above, participants with ALL or their caregivers will be asked to consent to: administration of PCV13, PPV23 and DTaP-IPV-Hib vaccines, and telephone and/or email contact from study team to collect information on AEFI. Those who have contraindications to or refuse one or two specific vaccines may still be included in the study. Participants and caregivers' questions will be answered and written informed consent will be obtained.

7.4 Confidentiality of Data

Confidentiality will be maintained within legal limits in the review of study records and consent forms, which may contain the identity of the subject. All appropriate measures will be taken to minimize the risk of a breach of confidentiality. Access to documents with personal identifiers including consent documents and patient contact information will be restricted to the site investigator and research nurse. Participants will be assigned a unique identifier that will be used on anonymized data collection forms and blood samples sent to the coordinating centre. Results of serological tests conducted and/or coordinated by the lead site will be transmitted to study sites using the patient's unique identifier. All measures will be taken to ensure that participants' confidentiality is maintained from samples send to, and results obtained from, external labs. Only denominalized data will be entered into the centralized database. The study site will be entered as a two-digit code and only the month and year of birth of the patient will be collected and entered to minimize the risk of patients being identified by their clinical information. Once the data have been verified and submitted to the central research database, the data will be locked preventing further changes. Access to the database will be restricted to the data manager and data analyst. The database will be stored on a password-protected secure server that will only be accessible to study staff.

7.5 Monitoring, Auditing, and Archiving

The study will not be monitored by an external agency. Audits or inspections may be made by the Research Ethics Board at the coordinating site or sub-sites to ensure that the study has been conducted in accordance with the protocol and ICH/GCP. The investigator will retain all source documents on-site, including consent forms and copies of case report forms for 2 years after completion of the study. Study records will be stored in long-term off-site storage for a minimum of 10 years.

7.6 Participant compensation

Participants will receive a $10 gift card as a token of appreciation for their participation.

7.7 Dissemination of results

Traditional and non-traditional dissemination methods will be used, including publications (2-3 manuscripts expected), presentations at national and international scientific meetings, presentations to expert committees advisory to public health, to the C^{17} Council, and Children's Oncology Group.

8. Budget

This study is funded by Canadian Institutes for Health Research and the Public Health Agency of Canada as part of the Canadian Immunization Research Network. In addition, Pfizer will be approached to provided in kind support to supply PCV13 to children who are not eligible for coverage under their provincial immunization programs (approximately 50 individuals).

Table 4. Overall Budget Summary

CI1302.CIRN Three Year (2014-2017) Project Budget Summary	
Fixed Costs for Lead Site*	9,676
Fixed Costs for 9 Subsites*	54,720
Variable Costs Vaccine Safety Evaluation†, N = 150	23,400
Variable Costs Vaccine Immunogenicity†, N = 200	35,950
Data Management and Analysis	25,208
Travel to conference (2x $1500)	3,000
Publication costs ($1000)	1,000
Laboratory Testing Costs	147,402
TOTAL BUDGET	**$ 300,356**

*Includes personnel costs (research coordinator) and expendables; †Includes personnel costs for patient enrollment, field supplies, compensation

Table 5. Sample subsite Budget*

CI1302.CIRN Three Year (2014-2017) Project Sub Site Budget		
Costs by Position and Type:		
SIC Nurse/Coordinator ($50/hr + 20% benefits):		
REB submission and renewals	$	2,880
Field Administration		1,800
Study Site Closure		360
Subject costs		
Vaccine Immunogenicity		
ALL Patients (3h/subject), **N = 20**		3,540
Controls (1.8h/subject), **N = 15**		1,620
Vaccine Safety Evaluation (2.6/subject), **N = 20**		1,560
Participant compensation ($10/participant) N=35		350
Expendables:		
Communications: Phone/Fax/Teleconference		200
General Office Supplies		200
Photocopying/Printing		200
Archival of Study Documents		200

Laboratory Shipping Costs		600
Vaccine Immunogenicity Field Supplies		550
TOTAL BUDGET	**$**	**14,060**

*Based on estimated number of patients recruited at sites recruiting control subjects. *Site budgets do not include lab testing costs, which should be invoiced quarterly

8.1 Budget Description

8.1.1 Personnel costs

Research coordinator/nurse
Fixed costs: Site set-up & coordination (50 h per site in year 1 and 20h per site in years 2-3)
Prepare documents for REB approval and renewal, develop contacts with personnel in oncology clinic and outpatient laboratory (e.g., booking clerks, clinic nurses, physicians) to ensure that study personnel are notified when eligible patients will be seen, and that data forms are completed and informed consent requested. Store consent forms, source documents and patient contact information. Additional 15h per year allocated to lead site to coordinate receiving/shipping/storage of samples and collection of case report forms.

Variable costs:
ALL patients: Explain the study and consent form, and invite the patient to sign the consent form. Complete clinical evaluation, review immunization records, complete case report forms. Coordinate bloodwork and administer immunizations. Conduct telephone interviews after vaccination to assess the occurrence of AEFI, report AEFI. Transmit case report forms and patient samples to the coordinating center in Halifax where data will be entered in the central database. Respond to the queries regarding the information on that patient.

Control participants: Approach participants in outpatient laboratory, describe study, and invite them to participate. Review eligibility, obtain informed consent, coordinate blood collection, obtain immunization record, submit information to data centre.

Data manager & Statistical Analyst
Include database development, data entry at coordinating site, data cleaning, development of the statistical analysis and conduct of the analysis.

Financial administrator
Develops study budget, drafts contracts for subsites and coordinates payment.

8.1.2 Laboratory costs

Include cost, clinical lab set up fees, baseline and post-immunization vaccine serologies for cases and controls, and immunologic testing (e.g., T and B cell subsets) when not covered as part of routine clinical care, shipping costs and field supplies.

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