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Waning Vaccine Immunity and Vaccination Responses in Children Treated for Acute Lymphoblastic Leukemia: A Canadian Immunization Research Network Study

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Background. There is no uniform guideline for postchemotherapy vaccination of children with acute lymphoblastic leukemia (ALL). We evaluated waning immunity to 14 pneumococcal serotypes, pertussis toxin (PT), tetanus toxoid (TT) and varicella, and immunogenicity of postchemotherapy diphtheria, tetanus, pertussis, hepatitis B, polio, and *Haemophilus influenzae* type b (DTaP-IPV-Hib) and pneumococcal vaccination among previously vaccinated children treated for ALL.

Methods. This was a multicenter trial of children with ALL enrolled 4–12 months postchemotherapy completion. Exclusion criteria included: infant ALL, relapsed ALL, and stem cell transplant recipients. Immunocompetent children were recruited as controls. Postchemotherapy participants received DTaP-IPV-Hib and 13-valent pneumococcal conjugate vaccine (PCV13) concurrently, followed by 23-valent pneumococcal polysaccharide vaccine (PPV23) 2 months later. Serology was measured at baseline, 2 and 12 months postvaccination. Adverse events were captured via surveys.

Results. At enrollment, postchemotherapy participants (n = 74) were less likely than controls (n = 78) to be age-appropriately immunized with DTaP (41% vs 89%, $P < .001$) and PCV (59% vs 79%, $P = .008$). Geometric mean concentrations (GMCs) to TT, PT, PCV serotypes, and varicella were lower in postchemotherapy participants than controls after adjusting for previous vaccine doses ($P < .001$). Two months postvaccination, GMCs to TT, PT, and PCV serotypes increased from baseline ($P < .001$ for all antigens) and remained elevated at 12 months postvaccination. Antibody levels to PPV23 serotypes also increased postvaccination ($P < .001$). No serious adverse events were reported.

Conclusions. Children treated for ALL had lower antibody levels than controls against pneumococcal serotypes, tetanus, pertussis, and varicella despite previous vaccination. Postchemotherapy vaccination with DTaP-IPV-Hib, PCV13, and PPV23 was immunogenic and well tolerated. Children with ALL would benefit from systematic revaccination postchemotherapy.

Clinical Trials Registration. NCT02447718.

Keywords. chemotherapy; immunization; immunosuppression; vaccination.

Despite marked improvements in survival, infection remains an important cause of morbidity and mortality in children with acute lymphoblastic leukemia (ALL), with the risk persisting for years after therapy [1–4]. The incidence of invasive pneumococcal disease (IPD) among children with acute leukemia is >200 times greater than among healthy children [5, 6]. Survivors of ALL also have an increased risk of disseminated disease and death from measles and varicella [7–10]. Being fully immunized before diagnosis of ALL may not offer complete protection as vaccine failures have been reported [10–12]. Community-wide outbreaks of measles and pertussis underscore the importance of protecting children with ALL against vaccine-preventable diseases [13, 14].

Although there is evidence that antibody titers to vaccine antigens wane during treatment in children who were vaccinated prior to chemotherapy [15–19], knowledge gaps remain. Despite their high risk of IPD, data on persistence of immunity to *Streptococcus pneumoniae* serotypes and responses to pneumococcal conjugate vaccine (PCV) are limited in children with

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ALL who received PCV before chemotherapy. In addition, few studies have examined varicella immunity in previously vaccinated children.

There are no uniform guidelines for postchemotherapy vaccination. Guidelines in Europe, Australia, and the United Kingdom recommend several vaccines for patients with leukemia including diphtheria-tetanus-acellular pertussis (DTaP), inactivated polio vaccine (IPV), *Haemophilus influenzae* type b conjugate vaccine (Hib), and PCV starting 3–6 months postchemotherapy [20–22]. European and Australian guidelines also recommend varicella vaccination. In contrast, there are no specific vaccination recommendations after ALL therapy in Canada or the United States [2, 23]. A survey of pediatric hematology/oncology centers in Canada revealed variable practices, with 45% of centers routinely recommending revaccination after chemotherapy, 45% recommending only catch-up vaccines, and physician-dependent practice at 1 center [24].

The study objectives were to evaluate among previously vaccinated children who completed ALL therapy: 1) waning immunity to *S. pneumoniae* serotypes, tetanus toxoid (TT), pertussis toxin (PT), and varicella; and 2) immunogenicity and safety of DTaP-IPV-Hib, 13-valent PCV (PCV13), and 23-valent pneumococcal polysaccharide (PPV23) vaccinations.

METHODS

Study Design and Participants

This was a prospective multicenter clinical trial at 10 pediatric hematology/oncology centers across Canada. Inclusion criteria for children in the ALL treatment group were: previous diagnosis of ALL at ≥1 year of age, within 4–12 months of completing chemotherapy at enrollment, and no vaccinations other than influenza since completing chemotherapy. Exclusion criteria were: diagnosis of infant ALL, evidence of disease relapse, history of primary immunodeficiency (except related to Down syndrome), stem cell transplant, and blood products <3 months before enrollment.

Controls were recruited at 3 study sites (Halifax, NS; Toronto, ON; Edmonton, AB) from among children requiring routine outpatient bloodwork, previous vaccine trial participants, and Canadian Laboratory Initiative on Pediatric Reference Intervals (CALIPER) project participants [25]. Inclusion criteria for controls were: age 3–18 years, no known immunodeficiency or recent immunosuppressive therapy, and no recent blood products. Controls were matched to participants with ALL 1:1 by age at blood collection ±6 months.

Ethics

The study was approved by the Research Ethics Boards at all participating sites (Clinicaltrials.gov identifier: NCT02447718). Participants and/or caregivers provided written informed consent to participate.

Study Procedures

Participants Treated for ALL

Baseline clinical assessment and chart review were performed. Varicella serology at ALL diagnosis (measured using standard clinical assays) was extracted from medical records. Vaccination records were retrieved from parents, primary care providers, public health, or medical records. Participants underwent venipuncture for immunologic markers and serology, following which they received PCV13 (Prevnar®13, Pfizer Canada Inc.) and DTaP-IPV-Hib (Pediacel®, Sanofi Pasteur Ltd or Infanrix®-IPV/Hib, GlaxoSmithKline Inc.). Two months later PPV23 (Pneumovax® 23, Merck Canada Inc. or Pneumo 23®, Sanofi Pasteur Ltd) was administered. Serum was collected approximately 2 and 12 months after the first vaccination.

Controls

These participants completed a health questionnaire, vaccination records were reviewed, and they underwent venipuncture for serologic testing. Banked serum was used if available.

Clinical Monitoring

Solicited and unsolicited adverse events, impact on daily activities, and healthcare visits were captured through telephone interviews conducted by nurses or research coordinators 8–10 and 30–33 days after each vaccination using a standard questionnaire.

Laboratory Analysis

Whole blood samples from children with ALL were processed at local clinical laboratories for complete blood count and differential, quantitative immunoglobulins, and T and B lymphocyte subsets using standard methods. Participant results were compared to standard age-specific reference ranges or published values in healthy children [26].

Sera from all participants were processed, frozen, and batch-shipped to the Canadian Center for Vaccinology for analysis. Antibodies against PT and TT were measured by enzyme immunoassays using standard methodology [27]. The lower limit of quantification (LLQ) for PT was 7 enzyme-linked immunosorbent assay units (EU) per mL. The LLQ for TT was 0.015 IU/mL. Samples testing below the LLQ were reported as half the LLQ.

Varicella-zoster virus (VZV) immunoglobulin G (IgG) testing was performed using the Bioplex 2200 MMRV IgG kit on a Bioplex 2200 Instrument (Bio-Rad Laboratories Ltd, Montreal, QC). Results were reported as the antibody index.

Pneumococcal serotype-specific IgG was measured to 14 serotypes: PCV13 serotypes 1, 3, 4, 6B, 7F, 9V, 14, 18C, 19F, 23F, and PPV23 serotypes 11A, 12F, 15B, 33F. Testing was conducted at the McGill University Health Centre using published methodology [28, 29].

Statistical Analysis

The primary outcomes were geometric mean antibody concentrations (GMCs) to 10 PCV serotypes, PT, TT, and varicella in participants treated for ALL versus controls, and GMCs at 2 and 12 months postbooster vaccination versus baseline among participants treated for ALL. Secondary outcomes were proportions of participants with protective antibody levels to PCV serotypes (≥0.35 μg/mL, as per World Health Organization criteria [30]), TT (≥0.1 IU/mL), and varicella (antibody index > 1) at each time point and geometric mean ratios (GMRs) at 2 months postvaccination versus baseline. GMCs and GMRs were reported with 95% confidence intervals (CIs).

In descriptive analyses, differences in proportions were assessed by χ^2 test or Fisher exact test for cell sizes <5. Differences among continuous variables were compared using analysis of variance or Student *t*-tests. Statistical significance was defined as $P < .05$. Statistical analyses were conducted using SAS® version 9.4 (SAS Institute, Cary, NC, USA).

Participants treated for ALL and controls were compared in unmatched analyses due to significant differences in vaccine history between groups (see Results). Baseline GMCs were compared using linear regression models on the logarithmic scale adjusted for previous vaccine doses. GMCs postvaccination were compared to baseline GMCs using linear mixed models.

Among participants treated for ALL, we assessed predictors of baseline seroprotection against TT, varicella, and pneumococcal serotypes, and predictors of vaccine response in logistic regression models. TT and PT vaccine responses were defined as GMR ≥ 4, and PCV13 response was defined as GMR ≥ 4 to 7 of 10 PCV serotypes tested. Potential predictors included sex, age, number of previous vaccine doses, interval from chemotherapy to baseline assessment, treatment for standard risk versus high risk or very high risk ALL, chemotherapy protocol (Children's Oncology Group [COG] or Dana Farber Cancer Institute, Supplementary Tables S1 and S2), and CD4+ T cells <10th percentile for age. A threshold of $P < .1$ in univariate models was used to select predictors to include in multivariable models.

Analysis of adverse events following immunization was descriptive. Severe events were defined as interfering with daily activities and/or requiring medical attention. Serious adverse events were those requiring hospitalization or resulting in permanent disability or death.

RESULTS

From November 2015 to September 2017, 78 participants treated for ALL and 78 controls were enrolled; 4 participants in the ALL group withdrew or were excluded prior to the baseline assessment (Figure 1). Forty-five percent of the ALL group were classified as having had high risk or very high risk ALL

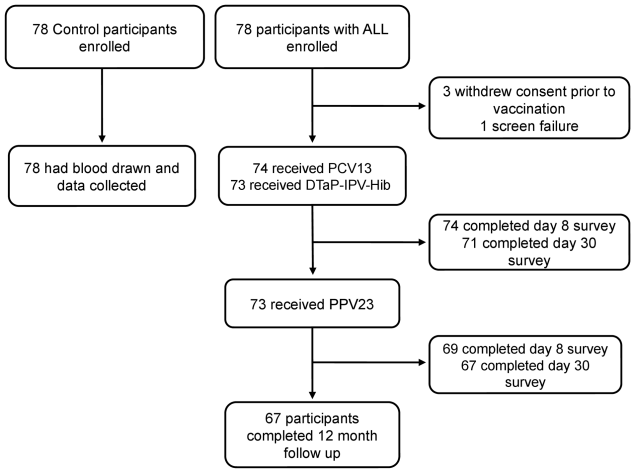

Figure 1. Participant flow chart. Abbreviations: DTaP-IPV-Hib, diphtheria-tetanus-acellular pertussis-inactivated polio-*Haemophilus influenzae* type b vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

(Table 1). At enrollment, 27–30% had total CD3 + T cells, CD4 + T cells, and CD8 + T cells below the 10th percentile for age [26], and 14% had low IgG levels.

Participants treated for ALL were significantly less likely than controls to be up to date for age with childhood vaccinations (Table 2 and Supplementary Table S3). Among participants aged ≥6 years, 41% of the ALL group had received all 5 recommended doses of DTaP versus 89% of controls ($P < .001$). Vaccination status at ALL diagnosis was not assessed; however, despite being >12 months of age at diagnosis, participants treated for ALL were less likely than controls to have received PCV at ≥12 months of age (59% vs 79%, $P = .008$).

Baseline Antibody Levels Among Participants Treated for ALL and Controls

GMCs were significantly lower among participants treated for ALL than controls for all 10 PCV serotypes tested in models adjusted for previous vaccine doses (Table 3). Most postchemotherapy participants had antibody levels below protective levels for PCV serotypes.

GMCs to PT, TT, and varicella were significantly lower among children treated for ALL than controls ($P < .001$). Seventy percent of children treated for ALL had seroprotective TT antibody levels versus 100% of controls ($P < .001$). Among participants without previous varicella vaccination, 7/17 participants with ALL and 7/11 controls were seropositive.

Forty-eight postchemotherapy participants were varicella seropositive at ALL diagnosis, of whom 11 (23%) remained varicella seropositive after chemotherapy and 37 (77%) had indeterminate or negative serology. Six of 11 persistently seropositive participants had not received varicella vaccination. Six patients with indeterminate serology at diagnosis

Table 1. Characteristics of Participants With ALL (N = 74) and Their Immunologic Markers at Enrollment

Characteristics	Participants With ALL (N = 74)		
Age at ALL diagnosis in years			
median, range	5	1–17	
ALL disease risk category[a]	n	%	
Standard risk	40	54	
High risk	27	36	
Very high risk	6	8	
Unknown	1	1	
Treatment protocol			
Children's Oncology Group	49	66	
Dana Farber Cancer Institute	25	34	
Interval from last chemotherapy to serology, months			
median, range	6	4–10	
Immunologic markers at enrollment	Median (cells $\times 10^9$/L)	IQR	Below 10th centile for age [26] n (%)
Total WBC count (N = 69)	6.5	5.3–7.7	9 (13)
Total lymphocyte count (N = 73)	2.3	1.7–2.9	21 (29)
Lymphocyte subsets (N = 60)			
CD3 + T cells	1.4	1.1–1.9	18 (30)
CD4 + T cells	0.8	0.6–1.0	16 (27)
CD8 + T cells	0.5	0.3–0.7	18 (30)
NK cells (CD56+/CD16+)	0.2	0.1–0.2	9 (16)
CD19 + B cells	0.6	0.4–0.7	3 (5)
Total serum IgG (N = 71)	8.5 g/l	7.1–11.1	10 (14)[b]

Abbreviations: ALL, acute lymphoblastic leukemia; IgG, immunoglobulin G; IQR, interquartile range; NK, natural killer; WBC, white blood cell.

[a]Disease risk category based on patient characteristics at leukemia diagnosis reflects intensity of chemotherapy.

[b]Represents proportion below lower limit of normal for age.

Table 2. Pre-enrollment Immunization History Among Participants With ALL (N = 74) and Control Participants (N = 78)

	Participants With ALL (N = 74)	Controls (N = 78)	*P*
Age at baseline blood draw			
Median (range) in years	8.1 (3.8–19.3)	8.3 (3.5–18.9)	
Sex	n (%)	n (%)	
Male	37 (50)	40 (51)	
Female	37 (50)	38 (49)	
Previous doses of DTaP or Tdap			<.001
0	2 (3)	0 (0)	
1–3	12 (16)	1 (1)	
4	36 (49)	17 (22)	
≥5	24 (32)	60 (77)	
Previous doses of PCV			.005
0	19 (26)	9 (12)	
1–2	10 (14)	2 (3)	
≥3	45 (61)	66 (85)	
Unknown	0	1 (1)	
Received ≥1 dose PCV at ≥12 months of age	44 (59)	62 (79)	.008
Received ≥1 dose PCV13	34 (46)	38 (49)	.75
Previous doses of varicella vaccine			<.001
0	17 (23)	11 (14)	
1	48 (65)	26 (33)	
≥2	9 (12)	40 (51)	
Unknown	0 (0)	1 (1)	
Interval from last vaccine dose to baseline blood draw, years	Mean (SD)	Mean (SD)	
DTaP/Tdap-containing vaccine	6.0 (2.7)	3.7 (2.5)	<.001
PCV	5.4 (2.3)	7.2 (3.4)	<.001
Varicella	6.5 (3.2)	5.2 (4.2)	.052

Abbreviations: ALL, acute lymphoblastic leukemia; DTaP, diphtheria-tetanus-acellular pertussis vaccine; IQR, interquartile range; PCV, pneumococcal conjugate vaccine; SD, standard deviation; Tdap, reduced antigen formulation tetanus-diphtheria-acellular pertussis vaccine.

were seronegative postchemotherapy. One previously vaccinated participant converted from negative to positive serology postchemotherapy without receiving further vaccination.

Immune Responses to DTaP-IPV-Hib, PCV13, and PPV23 Vaccination

GMCs to PT, TT, and PCV13 serotypes increased 2 months postvaccination and remained significantly above baseline levels at 12 months postvaccination ($P < .001$ for all antigens) (Table 4). Approximately 10 months post-PPV23, GMCs were significantly above prevaccination levels for PPV serotypes 11A, 12F, 15B, and 33F. GMRs for PCV serotypes ranged from 3.7 (2.9–4.8) for serotype 19F to 13.0 (9.3–18.0) for serotype 14. Two months post-PCV13, 61% of participants had seroprotective IgG levels against all PCV13 serotypes tested, decreasing to 34% by 12 months.

Two months post-DTaP-IPV-Hib, GMR for TT was 24.5 (16.8–35.8). At 12 months postvaccination, 97% of participants remained seroprotected against TT.

Predictors of Baseline Seroprotection and Vaccine Response Among Participants Treated for ALL

Potential predictors of seroprotective titers to TT and varicella at baseline were assessed in logistic regression models (Table 5). Only 5% of participants were protected against all PCV7

Table 3. Geometric Mean Concentrations (95% Confidence Intervals) and Seroprotection Among Participants With ALL Versus Controls

	Participants With ALL				Control Participants			
Vaccine Antigens	N	GMC[a]	95% CI	% Seroprotected[b,c]	N	GMC[a]	95% CI	% Seroprotected[b,c]
Pneumococcal serotype (μg/mL)	73				78			
1		0.19	.16–.22	16		0.52	.41–.66	58
3		0.17	.14–.21	15		1.01	.72–1.42	68
4		0.19	.16–.22	21		0.54	.43–.68	54
6B		0.38	.29–.50	36		1.20	.92–1.57	83
7F		0.26	.20–.33	33		0.70	.57–.87	77
9V		0.45	.37–.55	56		0.92	.77–1.10	88
14		0.46	.35–.59	52		1.76	1.24–2.50	88
18C		0.21	.16–.27	26		0.49	.38–.62	56
19F		0.99	.77–1.26	82		3.21	2.73–3.76	99
23F		0.29	.23–.36	30		1.15	.87–1.52	81
Pertussis toxin (EU/mL)	71	4.10	3.67–4.58	N/A	78	10.35	8.15–13.16	N/A
Tetanus toxoid (IU/mL)	71	0.16	.12–.20	70	78	1.73	1.26–2.37	100
Varicella (AI)	69	0.33	.24–.45	20	78	1.00	.77–1.29	53

Abbreviations: AI, antibody index; ALL, acute lymphoblastic leukemia; CI, confidence interval; GMC, geometric mean concentration; IgG, immunoglobulin G.

[a] $P < .001$ for all comparisons of GMCs between cases and controls in linear regression models on the log scale adjusted for previous vaccine doses.

[b] Seroprotection was defined as *Streptococcus pneumoniae* IgG ≥0.35 ug/mL based on World Health Organization criteria, tetanus toxoid IgG ≥0.1 IU/mL, and varicella antibody index >1.

[c] $P < .001$ for all comparisons of seroprotection between cases and controls by χ^2 test.

serotypes, too few to model that outcome. For TT, male sex and receipt of ≥4 doses of DTaP before enrollment were independent predictors of seroprotection in the multivariable model. There were no differences between boys and girls in regards to age, ALL risk category, treatment protocol, or previous vaccine doses. Protection against varicella was associated only with older age. Associations between varicella seroprotection and previous vaccine doses could not be assessed due to small cell size; however, in a stratified analysis varicella GMC was not associated with previous doses ($P = .12$) (Supplementary Table S4).

Predictors of response to TT, PT, and PCV13 (GMR ≥ 4) were assessed in logistic regression models (Table 6). Treatment

Table 4. Geometric Mean Concentrations and Geometric Mean Ratios to Pertussis Toxin, Tetanus Toxoid, and Pneumococcal Serotypes Pre- and Post-DTaP-IPV-Hib, PCV13, and PPV23 Vaccination in Children With ALL

	Prevaccination (N = 73)		2 months Postvaccination (N = 67)		12 months Postvaccination (N = 66)		GMR 2 mos vs prevaccination
Antigen	GMC	95% CI	GMC[a]	95% CI	GMC[a]	95% CI	(95% CI)
Pertussis toxin IgG (EU/mL)	4.10	3.67–4.58	30.67	22.25–42.29	10.39	7.76–13.91	7.63 (5.53–10.53)
Tetanus toxoid IgG (IU/mL)	0.16	.12–.20	4.00	2.57–6.22	1.08	.77–1.52	24.49 (16.77–35.76)
Pneumococcal serotype (μg/mL)							
1	0.19	.16–.22	1.66	1.29–2.13	1.04	.83–1.31	8.72 (6.83–11.14)
3	0.17	.14–.21	0.75	.56–1.00	0.42	.32–.56	4.61 (3.46–6.15)
4	0.19	.16–.22	1.45	1.09–1.92	0.81	.60–1.09	7.76 (5.94–10.15)
6B	0.38	.29–.50	3.07	2.12–4.45	1.65	1.14–2.40	8.62 (5.79–12.83)
7F	0.26	.20–.33	2.05	1.68–2.50	1.01	.82–1.24	8.29 (6.55–10.48)
9V	0.45	.37–.55	2.40	1.90–3.03	1.43	1.17–1.74	5.53 (4.24–7.22)
14	0.46	.36–.59	5.52	4.12–7.41	4.38	3.34–5.75	12.98 (9.35–18.03)
18C	0.21	.16–.26	2.18	1.70–2.79	1.21	.97–1.50	10.51 (8.16–13.55)
19F	0.99	.77–1.26	3.68	3.02–4.48	3.21	2.68–3.83	3.72 (2.90–4.77)
23F	0.29	.23–.36	2.46	1.78–3.39	1.41	1.07–1.86	9.24 (6.63–12.89)
PPV23 serotypes not in PCV13			Pre-PPV23		10 months post-PPV23		GMR 10 mo vs pre-PPV23
11A	0.31	.25–.38	0.35	.28–.44	0.75	.58–.96	2.08 (1.70–2.55)
12F	0.10	.08–.11	0.14	.12–.18	0.21	.17–.25	1.40 (1.14–1.72)
15B	0.51	.39–.68	0.69	.52–.93	1.64	1.20–2.23	2.30 (1.83–2.88)
33F	0.27	.21–.34	0.36	.28–.47	1.38	1.02–1.88	3.67 (2.73–4.93)

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; DTaP-IPV-Hib, diphtheria-tetanus-acellular pertussis-inactivated polio-*Haemophilus influenzae* type b vaccine; GMC, geometric mean concentration; GMR, geometric mean ratio; IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

[a] $P < .001$ for all comparisons of GMCs at 2 months versus prevaccination and GMCs at 12 months versus prevaccination.

Table 5. Logistic R Analysis of Predictors of Baseline Protective Antibody Titers to Tetanus Toxoid (≥0.1 IU/mL) and Varicella (Antibody Index > 1) Among Participants With ALL

		Univariate Logistic Models			Multivariate Logistic Models		
Antigen	Covariates	Overall *P* value	OR	95% CI	Overall *P* value	Adjusted[a] OR	95% CI
Tetanus toxoid	Sex	.03			.02		
	Male		Ref			Ref	
	Female		0.30	.10–.90		0.22	.06–.79
N = 70	Treatment protocol	.91					
	COG		Ref				
	DFCI		1.06	.36–3.13			
	Risk category	.89					
	Standard		Ref				
	High/Very high		0.93	.33–2.60			
	Previous DTaP doses	.03			.02		
	<4		Ref			Ref	
	4		4.44	1.15–17.19		6.29	1.40–28.38
	≥ 5		7.60	1.61–35.91		10.01	1.85–54.21
	Interval since last chemotherapy	.17					
	4–5 months		Ref				
	6–7 months		0.98	.29–3.31			
	≥ 8 months		0.18	.02–1.29			
	Age at baseline blood draw	.20					
	<8 years of age		Ref				
	8–11 years of age		2.50	.69–9.12			
	≥12 years of age		2.89	.69–12.02			
	CD4+ T-cell count	.90					
	≥10th percentile		Ref				
	<10th percentile		1.09	.28–4.15			
Varicella[b]	Sex	.35					
N = 69	Male		Ref				
	Female		0.57	.18–1.84			
	Treatment protocol	.28					
	COG		Ref				
	DFCI		1.90	.59–6.11			
	Risk category	.26					
	Standard		Ref				
	High/Very high		1.96	.61–6.29			
	Interval since last chemotherapy	.94					
	4–5 months		Ref				
	6–7 months		1.10	.30–4.08			
	≥ 8 months		0.75	.07–8.38			
	Age at baseline blood draw	.02					
	<8 years of age		Ref				
	8–11 years of age		7.38	1.32–41.46			
	≥12 years of age		12.44	2.19–70.67			
	CD4+ T-cell count	.11					
	≥10th percentile		Ref				
	<10th percentile		3.13	.79–12.43			

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; COG, Children's Oncology Group; DFCI, Dana Farber Cancer Institute; DTaP, diphtheria-tetanus toxoid-acellular pertussis; OR, odds ratio; Ref, reference category.

[a]OR adjusted for other variables in the model.

[b]Cell sizes were insufficient to assess previous doses or interval from last chemotherapy in univariate model.

for high or very high risk ALL was associated with lower response to PCV13 and receipt of ≥4 DTaP doses before enrollment was associated with higher response to PT. No significant predictors of response to TT were identified.

Safety Outcomes

Adverse events were reported by 76% of participants after DTaP-IPV-Hib and PCV13 and by 67% after PPV23 (Table S5). Symptoms that interfered with or prevented daily activities were

Table 6. Logistic Regression Analysis of Predictors of Geometric Mean Ratio ≥4 at 2 Months Postvaccination Versus Baseline to 7 of 10 Pneumococcal Conjugate Vaccine Serotypes, Tetanus Toxoid, and Pertussis Toxin Among Participants With ALL

Antigen	Covariates	Overall *P* value	OR	95% CI	Overall *P* value	Adjusted[a] OR	95% CI
PCV13[b]	Sex	.80					
	Male		Ref				
N = 66	Female		1.13	.42–3.03			
	Treatment protocol	.29					
	COG		Ref				
	DFCI		1.79	.61–5.24			
	Risk category	.01			.02		
	Standard		Ref			Ref	
	High/Very high		0.26	.09–.75		0.23	.07–.79
	Received PCV ≥12 months of age	.17					
	No		Ref				
	Yes		2.00	.74–5.42			
	Interval since last chemotherapy	.34					
	4–5 months		Ref				
	6–7 months		0.38	.11–1.38			
	≥8 months		0.44	.07–2.90			
	Age at baseline blood draw	.03			.06		
	<8 years of age		Ref			Ref	
	8–11 years of age		0.22	.06–.77		0.19	.05–.74
	≥12 years of age		0.27	.08–.97		0.56	.13–2.31
	CD4+ T-cell count	.43					
	≥10th percentile		Ref				
	<10th percentile		1.8	.42–7.71			
Tetanus toxoid[c]	Sex	.38					
N = 63	Male		Ref				
	Female		2.22	.38–13.11			
	Treatment protocol	.34					
	COG		Ref				
	DFCI		2.92	.32–26.70			
	Risk category	.49					
	Standard		Ref				
	High/Very high		0.52	.08–3.40			
	Previous DTaP doses	.99					
	<4		Ref				
	4		0.82	.08–8.75			
	≥5		0.86	.07–10.66			
	Age at baseline blood draw	.50					
	<8 years of age		Ref				
	8–11 years of age		0.36	.05–2.38			
	≥12 years of age		1.00	.08–12.00			
	CD4+ T-cell count	.57					
	≥10th percentile		Ref				
	<10th percentile		0.49	.04–5.98			
Pertussis toxin	Sex	.93					
N = 63	Male		Ref				
	Female		1.05	.36–3.03			
	Treatment protocol	.26					
	COG		Ref				
	DFCI		1.96	.60–6.40			
	Risk category	.18					
	Standard		Ref				
	High/Very high		0.48	.16–1.42			
	Previous DTaP doses	.02					

Table 6. Continued

Antigen	Covariates	Overall *P* value	OR	95% CI	Overall *P* value	Adjusted[a] OR	95% CI
	<4		Ref				
	4		5.50	1.29–23.39			
	≥5		8.50	1.68–42.98			
	Interval since last chemotherapy	.14					
	4–5 months		Ref				
	6–7 months		2.49	.74–8.40			
	≥8 months		0.52	.07–4.00			
	Age at baseline blood draw	.14					
	<8 years of age		Ref				
	8–11 years of age		1.99	.56–7.00			
	≥12 years of age		4.97	.95–25.99			
	CD4+ T-cell count	.17					
	≥10th percentile		Ref				
	<10th percentile		4.5	.51–39.44			

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; COG, Children's Oncology Group; DFCI, Dana Farber Cancer Institute; DTaP, diphtheria-tetanus toxoid-acellular pertussis; GMR, geometric mean ratio; OR, odds ratio; PCV, pneumococcal conjugate vaccine; Ref, reference category.
[a]OR adjusted for other variables in the model.
[b]Outcome was geometric mean ratio ≥4 to at least 7 of 10 PCV serotypes.
[c]Cell sizes were insufficient to assess previous doses or interval from last chemotherapy in univariate models.

reported by 9% of participants after DTaP-IPV-Hib/PCV13 and 10% after PPV23. Eight participants had 10 healthcare visits for adverse events; only 3 events were possibly related to vaccination, and 7 were unrelated (Table S6). No serious adverse events were reported.

DISCUSSION

Children who completed ALL therapy had markedly lower antibody levels against *S. pneumoniae*, pertussis toxin, tetanus toxoid, and varicella than immunocompetent children, independent of vaccination history. Nearly all participants with ALL had nonprotective or undetectable antibody levels to 1 or more antigens, suggesting vulnerability to vaccine-preventable diseases following chemotherapy. These children demonstrated good serological responses to DTaP-IPV-Hib and PCV13 administered 4–12 months postchemotherapy, with most achieving protective antibody levels to TT and PCV serotypes. DTaP-IPV-Hib, PCV13, and PPV23 were also well tolerated; no serious adverse events were reported.

Seventy percent of children treated for ALL had normal total IgG, B-cell and T-cell counts at enrollment, suggesting that suppression of specific antibody production may persist beyond apparent immune reconstitution. Increased age, a potential marker of previous varicella infection, was associated with seroprotection against varicella, whereas most persistently seropositive participants treated for ALL appeared to be immune through infection. These results suggest that infection may provide more durable protection than vaccination in this population. Male sex and receipt of ≥4 DTaP doses were independent predictors of seroprotection against TT. The latter finding was surprising as COG protocols recommend 3 years of chemotherapy for boys and 2 years for girls. We did not identify any differences in clinical or demographic characteristics between boys and girls to explain this finding; further assessment of sex-related differences in vaccine titers is needed. Reassuringly, responses to DTaP-IPV-Hib and PCV13 did not differ by sex. High or very high risk ALL was associated with lower response to PCV13 but not to DTaP-IPV-Hib.

Our findings are consistent with those of other studies showing that children with ALL have lower than expected protection against vaccine antigens postchemotherapy. In previous studies, 25–35% of patients who completed ALL therapy were susceptible to tetanus and diphtheria, and 70–71% were susceptible to pertussis [15, 19]. In a Canadian study (2000–2012), 54% of patients had nonprotective antibody levels to TT, and 48% were VZV seronegative following ALL therapy [18]. Patients with previous varicella vaccination were more likely to be seronegative than those with a history of chickenpox (63% vs 19%) [18]. Some studies have identified predictors of lower vaccine titers postchemotherapy, including higher intensity chemotherapy and younger or older age, but no consistent risk factors have emerged [16–18, 31]. Our study is the first to our knowledge to report differences in antibody levels by sex; previous studies did not assess sex as a predictor variable.

Similar to our results, a clinical trial of PCV13 in children with cancer who previously received PCV7 showed that only 30–60% were seroprotected against each serotype [32]. Studies conducted prior to the introduction of infant PCV programs also reported lower pneumococcal antibody concentrations in children with ALL than age-matched controls [33, 34]. These findings and the

current study argue for the need for PCV13 vaccination for all patients treated for ALL, regardless of vaccination history.

Responses to postchemotherapy vaccination vary between studies [15, 16, 35]. In one study of 46 children 1–18 years of age, DTaP-IPV-Hib vaccination ≥6 months postchemotherapy for ALL resulted in over 90% of subjects achieving protective levels and/or a ≥4-fold increase in titers to TT, polio, and Hib [35]. Similar to our results, TT titers remained above protective levels at 1 year postvaccination among 16 participants tested. Other studies also reported good short-term responses to DT and Hib vaccination [16, 18]. Following PCV13 vaccination in children with cancer, 64–100% of participants achieved antibody levels ≥0.35 µg/mL to PCV serotypes at 4 weeks postvaccination [32]. These studies did not assess persistence of antibody responses.

Short-term responses to PCV13 and the TT component of DTaP-IPV-Hib in this study were similar to responses observed in healthy children in clinical trials [36, 37]. However, responses to acellular pertussis appeared to be lower in our study, peaking at GMC 31 EU/mL, compared with GMCs of 100–150 EU/mL in healthy children [37, 38]. Although PT antibody levels in this study waned to just above the threshold of detection by 12 months, they were comparable to levels seen in healthy children [39].

Our results support current Australian, European, and UK immunization recommendations for children who complete ALL therapy [20–22], which differ from those of the US Advisory Committee on Immunization Practices and Canadian National Advisory Committee on Immunization [2, 23, 40]. These advisory bodies recommend PCV13 and Hib for children with hematologic malignancies but do not specify at what stage of treatment they should be administered, and neither recommends routine vaccinations after chemotherapy. Based on our results, we recommend vaccination starting 4 months postchemotherapy with DTaP and PCV13, and consideration of varicella vaccine in all children treated for ALL, regardless of age or previous immunization history.

This study had limitations. First, except for varicella, antibody levels to vaccine antigens were not measured before chemotherapy, so we cannot confirm that chemotherapy was the cause of low postchemotherapy titers. However, children with ALL would be expected to be immunocompetent prior to their diagnosis, and longitudinal studies have documented decreases in antibody levels to TT and pertussis during chemotherapy [31], supporting the hypothesis that chemotherapy hastens waning of immunity. We did not assess immunization status at ALL diagnosis and therefore could not confirm whether postchemotherapy participants were underimmunized for age before diagnosis relative to their peers. Although differences in titers between children treated for ALL and controls were significant after adjustment for number of vaccine doses received, it is possible that differences in doses affected the differences in titers we observed. We were unable to assess antibodies to other pertussis antigens (eg, filamentous hemagglutinin, pertactin), which might have provided a more complete assessment of pertussis immunity than anti-PT antibodies alone [39]. Prechemotherapy varicella immune status was measured using different assays across the study centers, which may have varying sensitivity; however, validation data show that the BioPlex MMRV assay we used is more sensitive than other commercial assays [41].

The study had notable strengths. The inclusion of immunocompetent controls provided a more relevant comparator group than published clinical trial data in healthy children that previous studies have used. In addition, we assessed persistence of antibody responses at 12 months postvaccination. By including participants eligible for universal PCV and varicella vaccination treated at centers using the most common types of chemotherapy protocols used in North America, our results should be generalizable to patients treated for ALL across North America.

CONCLUSION

Previously immunized children treated for ALL experience decreased antibody levels to *S. pneumoniae*, tetanus toxoid, pertussis toxin, and varicella greater than would be expected due to delays in receiving age-appropriate vaccinations. Administration of DTaP-IPV-Hib and PCV13 followed by PPV23 starting at least 4 months postchemotherapy is immunogenic and well tolerated. These findings argue for the need for, and benefit of, systematic revaccination of children of all ages following chemotherapy for ALL.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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