Title:	A prospective cohort study to define infectious burden, the seroprevalence of vaccine preventable pathogens and immune recovery in the first year following completion of therapy in patients with acute lymphoblastic leukemia (ALL)
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ABBREVIATIONS AND DEFINITIONS OF TERMS

ALL	Acute lymphoblastic leukemia
CCSS	Childhood Cancer Survivor Study
CHOP	Children's Hospital of Philadelphia
COG	Children's Oncology Group
CRB	Central Review Board
CT	Computed Tomography
DFCI	Dana-Farber Cancer Institute
HCT	Allogeneic Hematopoietic Cell Transplantation
HMH	Household Material Hardship
IgG	Immunoglobulin G
IRB	Institutional Review Board
IPD	Invasive Pneumococcal Disease
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
PMBCs	Peripheral blood mononuclear cells
REDCap™	Research Electronic Data Capture
Tfh	T follicular helper cells

ABSTRACT

Context:

Advancements in therapy have led to significant improvement in outcomes for children diagnosed with acute lymphoblastic leukemia (ALL), with overall survival rates now exceeding 90%. Although this therapy is lifesaving, it is well known to impact vaccine- and infection-acquired immunity. The morbidity and mortality associated with infection is significant but education, early diagnosis and prevention through vaccination has the potential to improve outcomes. Assessing infection risk and longitudinal recovery of immune function post-ALL therapy are necessary to establish evidenced based therapeutic approaches.

Objectives:

There are three main objectives to be accomplished by Aim 1 and Aim 2. Aim 1 will be to determine the overall infection incidence rate within the first year following completion of therapy for ALL, compared with the incidence of infection in matched healthy controls during the same time period. Aim 2 will describe seroprevalence for pneumococcus, varicella, and measles at approximately 3, 6, and 12 months following completion of therapy in patients with ALL and describe B and T lymphocyte subset recovery, specifically CD4+ T follicular helper cells (Tfh), using peripheral blood mononuclear cells (PMBCs) at about 3, 6, and 12 months following completion of ALL therapy

Study Design:

This study will assemble a prospective, multicenter observational cohort of approximately 115 patients that are completing ALL chemotherapy at one of several pediatric hematology/oncology centers in the US (Children's Hospital of Philadelphia (CHOP), Lurie Children's Hospital of Chicago, Seattle Children's Hospital, Helen DeVos Children's Hospital, Children's Hospital at Vanderbilt, Christus Children's Hospital (Baylor College of Medicine), and Children's Hospital Los Angeles). Consented subjects will have a baseline enrollment visit followed by monthly check-ins via phone and/or chart review to determine if the enrolled patient had any documented viral or bacterial infections or symptoms (Aim 1) and 2) in-person visits at roughly 3, 6, and 12 months post-completion of ALL therapy to obtain blood samples to perform immune function studies (Aim 2).

For comparison of infection rates in patients post-ALL therapy to those of healthy control patients, once the follow-up period for the enrolled ALL cohort patients has ended, a cohort of matched healthy control patients will be assembled. Controls will be selected at a ratio of 3:1, with the full healthy control cohort including up to 330 total patients. The healthy control patients will be followed for the same one-year period as their matched ALL cohort patients. Control patients will be selected from patients who received care at CHOP beginning in 2022 and matched to ALL cohort patients based on age and sex.

Setting/Participants:

This is a multicenter study at several pediatric hematology/oncology centers in the US (CHOP, Lurie Children's Hospital of Chicago, Seattle Children's Hospital, Helen DeVos Children's Hospital, Children's Hospital at Vanderbilt, Christus Children's Hospital (Baylor College of Medicine), and Children's Hospital Los Angeles). The study cohort will consist of up to 110 evaluable patients prospectively enrolled over the course of this study. Eligible patients include: Children, adolescents, and young adults diagnosed with B or T ALL at age 12 months or older; have completed up-front ALL therapy within the past three months or will complete ALL therapy in the upcoming three months, and are three years of age or older at time of enrollment. Patients who have a diagnosis of infant ALL, evidence of disease relapse, have a history of primary immunodeficiency (except related to Down Syndrome), received a stem cell transplant or cellular immunotherapy, or prior malignancy or condition requiring chemotherapy other than for current ALL diagnosis will be excluded.

All matched healthy control patients will be selected from the Children's Hospital of Philadelphia's Pediatric Research Consortium patient population regardless of where their matched ALL cohort patient was enrolled in the study.

Study Measures:

Aim 1 will capture any infection documented at any inpatient or outpatient encounter documented by the managing medical team in the first year after completing ALL chemotherapy. An incident infection rate will be calculated for the cohort and compared with that of age- and sex-matched healthy controls during the same time period. The secondary aim will assess the seroprevalence for pneumococcus, varicella and measles among study subjects at approximately 3, 6, and 12 months after completion of therapy. This aim will also describe B and T lymphocyte subset recovery at these same timepoints. The outcomes for Aim 1 and Aim 2 will be described by certain demographic characteristics and underlying diagnoses, as well as ALL treatment protocol. Additionally, laboratory reports will be prospectively collected. These data will serve to define the infection rate in the first year after completing ALL chemotherapy and inform immune recovery overall and to specific vaccine preventable illnesses (i.e. varicella, measles, and pneumococcus).

FIGURE 1: STUDY DIAGRAM

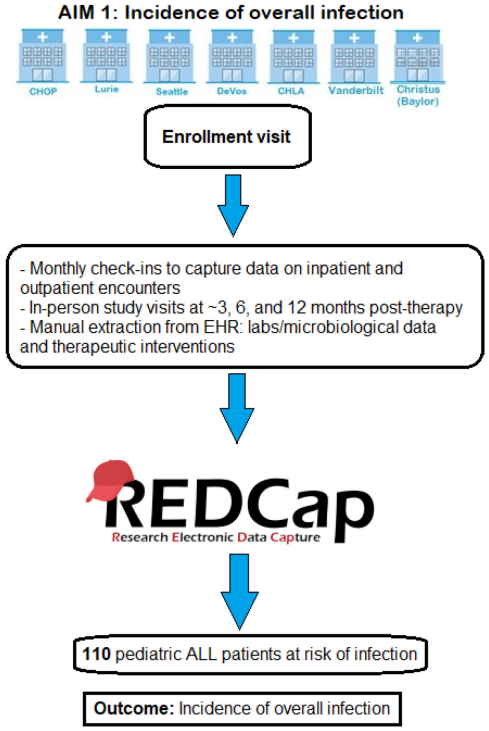
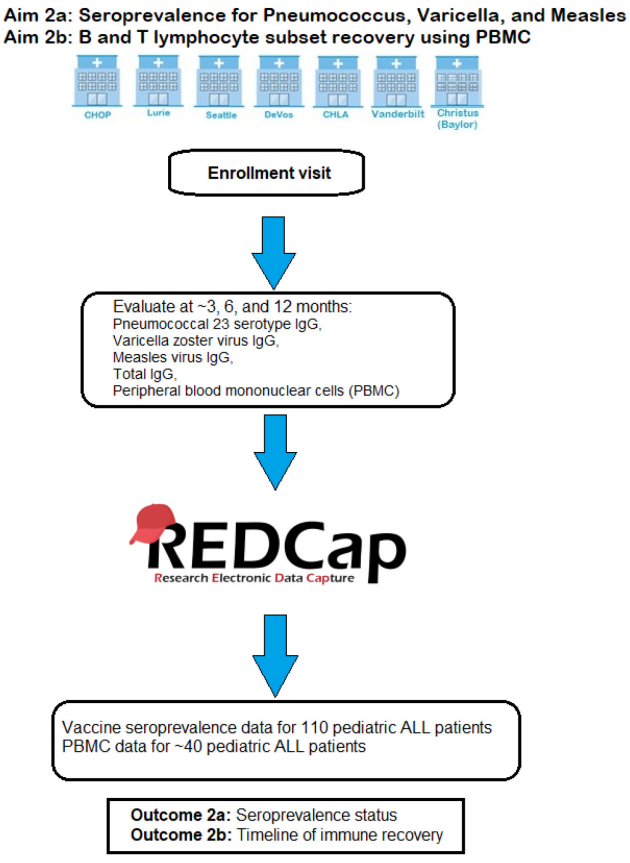


FIGURE 2: STUDY DIAGRAM



1 BACKGROUND INFORMATION AND RATIONALE

1.1 Introduction

The treatment modalities of childhood cancer often have a significant impact on the immune system on survivors of childhood cancer. Although there is a robust body of literature that describes immunological outcomes, testing recommendations, and revaccination guidelines after allogeneic hematopoietic cell transplantation (HCT), immunological assessments are not routinely included in surveillance guidelines for survivors of childhood cancer that have not received HCT. As a result, survivorship care providers might not fully consider the impaired recovery of a child's immune system after cancer treatment if the child has not undergone HCT. Currently, survivors of childhood cancer who received standard therapy and missed scheduled vaccinations during their cancer therapy restart their vaccination schedule anywhere between 6 to 12 months after completion of treatment. For patients that completed a vaccine series, the Children's Oncology Group (COG) Hematopoietic Cell Transplant/ Immune/Dermatology Late Effects Taskforce recommends that providers and survivors consider either the use of boosters for previously administered vaccines, or the measurement of titers on which to base the administration of boosters. Despite these recommendations there are limited data on timing of immune reconstitution after ALL chemotherapy and effectiveness of the response to vaccines if administered. It is also acknowledged that there is a paucity of data on the frequency and outcome of infections among survivors in the first year after completion of therapy. Determining the frequency of infection in the first year post chemotherapy and documenting the recovery of immune function overall and to specific vaccine preventable pathogens will provide foundational data to guide current clinical decision-making and inform future clinical trials.

1.2 Relevant Literature and Data

Advancements in therapy have led to significant improvement in outcomes for children diagnosed with ALL, with overall survival rates now exceeding 90%. Although this therapy is lifesaving, its use is well known to impact vaccine- and infection-acquired immunity.[1, 2] As a result, infection remains a significant cause of morbidity and mortality during therapy.[3, 4] Published literature has documented that children with ALL have a 10-fold higher risk of invasive pneumococcal disease (IPD) during treatment for their cancer, with the highest risk occurring during maintenance chemotherapy.[5, 6] Importantly, this risk likely persists beyond the period of therapy receipt. The Childhood Cancer Survivor Study (CCSS) reported that survivors of all cancer were 1.6 to 2.7 times more likely to be hospitalized for infection >5 years following the completion of therapy compared with age-matched and sex-matched individuals in the general population.[7] While these data are compelling there is a paucity of data documenting the frequency of infections or type of infections that occur in the first year following completion of therapy in children and adolescents with ALL.[4, 8] As such, clinicians do not have the necessary information to discuss infection risk with parents and their patients in this post-therapy period.

Additionally, there are limited data regarding the retention of seroprevalence for vaccine preventable infections during this post chemotherapy period.[9] Significant interest exists in revaccinating children and adolescents after completion of therapy for ALL, however, the

necessity of such an intervention has not been clearly defined.[10] Studies completed to date document that some children have low antibody titers to vaccine antigens immediately following treatment with therapy.[1, 11, 12] However, these studies did not consider the possibility that patients further removed from their therapy will have more robust immune function recovery inclusive of vaccine antigen specific immune response. It is necessary to assess longitudinal recovery of immune function post-ALL therapy to better inform the need for revaccination among these children.

The proposed multicenter study will serve to define infection rates in the post-ALL therapy period in children, adolescents, and young adults and define the seroprevalence for vaccine specific antigens as well as presence of lymphocyte subsets at discrete time-points after therapy completion. These data will be immediately informative to clinicians aiming to manage expectations of parents for infection risk in their child post ALL therapy. Additionally, this prospective cohort represents an ideal opportunity to compare management decisions for children regarding timing of vaccination following completion of ALL therapy. Currently, The National Comprehensive Cancer Network (NCCN) recommend that survivors of childhood cancer who received standard (non- HCT) therapy and missed scheduled vaccinations during their cancer therapy should be given all vaccinations that were missed, beginning at 6 to 12 months after completion of treatment. Based upon lower-level evidence, the NCCN recommends that survivors of childhood cancer who were fully vaccinated before diagnosis, and who were treated with chemotherapy or radiotherapy (non- HCT), or both, engage with their provider in a shared decision making to determine approaches to revaccination that might be considered for the individual survivor[11].

One such approach might be to administer booster doses for all routine vaccinations without checking pre-vaccination titers. A different approach would be to measure antibody titers to determine levels of seroprotection first and then recommending booster doses if inadequate levels of seroprotection are found. Finally, in the absence of data for necessity to administer booster dosing, some centers may elect not to measure antibody titers or provider booster dosing. Not surprisingly, these options have led to variability in practice, even when centers have developed institution-specific guidelines.[13] A survey of Canadian pediatric oncology centers found wide variation in the performance of post-treatment titers and reimmunization practices for survivors of ALL who have not had HCT.[14] Data from this descriptive study will serve to inform future comparative trials designed to optimize vaccination protocols in the period after completion of ALL therapy.

At the end of 2024, the Children's Oncology Group reported data from a randomized controlled trial revealing improved effectiveness of ALL chemotherapy regimens inclusive of the novel biological agent blinatumomab. The improved outcomes of patients receiving ALL chemotherapy inclusive of blinatumomab has led to immediate transition to this regimen as standard of care for most patients with ALL. While blinatumomab may have improved effectiveness for cure of cancer it may alter immune reconstitution trajectories in the survivorship period.[15] Because most of this study cohort was enrolled prior to the institution of blinatumomab as standard of care, it is uniquely positioned to now enroll ALL survivors that have or will have received blinatumomab as part of their chemotherapy

regimen. Including blinatumomab recipients will provide exploratory data on potential differences in immune reconstitution between patients receiving this new standard of care relative to prior standard of care ALL chemotherapy regimens.

1.3 Compliance Statement

This study will be conducted in full accordance all applicable local Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46 and the HIPAA Privacy Rule. All episodes of noncompliance will be documented. The investigators will perform the study in accordance with this protocol, will obtain consent and assent, and will report unanticipated problems involving risks to subjects or others in accordance with The Children's Hospital of Philadelphia IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

2 STUDY OBJECTIVES

2.1 Primary Objective (or Aim)

Aim 1: To determine the overall infection incidence rate within the first year following completion of therapy for acute lymphoblastic leukemia and compare that rate with the rate of infections occurring in age- and sex-matched healthy control patients during the same time period.

- Sub-aim: To examine infection incidence in patients who received the monoclonal antibody blinatumomab as part of their ALL treatment protocol versus that of patients who did not receive blinatumomab.

2.2 Secondary Objective (or Aim)

Aim 2a: To describe total IgG levels and specific seroprevalence for pneumococcus, varicella, and measles at approximately 3, 6, and 12 months following completion of therapy in patients with ALL

Aim 2b: To describe B and T lymphocyte subset recovery, specifically CD4+ Tfh, using PMBCs at approximately 3, 6 and 12 months following completion of ALL

- Sub-aim: To examine the immune function markers as outlined above in patients who received the monoclonal antibody blinatumomab as part of their ALL treatment regimen versus patients who did not receive blinatumomab.

3 INVESTIGATIONAL PLAN

3.1 General Schema of Study Design

This is a prospective, multicenter observational study that will assemble a cohort of approximately 115 patients that recently completed or are about to complete ALL therapy at

one of several pediatric hematology/oncology centers in the US (CHOP, Lurie Children's Hospital of Chicago, Seattle Children's Hospital, DeVos Children's Hospital, Children's Hospital at Vanderbilt, Christus Children's Hospital (Baylor College of Medicine), and Children's Hospital Los Angeles), including a sub-cohort of 20-25 patients who received blinatumomab as part of their chemotherapy regimen. The same 115 individuals will contribute to both Aim 1 and Aim 2 (Figure 1 and Figure 2). Only patients receiving care at a participating site will be eligible for enrollment in this cohort.

3.2 Total Number of Study Sites/Total Number of Subjects Projected

3.2.1 Duration of Study Participation

Patients will be followed from the date of enrollment until the first of the following events: approximately one year from completion of therapy, loss to follow-up or death.

Data abstraction from the medical record will be used to determine their end of therapy date. Their medical record will also be examined to collect specified relevant data related to reported infectious history as well as vaccination history. The in-person enrollment visit will require approximately one-hour of direct contact with the patient and caregiver to obtain consent (and when necessary, assent) and to complete the enrollment encounter. Once enrolled, followed by in-person visits at approximately 3, 6, and 12 months. At these visits an interim infectious history will be obtained and patients will have blood drawn for research assays as detailed below. These visits and the associated blood draw will be aligned with regularly scheduled oncology visits. The blood specimen will be drawn by the oncology nursing team and/or phlebotomy and whenever possible will be obtained at the same time as a clinical blood draw. Between in-person visits, study staff will contact caregivers for enrolled patients via phone call, text message, or email (as preferred by caregiver) to capture interim infection events. If text message or email is used to contact caregiver, but additional information is needed, a phone call will be made when necessary.

At the end of participants' study follow-up periods, age- and sex-matched healthy control patients will be identified from the CHOP Pediatric Research Consortium (PeRC) for comparison. Three controls will be randomly selected from a list of otherwise healthy individuals with similar age and sex and matched to each ALL patient enrolled. Infection events will be captured for these controls during the same time period the study participant was followed to compare the rate of infection events in the post-ALL therapy cohort with that of matched healthy controls.

3.2.2 Total Number of Study Sites/Total Number of Subjects Projected

The study will be conducted at seven investigative sites in the United States. Other sites may be added in the future. It is expected that approximately 115 subjects will be enrolled over the course of this study to produce 110 evaluable subjects. Evaluable patients will be defined as patients that are enrolled and at least one blood specimen collected.

For each of the 110 enrolled evaluable subjects in the ALL cohort, at the end of the follow-up period, three age- and sex-matched healthy control patients will be selected for comparison, to assemble a cohort of 330 total healthy control patients. The full cohort,

including both ALL patients and 3:1 matched controls, is anticipated to include 440 evaluable patients.

3.3 Study Population

3.3.1 Inclusion Criteria for ALL Cohort

1. Children, adolescents, and young adults ages 3 years to 31 years diagnosed with B or T ALL at age 12 months or older

2. Completed ALL chemotherapy within the past three months or will complete ALL chemotherapy in the upcoming three months (+/- 4 weeks)

    - **Blinatumomab sub-cohort (n = 20-25):** received ALL chemotherapy including the monoclonal antibody blinatumomab

3. Three years of age or older at time of enrollment.

3.3.2 Exclusion Criteria for ALL Cohort

1) Diagnosis of infant ALL

2) Evidence of disease relapse

3) History of primary immunodeficiency (except related to Down Syndrome)

4) History of a stem cell transplant or cellular immunotherapy

5) History of prior malignancy or condition requiring chemotherapy other than for current ALL diagnosis.

Subjects that do not meet all the enrollment criteria may not be enrolled. Any violations of these criteria must be reported in accordance with IRB Policies and Procedures.

3.3.3 Inclusion/Exclusion Criteria for Matched Healthy Controls Cohort

Matched healthy control patients will be selected based on age- and sex-matching to ALL cohort patients. All healthy patients who received care at the Children's Hospital of Philadelphia beginning in 2022 during the follow-up period that the ALL cohort patients are followed for the study will be eligible for inclusion in the matched cohort.

Patients with a history of any oncologic diagnosis or other condition that could predispose them to a higher risk of infection (e.g., primary immunodeficiency except related to Down syndrome, receipt of chemotherapy or immunomodulating drugs for treatment of any condition, etc.) will be excluded from the healthy controls cohort to ensure a comparator group that mirrors the typical population of healthy children as closely as possible.

4 STUDY PROCEDURES

4.1 Screening

A registry of patients diagnosed with ALL that are expected to complete therapy on or after December 1, 2021 will be complied to identify potentially eligible patients. Subjects will be screened for eligibility in accordance with inclusion and exclusion criteria outlined in section 3.3. The following will be performed during screening:

- Medical record review to identify potentially eligible patients
- Completion of a screening log for all screened patients to ensure study eligibility
- Approach eligible patients for informed consent and, if appropriate, child assent

4.2 Visit schedule

4.2.1 Visit

Once enrolled, subjects will have a baseline visit, followed by in-person visits at approximately 3, 6, and 12 months. Prior to or at the time of the baseline visit, vaccination records will be obtained. At the baseline and follow-up visits an interim infectious history will be obtained. Patients will have blood drawn for research assays as detailed below at 3-, 6-, and 12-month visits.

4.3 Observational Period

Patients will be followed up to approximately one year from enrollment. Patients will also have specified relevant data collected from prior to the day of enrollment. During the observational period, the following will be performed:

- Data abstraction from the Medical Record

4.4 Subject Completion/Withdrawal

Subjects may withdraw from the study at any time without prejudice to their care.

5 STUDY EVALUATIONS AND MEASUREMENTS

5.1 Screening and Monitoring Evaluations and Measurements

5.1.1 Medical Record Review

Variables to be abstracted into the REDCap™ database from the medical charts of ALL cohort patients enrolled at each site will include the following:

- Date of study days
- Weight
- Height
- Demographics (sex, race, ethnicity)
- Underlying conditions (e.g., type of leukemia)
- Co-morbid conditions
- Laboratory values (e.g. Creatinine, AST, ALT, Bilirubin, coagulation profile, WBC, platelets)
- Level of illness (e.g. need for ICU admission, intubation, vasopressors)
- Immune suppression therapies most recently associated with the qualifying condition
- Vital status at last date of follow-up
- Vaccination records
- Social determinants of health-related data (e.g. block group number (zip code plus 4) of residence, insurance type) (Optional – to be collected only for ALL cohort patients/families who consent to having these data collected and for healthy control patients)

Results from the following reports will be collected when available

- Pathology reports
- All radiology reports
- Microbiology results
- Non-culture mycology testing (e.g., Histoplasma urine antigen)
- Interventional radiology reports
- Surgical and procedural reports (e.g. bronchoscopy, eye and sinus exams)

Variables to be collected for matched healthy control cohort patients selected from CHOP's PeRC include:

- Date of study days (assigned to mirror the follow-up period of the matched ALL cohort patients)
- Demographics (sex, race, ethnicity, age)
- Underlying conditions
- Co-morbid conditions
- Laboratory values (e.g. Creatinine, AST, ALT, Bilirubin, coagulation profile, WBC, platelets)
- Details of any infection-related healthcare encounters occurring during the assigned study period (e.g. date of infection(s), lab results related to infection, physical examination findings, medications)
- Level of illness (e.g. need for ICU admission, intubation, vasopressors)
- Vaccination records
- Social determinants of health-related data (e.g. block group number (zip code plus 4) of residence, insurance type)

Results from the following reports will be collected when available and related to infections occurring in the study follow-up period:

- Pathology reports
- All radiology reports
- Microbiology results
- Non-culture mycology testing (e.g., Histoplasma urine antigen)
- Interventional radiology reports

5.1.2 Laboratory Evaluations

5.1.2.1 Baseline Blood Specimen Collection

Patients enrolled in the ALL cohort will have blood collected at approximately 3, 6, and 12 months once inclusion criteria are met.

A maximum of 25 ml of whole blood will be collected into separate tubes and processed for eventual testing as detailed below. Any subject that is less than 5 kg is not eligible for the study. Therefore, no more than 5 ml/kg of blood will be obtained from any subject during a

12-week period. Processed specimens will be stored at -80°C at each site. Approximately every 3 to 6 months, specimens will be batch shipped from participating sites to the central laboratory where antibody testing will be performed. Relevant CHOP specimens will be tested for immune function evaluation. Results will not be available to clinicians in real time. Subjects will have the option to consent to storage of excess blood samples for future non-genetic and genetic studies. These sample remnants will be held at a central laboratory.

5.1.2.1.2 Blood Specimen Testing Pneumococcal, Varicella zoster virus (VZV), and Measles virus immunoglobulin G (IgG) and Total IgG for ALL cohort participants

Blood samples collected at each visit will be processed for serum extraction. Serum will be stored locally and batched shipped to the central laboratory for performance of the following antibody specific assays: Pneumococcal 23 serotype specific IgG (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). These 23 Pneumococcal serotypes were included because, as a group, they account for approximately 90% of invasive pneumococcal infections. Additionally, varicella zoster virus (VZV) and measles virus IgG assays will be performed. Testing for these assays will be performed by Mayo Clinic BioPharma Diagnostics. Participant results will be compared to standard age specific reference ranges of healthy children.

Serum from these samples will also be used to obtain a total IgG level to aid in interpretation of pneumococcal, varicella, and measles IgG results. This testing will be performed at the CHOP Translational Core Laboratory.

5.1.2.1.3 Laboratory Analysis for Peripheral Blood Mononuclear Cells and CD4+ T-Follicular Helper Cells for ALL cohort participants

For a subset of enrolled ALL cohort patients (estimated to be 40, including up to 10 patients who received blinatumomab as part of their chemotherapy regimen), blood samples will be processed for cellular immunophenotyping. Blood samples will be collected into sodium heparin tubes at approximately 3, 6 and 12 months following the completion of therapy, processed for peripheral blood mononuclear cells, and cryopreserved. Deep cellular immunophenotyping of the recovering immune system will be performed using high dimensional flow cytometry and T cell receptor (TCR) sequencing in the laboratory of Dr. Laura Vella at the Children's Hospital of Philadelphia:

(1) High Dimensional Flow cytometry: The frequency and phenotype of B and T lymphocytes, with a specific interest in Tfh, will be measured across the three time points and compared to healthy reference controls. The high-dimensional (30-marker) panel has been optimized for use on the Cytek Aurora spectral cytometer and will allow for deep phenotyping beyond Tfh and B cell subsets, resulting in >200 features of returning mononuclear cells.

(2) Sorting and TCR sequencing of Tfh and non-naïve CD4 T cells: The clonal diversity will be measured by isolating desired cell populations with a BD Aria II cell sorter and extracting nucleic acid for Adaptive Biotechnology (TCR) sequencing. Clonality scores will be tracked over time and compared to the TCR sequence diversity of healthy subjects.

These cellular assays will serve as exploratory measures of immune recovery and vaccine readiness after ALL therapy.

5.1.3 Social Determinants of Health Survey

Participants in this study will be offered the opportunity at the time of enrollment to participate in a brief, one-time Household Survey (Appendix A) intended to capture self-reported data related to social determinants of health and household material hardship (HMH) (e.g., food and/or housing insecurity, lack of access to reliable transportation, etc.).[16] The survey will be hosted within the study REDCap™ database, and the participant (age 18 or older) or parent/guardian will be provided a secure link to access the survey after consenting to participate. Limited English proficiency participants and families will also be eligible to complete the survey but will do so in person via an interpreter if they consent to survey participation.

The Household Survey to be used in this study is based on an abbreviated version of the Household Material Hardship surveys developed by the Dana-Farber Cancer Institute (DFCI) and utilized in clinical trials DFCI 16-001 (NCT03020030), COG AALL1731 (NCT03914625) and COG ANBL1531 (NCT03126916), with demonstrated feasibility of data collection and minimal site or family burden. The Household Survey,[17] developed by the Bona Lab at the DFCI, includes single-item evaluations of self-reported race, ethnicity and health literacy utilizing a validated 1-item screen,[18] educational attainment, HMH, and household income.

Data collected via this survey is intended to be exploratory and will be used to inform further study of possible disparities in infection rates and immune reconstitution.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint

The primary endpoint for Aim 1 of this study is to determine the incident infection rate in a cohort of subjects in the first year following completion of ALL therapy. Infections will include both clinical and/or microbiologically confirmed infections. All unique infections for a given subject will be captured and included in the final infection rate per person time estimate. Infections will also be reported in subsets of infections such as microbiologically confirmed (i.e., bacteremia, urinary tract infection or pneumonia with a positive sputum culture) or clinically defined infections. Additionally, a specific subset of infections to be described are sinopulmonary infections. This will include a medical encounter for otitis media, sinusitis, or pneumonia for which an antibiotic was prescribed. Infection events for matched healthy control patients will also be captured and used for comparison to the incident infection rate determined for the ALL participants.

The primary endpoint for Aim 2a is the proportion of patients with measles, varicella and pneumococcus antibodies at each study timepoint. Of note, pneumococcal serology results will include 23 serotypes: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F. Patients with detectable antibody to 50% or more of these serotypes will be considered to have seroprevalence for pneumococcus. This aim will also describe the total IgG levels at each time point at the individual and cohort level. Understanding the total IgG level will inform interpretation of vaccine-specific serology measures.

6.2 Secondary Endpoint

The secondary endpoint for Aim 2b will be the frequency and phenotype of circulating B and T lymphocytes, which will be measured at roughly 3, 6, and 12 months for each subject. We specifically have an interest in the recovery of Tfh as they provide required help to B cells in the follicles of lymphoid tissues.[19]

6.3 Statistical Methods

6.3.1 Baseline Data

Baseline and demographic characteristics will be summarized by standard descriptive summaries. Categorical variables will be summarized by frequencies while continuous variables will be summarized by using mean, standard deviation, median, twenty-fifth and seventy-fifth percentiles, minimum and maximum.

6.3.2 Analysis of Aim 1

Aim 1 (total number of unique infections identified within the first year after completing chemotherapy) will be reported as a rate per 1000 follow-up days. This rate will be reported for the entire cohort, by study site, and by demographics (e.g., age, race, gender). This outcome will also be reported within subsets of infection type (i.e., microbiologically documented infections and bacterial sinopulmonary infections) also reported as a rate per

1000 follow-up days for the entire cohort, by study site and by specific demographic variables. All infection rates will be reported as a post estimate with 95% confidence intervals. Patients will be censored at time of lost to follow-up or death.

Infection rates for enrolled patients will also be compared to those of controls matched on age and sex selected from the CHOP Pediatric Research Consortium (PeRC). Three healthy controls will be selected for each participant for a case to control ratio of 1:3. Control patient infection data will be obtained for the same follow-up time period as that of the matched case patient in order to match risk for infection from seasonal pathogens (e.g., if a case patient completed ALL therapy and enrolled in the study in January 2023, infection data for the matched controls would be collected from January 2023 through December 2023, the same follow-up period as that of the case patient). All control patients will be randomly selected, and control data will be collected when follow-up is complete for participants in the ALL cohort.

Infection rates will also be generated for patients who received blinatumomab as part of their chemotherapy regimen and those who did not receive blinatumomab.

6.3.3 Analysis of Aim 2

The total IgG levels and specific seroprevalence proportions for each of the three pathogens (measles, pneumococcus, and varicella) of interest will be determined for the entire cohort and by demographics (e.g. age, race, gender) at each study follow-up time point (i.e. about 3, 6 and 12 months). Additionally, seroprevalence at each time point will be described for subjects that had and had not completed their primary vaccine series before starting ALL chemotherapy, as well as for those who received blinatumomab as part of their chemotherapy regimen and those who did not.

T and B lymphocyte subsets will be measured for a subset of the 110 enrolled subjects. These measurements will be reported for each subject at approximately 3, 6, and 12 months. The trajectory of these measurements will be displayed graphically across the three timepoints of interest to assess relative recovery of lymphocyte quantities after completion of ALL chemotherapy.

6.3.4 Control of Bias and Confounding

For Aim 1, patients will be contacted once monthly for symptom reporting. Capture of the primary outcome will be dependent on completion of study visits, phone calls and complete data collection from the medical record. Accordingly, study procedural protocols will be implemented to ensure systematic approach for each enrolled subject. We will also develop a database that will inform a systematic approach to medical record review. This is a descriptive study and thus is not vulnerable to confounding.

To control for possible confounding in the comparison of infection incidence rates of ALL patients to those of healthy control patients, all healthy control patients will be matched to ALL cohort patients based on both age and sex, and controls will be assigned the same one-year “follow-up” period as those of their matched ALL cohort patients, to account for seasonal variation in infection rates as described above. Demographic data and vaccination histories

will be collected as outlined above for both ALL cohort patients and healthy controls to monitor for balance with respect to these important factors. Healthy control patients will be included only if they do not have pre-existing medical conditions that might put them at increased risk for infection to ensure assembly of a healthy cohort that most closely mirrors the general population of healthy children. Further, to reduce the risk of selection bias in the healthy control cohort, a waiver of consent and HIPAA authorization will be requested for these patients.

6.4 Sample Size and Power

This study aims to enroll 110 ALL cohort subjects across several centers for Aims 1 and 2. The complexity of specimen processing for Aim 2b will limit performance of these assays to approximately 40 of the overall 110 subjects.

For Aim 1, a cohort of 330 matched healthy control patients will be assembled for the purpose of comparison of infection incidence rates in healthy patients versus those who recently completed ALL therapy. Based on preliminary data collected on this study's cohort of ALL patients, the infection incidence rate in the first year after completion of chemotherapy is estimated to be 1.88 events per person-year. For this power calculation, we assume the rate of infection for the entire ALL cohort will mirror the currently estimated rate of 1.88 events per person-year, assume a two-sided type I error of 0.05, and range the values of overdispersion parameter from 1 to 3.

With 50 ALL patients and 150 matched healthy participants (1:3 match) and one year of follow up on each participant, the detectable effect size with at least 80% power is summarized in Table 1. For example, under the assumption of no overdispersion (overdispersion parameter=1), we will have 80.1% power to detect an IRR of 1.45, i.e., incidence rate of 1.88 for cancer cohort vs. 1.30 for healthy cohort. Under the conservative assumption of a larger overdispersion parameter of 3, we will have 80% power to detect an IRR of 1.90, i.e., incidence rate of 1.88 for cancer cohort vs. 0.99 for healthy cohort. Although we do not have an accurate estimate of the event rate in the healthy cohort, an IRR in the range of 1.45 to 1.90 represents a clinically meaningful effect size for which we will have sufficient power to detect.

Table 1. Power calculation Across Multiple Estimates of Baseline infection Event Rate, Detectable Incidence Rate Ratios, and Overdispersion Parameters

Infection event rate in the healthy cohort	IRR	Overdispersion parameter	Power
1.30	1.45	1	80.1%
1.19	1.58	1.5	81.0%
1.11	1.69	2	80.1%
1.04	1.81	2.5	81.2%
0.99	1.90	3	80.0%

The descriptive and comparative results from Aim 1 will provide important point estimates for infection in the first year post ALL chemotherapy that clinicians can use to manage family expectations for this recovery period.

Outcomes for Aim 2 are descriptive and thus power calculations are not provided. The point estimates for seroprevalence will inform if children retain protection against specific pathogens from vaccination administered prior to their diagnosis of and treatment for ALL. Point estimates for seroprevalence will be described for the entire cohort and by subsets of patient characteristics (e.g., chemotherapy inclusive of blinatumomab). The trajectory of recovery of B and T cell subsets will also be described for the sub-cohort of patients enrolled at CHOP. Differences in trajectories by patient specific characteristic (e.g., chemotherapy inclusive of blinatumomab) will also be explored. These granular descriptive immune function data will inform the need for revaccination in this patient population and if necessary, will provide guidance for the optimal design of revaccination studies.

7 STUDY ADMINISTRATION

7.1 Data Collection and Management

Data elements for this study will be obtained from outpatient and inpatient medical records managed at the local sites where subjects will be enrolled. Data will also be collected regarding specimen collection and the results of specimen processing. Data will be captured in a REDCap™ database. The data will be gathered and entered by trained data abstractors at the participating sites. Categories of data captured from the health records include, but are not limited to: demographics, baseline characteristics, comorbidities, laboratory results, clinical outcomes, medications received, and imaging, microbiology and pathology results as outlined in section 5.1.1.

The REDCap™ Database will be hosted by CHOP. REDCap™ is a software toolset and workflow methodology that supports the electronic collection and management of research and clinical trial data and relies on a thorough study-specific data dictionary defined in an iterative self-documenting. REDCap™'s Data access group function allows for confidential data entry and storage from multiple sites. At the time of enrollment and data entry initiation a unique study identifier will be assigned to each subject. Each enrolling site will maintain its own master list that will capture the local medical record number and the unique study identifier for enrolled subjects. Only study personnel approved at that site will have access to the site master list. The master list will be maintained in case there are any data fidelity issues in REDCap™ that would require re-abstraction of data. Access of members of the research team to any patient identifiers will be limited to the minimum necessary to carry out the proposed research. In addition, research material will be accessible only to members of the investigative team that have completed all required trainings in the Protection of Human Subjects. Individual site abstractors will only have access to their own site's data, not the data of the entire study from all centers. Study personnel at CHOP will have access to the entirety of the REDCap™ database for the purposes of database management, data cleaning, and data analyses.

The REDCap™ database has numerous pre-programmed edit checks to ensure complete, consistent and accurate data. These include logical checks, out-of-range checks, missing and completeness checks. After automated checks, the CHOP coordinator will manually verify data consistency and completeness. Discrepancies identified in data review will be queried for clarification. Once entry, review, and resolution of queries have been completed, the database will be closed.

In accordance with CHOP policy A-3-9, all study data, including PHI and the master list, and study-related documents will be maintained for a minimum of 6 years after completion of the study.

Data for matched healthy control patients will be obtained via automated pull from the EHR, supplemented by chart abstraction as needed to capture the same infection event data as is collected for the ALL cohort. REDCap™ will also be used to store data for controls.

7.2 Confidentiality

All data and records generated during this study will be kept confidential in accordance with Institutional policies and HIPAA on subject privacy and the Investigator and other site personnel will not use such data and records for any purpose other than conducting the study. Safeguards are described under Data Collection and Management. At the time of consent for this study, patients and their parents and/or legal guardians will be asked to also consent to the storage of any remaining research or clinical specimens collected for the purposes of completing the aims described in this study. Consent for future use of remaining specimen will be obtained for both non-genetic and genetic testing. Any specimen remaining after completion of this research project for patients that did not consent to future use will be destroyed. Remaining specimens of patients consenting to future use will be stored at a central laboratory. No personal information, such as names, contact information, or social security numbers, will be stored in the primary study database. Each clinical site will maintain a local patient master list linking the patients' unique study identification to their medical record number. This master list will be stored on a protected local institution location, for example, on a secure local server under password protection, and only accessible by local site personnel. Any future research on the remaining specimens or on the data collected will first require IRB approval.

7.3 Regulatory and Ethical Considerations

7.3.1 Risk Assessment

One potential risk involved in this study is loss of confidentiality. However, several safeguards will be in place to prevent disclosure of patient identifiable information as described above in Data Collection and Management. A secondary potential risk involved in this study is adverse events due to the collection of blood obtained from study subjects. Please see section 5.1.4.1 for maximum restrictions on blood draws. Further, every attempt will be made to time study blood draws with clinically dictated blood draws to reduce the number of venipuncture events that would otherwise not be clinically necessary.

7.3.2 Potential Benefits of Study Participation

The subjects involved in the study will not directly benefit from the proposed research. Results from the study can be applied in the future to all patients with ALL. Establishing the risk of infection and the clinical utility of vaccine titers and immune function studies will provide the necessary guidance to clinicians for more definitive therapeutic decisions in the future. These data will serve to inform future comparative trials designed to determine the utility of vaccination in the period after completion of ALL chemotherapy.

7.3.3 Risk-Benefit Assessment

This is a minimal risk study using data that will be collected prospectively from medical charts. The only potential risk would be loss of confidentiality. However, strict measures will be implemented to maintain confidentiality as detailed in this protocol. With the appropriate confidentiality measures in place, the risk to the subjects should be negligible. For the risk involved in obtaining blood collection, study teams will not obtain blood on a specific day if the clinical team determines that it will be detrimental to the study subject.

In view of the minimal risks to subjects participating in this study, and the considerable clinical and public health benefits which may ensue from it, the risk/benefit ratio is favorable.

7.4 Recruitment Strategy

Each study site will begin prospective identification of patients for enrollment in the ALL cohort once IRB approval is granted at their site. Recruitment will continue for the duration of this study. Methods for identification of eligible subjects will be dictated by the clinical infrastructure of each enrolling site. The primary screening point for each center will be a registry of patients with ALL that will complete therapy on or after December 1, 2021. Then that patient will be further assessed for eligibility criteria prior to approaching for enrollment. Parents and/or legal guardians and patients of assenting age who are eligible will be approached by site study staff either in person or by phone to inform them of the study.

Healthy control patients will be identified and selected from the CHOP Pediatric Research Consortium (PeRC) via medical record review. A list of eligible healthy controls for potential selection will be obtained via a data pull from CHOP's electronic health record (the Clinical Data Warehouse and/or Clarity) of patients meeting the outlined inclusion criteria for controls.

7.5 Informed Consent/Assent and HIPAA Authorization

It is our expectation that all enrolled sites will use the CHOP IRB as the IRB of record. CHOP will first attempt to set up agreements with each participating center to have CHOP serve as the Single IRB for the study. A letter from each local IRB stating that they will rely on CHOP as the IRB of record will be submitted to CHOP prior to the start of any study activities at each site. In the scenario in which a site's local IRB refuses to recognize CHOP as the Single IRB, that site will submit the study protocol and informed consents to their local IRB for review. Sites that refuse to recognize CHOP as the IRB of record must provide documentation of local IRB approval before enrolling. The signed informed consent form will be utilized and maintained at the local site in a secure location.

CHOP will submit a template informed consent document to the IRB with space for sites to customize the form to include local contact information and to meet any requirements set forth by their IRB. Once approved, this template will be distributed to all participating sites for modification as necessary. The site will submit the modified form back to the CHOP IRB for approval. Each site which requires translated versions of the informed consent document will have their site-specific forms translated and will submit those translations to the CHOP IRB for approval.

The eConsent process will be utilized to obtain and document informed consent whenever possible. Any eConsent forms will be submitted to the IRB for approval prior to use. When eConsent is not possible, a physical copy of the informed consent document will be signed and filed securely.

If the patient is under 18 years of age at the time of consent, the patient's parent(s) or legal guardian(s) will be asked to sign the informed consent form. Subjects that turn 18 years old during the study follow-up period will be re-approached for their consent prior to continued data collection. Among these subjects, age-appropriate assent will also be obtained from patients at least 7 years old in addition to parent/guardian consent.

Study staff will seek consent directly from any patients that are at least 18 years of age at the time of consent. Communication with a patient's care team will be used to provide a conservative assessment on whether adult patients are capable of consenting. If an adult is not capable of consenting, a review of the medical records or communication with the patient's care team will identify the Legally Authorized Representative on file for consent.

Upon approach, site study staff will explain the study in a thorough manner. Study staff will describe risk and benefit, purpose, all procedures and how to contact site study staff. Ample opportunity will be made for the study representative and the subject and their parent(s)/legal guardian(s) to share information and ask questions.

In the case of subjects or parent(s)/legal guardian(s) with limited English proficiency, the short form consent process, including use of hospital interpreter services, will be followed, and consent will be documented on paper.

This research will also utilize the PHI of decedents. In accordance with 45 CFR 164.512(i)(1)(iii), the use or disclosure being sought is solely for research on the protected health information of decedents, the protected health information being sought is necessary for the research, and, at the request of the covered entity (CHOP), documentation of the death of the individuals about whom information is being sought can be provided. Since decedents are no longer human subjects, their data/samples included in this research will not be included in the enrollment numbers for this study and research activities using these samples/data will not be reported as part of the continuing review.

For patients included in the matched healthy controls cohort, a waiver of consent/HIPAA authorization will be requested, as these patients will be identified and have existing data collected after the ALL cohort patients to which they are matched have completed their study follow-up period.

8 PUBLICATION

At the conclusion of this effort, we plan to submit an abstract for presentation at a national meeting. Subsequently, we anticipate that this body of work will result in one or more publications in a peer reviewed journal. No individually identifiable PHI will be published.

9 REFERENCES

1. van Tilburg CM, van Gent R, Bierings MB, Otto SA, Sanders EA, Nibbelke EE, Gaiser JF, Janssens-Korpela PL, Wolfs TF, Bloem AC, Borghans JA, Tesselaar K. Immune reconstitution in children following chemotherapy for haematological malignancies: a long-term follow-up. Br J Haematol. 2011 Jan;152(2):201-10. doi: 10.1111/j.1365-2141.2010.08478.x. Epub 2010 Nov 28. PMID: 21114483.
2. Lehrnbecher T, Schubert R, Behl M, Koenig M, Rose MA, Koehl U, Meisel R, Laws HJ. Impaired pneumococcal immunity in children after treatment for acute lymphoblastic leukaemia. Br J Haematol. 2009 Dec;147(5):700-5. doi: 10.1111/j.1365-2141.2009.07903.x. Epub 2009 Sep 18. PMID: 19764991.
3. Weil BR, Madenci AL, Liu Q, Howell RM, Gibson TM, Yasui Y, Neglia JP, Leisenring WM, Smith SA, Tonorezos ES, Friedman DN, Constine LS, Tinkle CL, Diller LR, Armstrong GT, Oeffinger KC, Weldon CB. Late Infection-Related Mortality in Asplenic Survivors of Childhood Cancer: A Report From the Childhood Cancer Survivor Study. J Clin Oncol. 2018 Jun 1;36(16):1571-1578. doi: 10.1200/JCO.2017.76.1643. Epub 2018 Apr 17. PMID: 29664715; PMCID: PMC5978467.
4. Mueller BA, Doody DR, Weiss NS, Chow EJ. Hospitalization and mortality among pediatric cancer survivors: a population-based study. Cancer Causes Control. 2018 Nov;29(11):1047-1057. doi: 10.1007/s10552-018-1078-0. Epub 2018 Sep 5. PMID: 30187228.
5. Shigayeva A, Rudnick W, Green K, Chen DK, Demczuk W, Gold WL, Johnstone J, Kitai I, Krajden S, Lovinsky R, Muller M, Powis J, Rau N, Walmsley S, Tyrrell G, Bitnun A, McGeer A; Toronto Invasive Bacterial Diseases Network. Invasive Pneumococcal Disease Among Immunocompromised Persons: Implications for Vaccination Programs. Clin Infect Dis. 2016 Jan 15;62(2):139-47. doi: 10.1093/cid/civ803. Epub 2015 Sep 9. PMID: 26354970.
6. Meisel R, Toschke AM, Heiligensetzer C, Dilloo D, Laws HJ, von Kries R. Increased risk for invasive pneumococcal diseases in children with acute lymphoblastic leukaemia. Br J Haematol. 2007 Jun;137(5):457-60. doi: 10.1111/j.1365-2141.2007.06601.x. PMID: 17488489.
7. Perkins JL, Chen Y, Harris A, Diller L, Stovall M, Armstrong GT, Yasui Y, Robison LL, Sklar CA; Childhood Cancer Survivor Study. Infections among long-term survivors of childhood and adolescent cancer: a report from the Childhood Cancer Survivor Study. Cancer. 2014 Aug 15;120(16):2514-21. doi: 10.1002/cncr.28763. Epub 2014 May 13. PMID: 24824782; PMCID: PMC4159255.
8. Pelland-Marcotte MC, Pole JD, Hwee J, Sutradhar R, Science M, Nathan PC, Sung L. Long-Term Risk of Infections After Treatment of Childhood Leukemia: A Population-Based Cohort Study Using Administrative Health Data. J Clin Oncol. 2019 Oct 10;37(29):2651-2660. doi: 10.1200/JCO.19.00570. Epub 2019 Aug 8. PMID: 31393747.
9. Guilcher GMT, Rivard L, Huang JT, Wright NAM, Anderson L, Eissa H, Pelletier W, Ramachandran S, Schechter T, Shah AJ, Wong K, Chow EJ.

Immune function in childhood cancer survivors: a Children's Oncology Group review. Lancet Child Adolesc Health. 2021 Apr;5(4):284-294. doi: 10.1016/S2352-4642(20)30312-6. Epub 2021 Feb 16. PMID: 33600774.

10. Rubin LG, Levin MJ, Ljungman P, Davies EG, Avery R, Tomblyn M, Bousvaros A, Dhanireddy S, Sung L, Keyserling H, Kang I; Infectious Diseases Society of America. 2013 IDSA clinical practice guideline for vaccination of the immunocompromised host. Clin Infect Dis. 2014 Feb;58(3):309-18. doi: 10.1093/cid/cit816. Erratum in: Clin Infect Dis. 2014 Jul 1;59(1):144. PMID: 24421306.
11. Top KA, Vaudry W, Morris SK, Pham-Huy A, Pernica JM, Tapiéro B, Gantt S, Price VE, Rassekh SR, Sung L, McConnell A, Rubin E, Chawla R, Halperin SA. Waning Vaccine Immunity and Vaccination Responses in Children Treated for Acute Lymphoblastic Leukemia: A Canadian Immunization Research Network Study. Clin Infect Dis. 2020 Dec 3;71(9):e439-e448. doi: 10.1093/cid/ciaa163. PMID: 32067048; PMCID: PMC7713683.
12. de la Fuente Garcia I, Coïc L, Leclerc JM, Laverdière C, Rousseau C, Ovetchkine P, Tapiéro B. Protection against vaccine preventable diseases in children treated for acute lymphoblastic leukemia. Pediatr Blood Cancer. 2017 Feb;64(2):315-320. doi: 10.1002/pbc.26187. Epub 2016 Oct 8. PMID: 27718310.
13. Crawford NW, Heath JA, Ashley D, Downie P, Buttery JP. Survivors of childhood cancer: an Australian audit of vaccination status after treatment. Pediatr Blood Cancer 2010; 54: 123–33.
14. Top KA, Pham-Huy A, Price V, et al. Immunization practices in acute lymphocytic leukemia and post-hematopoietic stem cell transplant in Canadian Pediatric Hematology/Oncology centers. Hum Vaccines Immunother 2016; 12: 931–36.
15. Gupta S, Rau RE, Kairalla JA, Rabin KR, Wang C, Angiolillo AL, Alexander S, Carroll AJ, Conway S, Gore L, Kirsch I, Kubaney HR, Li AM, McNeer JL, Militano O, Miller TP, Moyer Y, O'Brien MM, Okada M, Reshmi SC, Shago M, Wagner E, Winick N, Wood BL, Haworth-Wright T, Zaman F, Zugmaier G, Zupanec S, Devidas M, Hunger SP, Teachey DT, Raetz EA, Loh ML. Blinatumomab in Standard-Risk B-Cell Acute Lymphoblastic Leukemia in Children. N Engl J Med. 2024 Dec 7. doi: 10.1056/NEJMoa2411680. Epub ahead of print. PMID: 39651791.
16. Bilodeau M, Ma C, Al-Sayegh H, Wolfe J, Bona K. Household material hardship in families of children post-chemotherapy. Pediatr Blood Cancer. 2018;65(1):10.1002/pbc.26743. doi:10.1002/pbc.26743. PMID: 28941160
17. Bona K. Household Survey. Accessed 23 October 2023.
18. Sarkar U, Schillinger D, López A, Sudore R. Validation of self-reported health literacy questions among diverse English and Spanish-speaking populations. J Gen Intern Med. 2011;26(3):265-271. doi:10.1007/s11606-010-1552-1
19. Crotty S. A brief history of T cell help to B cells. Nat Rev Immunol. 2015 Mar;15(3):185-9. doi: 10.1038/nri3803. Epub 2015 Feb 13. PMID: 25677493; PMCID: PMC4414089.

10 APPENDICES

Appendix A. Household Survey

Household Survey

The goal of this survey is to gather information about a patient's life outside of the hospital. Researchers will use this information to study how we can provide better patient care in the future. The survey will take about 3 minutes to complete and includes questions about the patient's family, housing, utilities (heat/electricity/water), food and money. We understand some questions may feel personal or difficult to answer. You may skip any questions or stop completing the survey at any time. Survey answers are confidential and will not be shared with your treatment team nor placed in the patient's medical record. Survey data will be de-identified for research, so no information that identifies the patient or family will be shared.

Thank you!

What is your relationship to the patient participating in the immune recovery after leukemia research study?	◯ Parent ◯ Legal Guardian ◯ Legally Authorized Representative ◯ Self
Including yourself and the patient (child participating in the study), how many people are in your household?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 or more
Including yourself, how many people are in your household?	◯ 1 ◯ 2 ◯ 3 ◯ 4 ◯ 5 ◯ 6 ◯ 7 ◯ 8 or more
In the last 6 months, has lack of reliable transportation kept anyone in your family from medical appointments, meetings, work, or getting things needed for daily living?	◯ Yes ◯ No
In the last 6 months, was there a time you were homeless, or living in a shelter, hotel/motel, scattered site, transitional housing, or had no steady place to sleep (including now)?	◯ Yes ◯ No
In the last 6 months, was there a time you couldn't pay the rent or mortgage on time because you didn't have the money?	◯ Yes ◯ No
In the last 6 months, has the electric, gas, oil or water company sent a letter threatening to shut off services in your home for not paying bills?	◯ Yes ◯ No
In the last 6 months, did you have service disconnected on your telephone (including cell phones) because you couldn't pay the bills?	◯ Yes ◯ No
In the last 6 months, did you have a lack of reliable home internet (e.g., Wi-Fi)?	◯ Yes ◯ No

	Strongly Disagree (1)	Disagree (2)	Neutral (3)	Agree (4)	Strongly Agree (5)

In the last 6 months, we worried whether our food would run out before we got money to buy more.	○	○	○	○	○

	Strongly Disagree (1)	Disagree (2)	Neutral (3)	Agree (4)	Strongly Agree (5)
In the last 6 months, the food that we bought just didn't last, and we didn't have money to get more.	○	○	○	○	○

Which mode of transportation do you use most frequently?

- ○ Public (bus, regional rails, etc)
- ○ Private (car, van, truck, etc)
- ○ Other
- ○ Prefer not to say

If other, please specify here: _____

Do you rent or own your primary residence?

- ○ Rent
- ○ Own
- ○ Prefer not to say

What is your highest level of education attained?

- ○ High school diploma or equivalent (GED)
- ○ Undergraduate degree
- ○ Graduate degree (master's)
- ○ Doctoral degree (PhD, EdD, PsyD, PharmD, MD, DO, etc.)
- ○ Other
- ○ Prefer not to say

If other, please specify here: _____

	Not at all	A little bit	Somewhat	Quite a bit	Extremely
How confident are you in filling out medical forms by yourself?	○	○	○	○	○

What is your current employment status?

- ○ Employed full-time
- ○ Employed part-time
- ○ Unemployed and seeking employment
- ○ Unemployed and not seeking employment
- ○ Prefer not to say

What is your race?

- ☐ African American or Black
- ☐ American Indian or Alaska Native
- ☐ Asian
- ☐ Native Hawaiian or Other Pacific Islander
- ☐ White
- ☐ Other
- ☐ Prefer not to say

If other, please specify here: _____

Are you of Hispanic, Latino/a, or Spanish origin?	◯ Yes ◯ No
What is the race of the patient (child participating in the study)?	☐ African American or Black ☐ American Indian or Alaska Native ☐ Asian ☐ Native Hawaiian or Other Pacific Islander ☐ White ☐ Other ☐ Prefer not to say
If other, please specify here:	_____
Is the patient (child participating in the study) of Hispanic, Latino/a, or Spanish origin?	◯ Yes ◯ No
Please provide your best estimate of your total combined household income over the past year (If you prefer not to answer, please leave this blank) :	_____