

Allergy and infectious disease histories and the risk of childhood acute lymphoblastic leukaemia

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Summary

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Infectious disease histories were evaluated in a population-based case-control study of childhood acute lymphoblastic leukaemia (ALL) as it has been hypothesised that delays in early infections are associated with an increased risk of disease. Allergy histories were also assessed as part of a broader evaluation of the role of immune factors in ALL. Cases ($n = 255$) were diagnosed between 1980 and 1991 at one of four referral centres in a 31-county area of New York State; controls ($n = 760$) were a random sample of live births from the same region, frequency matched to cases by sex, race and birth year. Data were collected by mailed questionnaire, completed by case and control parents in 1995. Allergy and infectious histories before the age at leukaemia diagnosis for cases and an equivalent age for controls were evaluated. The adjusted odds ratio and 95% confidence interval [CI] associated with a positive history of any allergy was 0.58 [95% CI 0.38, 0.88] compared with a negative allergy history. The occurrence of several common childhood illnesses before 25 months of age and ALL were assessed, with both weak positive and weak inverse associations observed.

Overall, these analyses provide little support for the hypothesis that infection delay in early life is associated with an increased risk of ALL. Children with positive allergy histories reported significantly more infections than those with negative histories; however, effect modification of the infection-ALL associations by child allergy history was not observed. Nonetheless, these observations suggest the importance of assessing both allergy and infectious histories and their possible interactions when evaluating the association between these immune factors and childhood ALL.

Introduction

The aetiology of childhood acute lymphoblastic leukaemia (ALL), and specifically the role of infectious diseases in the development of disease has been under study for many years¹⁻⁷ as several characteristics of ALL such as seasonal variation and clustering are suggestive of an infectious origin.⁸⁻¹⁴ Kinlen has hypothesised¹⁵ that acute leukaemia is a rare response to a common infection due to the mixing of immunologically isolated populations with newcomers, resulting in a change in the infectious disease dynamics within the population. Results from several studies have provided support for this hypothesis.¹⁵⁻²¹

It has also been hypothesised that children with an abnormal pattern of infectious disease acquisition, par-

ticularly delays in early exposure, may be at increased risk of ALL.²²⁻²⁵ Under this theory (Greaves' delayed infection hypothesis), two separate genetic events would be responsible for the development of early B-lineage ALL, with the first mutation occurring spontaneously *in utero* during the developmental period of precursor B-cell expansion and the second sometime in early life following antigenic challenge. Greaves' hypothesis is also compatible with leukaemia resulting from a rare response to a common infection.^{26,27}

While studies assessing infectious disease histories and childhood cancer or leukaemia risks are numerous, results have been inconsistent, both in terms of the direction of effects and the specific infections showing a significant effect.^{1-7,28-33} In addition, results from stud-

ies assessing early childhood day-care experiences, a surrogate measure of infection exposure, have also been inconsistent; no associations between early child care and ALL were observed in two studies,^{7,34} while inverse associations were observed in several others.^{32,35–37} Mixed results were observed in a recent study conducted in Hong Kong;³³ reduced time spent at home during the first year of life was associated with a significantly reduced risk of ALL among children diagnosed between 2 and 6 years of age, whereas analyses specific for day care were not supportive of an association.

A few studies have been undertaken to assess the role of allergies in the development of childhood ALL; the majority support the view that a positive allergy history is associated with a reduced risk of ALL.^{28–30,38,39} Studies assessing allergy history and the risk of adult lymphatic-haematological malignancies are more frequent, with positive, inverse and null associations having been observed.^{40–51} In adults, allergies have been hypothesised to decrease cancer risk through heightened immune surveillance or to increase cancer risk via chronic antigenic stimulation and the enhanced opportunity for malignant transformation.^{40–42,52} Whether either of these mechanisms is relevant to the development of childhood ALL is unknown since disease onset occurs early in life, providing a limited latency period.

Recent studies evaluating the development of allergies have shown that the immune systems of children with one or more atopic first degree relatives, who develop atopy during the preschool period, retain a T-helper (Th) cell phenotype and cytokine profile characteristic of neonates (Th-2 phenotype), consistent with a postnatal maturational delay in T-cell competence.^{53–57} Children with negative family allergy histories, who do not develop atopy, rapidly develop the capability to produce interferon- γ and other Th-1 cytokines during the first year of life.⁵⁷ The Th-1 and Th-2 cells and their respective cytokines are distinct and mutually inhibitory, with differing functional roles in the immune response.^{58–60} These two types of T-helper cells also mediate host resistance and susceptibility to infectious diseases, and often skew the immune response to a particular infection toward one phenotype.^{60,61} Alternatively, infectious diseases appear to drive Th-1/Th-2 differentiation as well, further highlighting the complexity of the signalling mechanism for immune response;⁶⁰ for example, there is evidence that some infections such as measles and

tuberculosis are inversely associated with the occurrence of atopy.⁶²

Due to the biological inter-relationship between allergy development and infectious diseases in early life, we evaluated the roles of child allergy history and common infections in the development of childhood ALL as well as the potential for child allergy history to modify any infection–ALL associations. Both the occurrence and timing of these events were assessed.

Methods

The study was a population-based case-control investigation of childhood ALL in a 31-county area of western and central New York State. Potential cases were identified through the institutional tumour registries and departmental records at the four major medical centres in the area: Children's Hospital of Buffalo; Roswell Park Cancer Institute (Buffalo); Strong Memorial Hospital (Rochester) and the State University of New York Upstate Medical University (Syracuse). The cases ($n = 400$) were <15 years of age and residents of the 31-county area when diagnosed with histologically confirmed ALL (ICD-O histology code 9821.3 or ICD-9 code 204.0) between January 1980 and December 1991. Adopted children were ineligible for study as many of the prenatal exposures would have been unavailable from an adoptive parent. Approximately 88% of cases of childhood ALL among residents of the 31 counties were diagnosed at one of these institutions during the study period according to the New York State Department of Health (NYSDOH).

Controls were a random selection of live births from the 31-county area and were identified through the Live Birth Certificate Registry (NYSDOH). Controls ($n = 1563$) were frequency matched to cases at a 4:1 ratio on sex, race and birth year. Institutional Review Board approval for the study was granted by the University at Buffalo, the New York State Department of Health and each of the four medical centres providing cases.

Ten of 400 cases were excluded from the study; six were adopted and physician permission to contact the patient and family was denied in four instances. An additional 31 cases (8%) could not be located following a tracing strategy using telephone books, city directories, credit bureau and motor vehicle searches. Four of 1563 controls were also excluded from study; one was a case, the second was a sibling of the case, the third was a child of a case and the fourth had acute myeloid

enous leukaemia. An additional 188 controls (12%) could not be located.

Data collection

Data were collected using a mailed English language questionnaire completed by case and control parents. The completion time for the eight-page, 32 multi-part question instrument was approximately 30 min in the pretest. Topics covered included: pregnancy exposures; birth characteristics, early childhood infections, day care and infant feeding; index child and family history of allergies, cancer and immunological disorders and socio-economic-demographic information. Disease characteristics of cases (e.g. immunophenotype, age at diagnosis) were obtained from medical records at the time of case ascertainment. Four mailings were distributed from mid-November 1995 until early January 1996 and included: the initial solicitation letter and questionnaire, a thank-you post card and two additional letters and questionnaires to non-respondents only.⁶³ Seventy-one per cent (255/359) of case and 55 per cent (760/1371) of control parents responded to the series of four mailings.

Operational definitions

The age at diagnosis among cases was defined as the age at first bone marrow biopsy. Prior to data collection, potential controls were assigned a reference age at diagnosis, based on the frequency distributions of the age at diagnosis of cases born within the same year as the controls.

The index child's allergy history included parental reports and age at diagnosis of: asthma; eczema; a food, drug or bee allergy; a dust or pollen allergy; an allergy to cat or dog dander. A positive allergy history to any allergen was defined as an allergy to one or more of these allergens. Dust, pollen, cat or dog dander allergies were categorised as 'inhaled allergies'.

The child's allergy history before the diagnosis of leukaemia was the exposure of interest; consequently, at the time of analysis, positive allergy histories were divided into onset before or after the age at diagnosis of leukaemia among cases and the assigned reference age at diagnosis among controls. In order to determine the timing of allergy onset relative to leukaemia diagnosis or control reference age at diagnosis, the two ages were compared. Since the age at onset of each allergy among index children was collected in

years while the age at diagnosis of leukaemia or control reference age was available in months, six (months) was added to the age at onset of each allergy (e.g. a child developing eczema at 1 year of age was assigned an age of onset of eczema of 18 rather than 12 months).

Allergy histories for case and control parents included an identical list of allergy types as the children, plus the occurrence of plant/chemical allergy. Maternal and paternal histories were collected in separate sections of the questionnaire, with 8% of cases (21/255) and controls (64/760) missing the entire paternal allergy history. Initial analyses of the parental allergy history/ALL association included only cases and controls with allergy history data for both parents, with a positive parental history defined as at least one parent reporting one or more of these allergies. Because of the decrease in sample size, a second set of analyses was performed in which a positive parental allergy history was defined as: either parent having a positive history (determined from 92% of sample) or a positive maternal history for those cases and controls lacking a paternal history (8% of sample). The results from the two sets of analyses were not appreciably different; hence, only results employing the mixed parental allergy history definition are presented.

Data pertaining to common infections experienced (yes/no) before 25 months of age and the timing of first episodes of these infections were collected. The specific illnesses listed on the questionnaire included: colds, otitis media, streptococcal and sinus infections, vomiting, diarrhoea, influenza, croup, bronchiolitis, pneumonia, meningitis, septicaemia, skin infection, Coxsackie viral infections and other. Categories describing the timing of each infection were 0–6, 7–12, 13–18 and 19–24 months of age, with the notation 'check all that apply'. The occurrence (yes/no) and age of occurrence (in years) up to 6 years of age of measles, mumps, rubella, chickenpox and fifth disease were also collected.

Infectious diseases occurring before the diagnosis of leukaemia were of interest; consequently, infections occurring during or after a 6-month interval which included the age at leukaemia diagnosis or the control reference age were treated as non-events (censored). A similar strategy was employed for measles, mumps, rubella, chickenpox and fifth disease. Cases and controls lacking specific timing for an infection but with a 'yes' for that infection were censored if the age at diagnosis/reference age was ≤ 24 months (common

infections) or ≤ 72 months (measles, mumps, rubella, chickenpox, fifth disease).

Statistical analyses

Descriptive statistics employed included measures of central tendency and variation (Student's *t*-test) and categorical analyses using Pearson's Chi-square test. Unadjusted and adjusted odds ratios (OR) and 95% confidence intervals [CI] were calculated using unconditional logistic regression. Analyses were conducted using SPSS.⁶⁴ Potential covariable selection was based on the hypotheses under study and literature findings, with confounding defined as a change of $>10\%$ in the OR. Effect modification of the infection-ALL association by ever child allergy history was assessed using backward elimination, with a likelihood ratio statistic *P*-value of ≤ 0.05 indicative of interaction. Tests for linear trend across the ORs in infectious disease analyses were conducted using these variables in continuous rather than dummy coding form.

Index child allergy history logistic models were constructed for 'any allergy' and each type, with separate categories for 'before' and 'after' leukaemia diagnosis. Although not of aetiological interest, the 'after' category was not collapsed into none, the reference category, since differences in the immune system among children with and without allergies first appear during early childhood, even before allergic symptoms develop.^{57,65} Index children with multiple allergies appear in more than one comparison. Final covariable adjustment included maternal smoking (yes/no) and education (years), ever breast fed (yes/no), race (white/non-white), and birth year.

Analyses of each common infection during the first 2 years of life (yes/no) were undertaken to assess possible effect modification of the infection-ALL associations by ever child allergy history; logistic models were fitted for the total sample and following stratification by ever child allergy history. Effect modification was evaluated for each infection by adding the interaction term to the full model and assessing the significance using backward elimination. Ever child allergy history was used as the stratification variable since differences in the immune system which could influence infectious disease histories, occur even before allergic symptoms develop.^{57,60,61,65}

Logistic models were also fitted to assess the association between the age at first episode of each infection and childhood ALL. These analyses were conducted

for the total sample and for two subgroups of cases (B-lineage derived cases between 2 and 14 years at diagnosis and cases 2–5 years of age at diagnosis). Many of the common infections such as influenza, croup and bronchiolitis were reported infrequently; hence, the 6-month time intervals were collapsed into yearly intervals (first year of life, second year and none or later as reference) in all these models to stabilise the estimates. Other than chickenpox, the infections normally contracted once (e.g. measles) were rarely reported due to the presence of effective vaccines during the study period; hence, the time periods for these diseases were collapsed into occurrence during the first to second years of life, third to sixth years of life and none or later (reference). The covariables in the final adjusted infection-ALL models were maternal education, birth year, maternal smoking, ever breast fed and ever child allergy history (yes/no to any allergen). Day-care attendance before 2 years of age and birth order, two potential confounders providing an increase in exposure opportunity, did not appreciably change the ORs and were not included in the final adjusted models. Although some infections were positively associated with white race and male sex (data not shown), neither variable confounded the infection-ALL associations; these variables were omitted from the final models for the total sample, but retained in the subgroup analyses models since they were matching factors.

Results

As shown in Table 1, both cases and controls were predominantly white, with a slight excess of males in both groups; birth year distributions were similar for cases and controls with 80–85% of participants born after 1974. Maternal educational levels, smoking histories and family income were also similar for cases and controls as were birth order, the frequency of breast feeding at birth and day-care attendance before 2 years of age. Ninety per cent of cases were diagnosed with ALL after 2 years of age, with 61% diagnosed between 2 and 5 years of age. Eighty-six per cent of cases were classified as B-lineage derived ALL (early pre-B, pre-B, B lineage not otherwise specified, B-cell) while the remaining cases were categorised as T-cell ALL.

Matching factor information was available on eligible cases and controls who either did not respond to the questionnaire or could not be located. Non-participating cases ($n = 135$) and controls ($n = 799$) had similar gender and birth-year distributions as those who

Table 1. Sample characteristics by disease status, Western and Central New York Acute Lymphoblastic Leukaemia Study

Characteristics	Cases <i>n</i> = 255 <i>n</i> (%)	Controls <i>n</i> = 760 <i>n</i> (%)
Sex		
Male	144 (57)	427 (56)
Female	111 (43)	333 (44)
Race		
White	245 (96)	715 (94)
Non-white	10 (4)	45 (6)
Birth year		
1965–69	7 (3)	36 (5)
1970–74	34 (13)	105 (14)
1975–79	52 (20)	168 (22)
1980–84	104 (41)	282 (37)
1985–91	58 (23)	169 (22)
Maternal education, 1994		
≤12 years	106 (42)	274 (36)
13–15 years	92 (36)	294 (39)
16+ years	55 (22)	191 (25)
Mean (SD) years education	13.6 (2.5)	14.0 (2.6)
Family income, 1994		
<\$15 000	27 (12)	67 (9)
\$15 000–34 999	59 (26)	194 (28)
\$35 000–54 999	63 (28)	192 (28)
\$55 000–74 999	37 (16)	129 (19)
\$75 000+	40 (18)	114 (16)
Maternal smoking		
Yes	69 (27)	227 (30)
No	186 (73)	533 (70)
Infant feeding at birth		
Breast	119 (47)	388 (51)
Bottle	136 (53)	369 (49)
Birth order		
First	101 (40)	298 (40)
Second	99 (39)	272 (36)
Third or higher	54 (21)	182 (24)
Attended day care before 25 months of age		
Yes	57 (23)	165 (22)
No	193 (77)	586 (78)
Year of diagnosis ^a		
1980–82	55 (22)	176 (23)
1983–85	67 (26)	183 (24)
1986–88	67 (26)	206 (27)
1989–91	66 (26)	195 (26)
Age at diagnosis (years) ^a		
<2	26 (10)	57 (7)
2–5	155 (61)	430 (57)
6–9	40 (16)	142 (19)
10–14	34 (13)	131 (17)

$P > 0.05$ in all comparisons.

SD, standard deviation.

^aControls assigned a reference diagnosis date and age based on diagnosis date and age at diagnosis of cases.

responded (data not shown); however, non-white race was significantly more frequent among both non-participating cases (14%) and controls (17%) than among respondents.

Thirty-four per cent of case parents and 43% of control parents reported positive allergy histories among the index children ($P = 0.01$, see Table 2). The increased prevalence of allergies among controls was observed primarily for pollen, dust and cat or dog dander allergies. Positive parental allergy histories were reported more frequently by control parents, but not significantly so. Parental allergy histories were positively associated with index child allergy histories, breast feeding and mean parental educational levels, and inversely associated with maternal smoking during the index pregnancy (data not shown, $P \leq 0.05$ for both cases and controls for each comparison).

While a weak inverse association was observed between parental allergy history and ALL in the child (Table 3), a stronger association was observed between the index child's personal allergy history and ALL; the adjusted OR [95% CI] for personal allergy onset before leukaemia diagnosis was 0.58 [0.38,0.88]. Allergies to inhaled allergens and a food-drug-bee allergy before leukaemia diagnosis were also associated with significantly reduced risks of leukaemia. The point estimates

Table 2. Allergy histories (ever)^a among index children and their parents by case and control status, Western and Central New York Acute Lymphoblastic Leukaemia Study

	Cases <i>n</i> = 255 <i>n</i> (%)	Controls <i>n</i> = 760 <i>n</i> (%)
Ever child allergy HX ^{a*}		
Negative	167 (66)	432 (57)
Positive	86 (34)	323 (43)
Specific allergy types ^b		
Asthma	20 (8)	68 (9)
Eczema	34 (13)	87 (12)
Food-drug-bee	38 (15)	137 (18)
Pollen-dust*	25 (10)	160 (21)
Cat-dog dander*	8 (3)	73 (10)
Parental allergy HX ^a		
Negative	126 (49)	330 (43)
Positive	129 (51)	428 (57)

^aAllergy defined as report of at least one of the following; asthma, eczema, food-drug-bee, pollen-dust, or cat-dog dander allergy (child and parent) plus chemical-plant allergy (parent only).

^bAllergy types not mutually exclusive.

* $P \leq 0.05$.

Table 3. Parent and child^a allergy histories and the risk of childhood ALL, Western and Central New York Acute Lymphoblastic Leukaemia Study – logistic regression analyses

Variable	Cases (n = 255) n	Controls (n = 760) n	Adjusted ^b OR [95% CI]
<i>Parental allergy Hx^c</i>			
Positive	129	428	0.81 [0.61,1.09]
Negative	126	330	1.00 Reference
<i>Index child allergy Hx^a</i>			
<i>Any allergy^c</i>			
Before	34	153	0.58 [0.38,0.88]
After	36	130	0.71 [0.47,1.08]
None	167	430	1.00 Reference
<i>Asthma</i>			
Before	7	31	0.59 [0.25,1.37]
After	10	31	0.84 [0.40,1.76]
None	167	430	1.00 Reference
<i>Inhaled^d</i>			
Before	8	47	0.45 [0.21,0.97]
After	12	93	0.33 [0.18,0.62]
None	167	430	1.00 Reference
<i>Food-drug-bee</i>			
Before	11	72	0.40 [0.21,0.77]
After	18	49	0.95 [0.53,1.65]
None	167	430	1.00 Reference
<i>Eczema</i>			
Before	16	58	0.71 [0.40,1.28]
After	11	20	1.41 [0.66,3.02]
None	167	430	1.00 Reference

^aReference category in each model is a negative *ever* allergy history. Although the occurrence of allergies *after* leukaemia diagnosis is not of aetiological interest in the development of ALL, *after* was left as a separate category in this table since it is distinct from *none*, the reference. Children in the *before* category had a history of allergy prior to leukaemia diagnosis (cases) or the reference age at diagnosis (controls). Children with reports of more than one allergy type appear in more than one comparison.

^bOdds ratios adjusted for maternal smoking, education, breast feeding, birth year and race.

^cParental allergy history defined as at least one parent with asthma, pollen-dust, cat-dog dander, food-drug-bee, eczema or chemical-plant sensitivity. 'Any allergy' for the index child includes the same types listed for their parents except chemical-plant allergy.

^dInhaled allergens include pollen-dust or dander.

OR, odds ratio; CI, confidence interval.

for histories of prior asthma and prior eczema were also below one, but the confidence intervals were wide and included the null value.

Index child infections were reported with similar frequencies by case and control parents with the excep-

tion of diarrhoea, which was less frequent in cases (37%) than controls (45%), $P = 0.04$. Among all participants, the prevalence of one or more episodes before 2 years of age of colds was 85%, while it was 57% for otitis media, 29% for vomiting, 17% for chickenpox and 5–10% for streptococcal infections, influenza, croup, bronchiolitis and pneumonia. Sinus infections, skin problems, Coxsackie viral infections, measles, mumps, rubella and fifth disease were reported by less than 5% of both case and control parents (data not shown).

Both cases and controls with positive personal allergy histories (ever) reported more frequent infectious illnesses before 2 years of age than cases and controls with negative allergy histories. For example, the prevalence of one or more colds among controls with positive allergy histories was 88% as compared with 82% among controls with negative allergy histories. Similarly, otitis media was reported more frequently among controls with (63%) vs. controls without (50%) positive allergy histories, as were: streptococcal infections (13% with vs. 8% without); influenza (14% with vs. 7% without); pneumonia (7% with vs. 4% without); bronchiolitis (15% with vs. 7% without); vomiting (36% with vs. 24% without); and diarrhoea (52% with vs. 39% without) ($P < 0.05$ in each comparison listed). A similar pattern was observed among cases; however, only bronchiolitis (13% with vs. 5% without) and croup (19% with vs. 10% without) were found to be significantly more frequent among cases with positive allergy histories than among those with negative histories. Preliminary analyses assessing each infection-ALL association stratified by ever child allergy history (Table 4) were not strongly suggestive of effect modification; 6 of 9 infections had ORs in opposite directions but with overlapping CIs which included the null; the remainder of the ORs were in the same direction. Nonetheless, the ORs were lower for many of the infection-ALL associations among children with positive allergy histories than for those with negative allergy histories.

Analyses to assess the year of first occurrence of each common infection and the risk of ALL appear in Table 5. In the total sample analyses, reduced ORs were observed with first episodes of bronchiolitis, pneumonia and diarrhoea in both the first and second years of life. The CIs were wide in most instances and, with the exception of an occurrence of diarrhoea in the first year of life, included one. First occurrences of streptococcal infection, influenza, croup or vomiting

Table 4. Common infections during the first two years of life and the risk of childhood ALL. Results from the total sample and following stratification by ever child allergy history, Western and Central New York Acute Lymphoblastic Leukaemia Study – logistic regression analyses

	Total sample			Negative allergy history			Positive allergy history		
	Cases <i>n</i> = 255 <i>n</i> (%)	Controls <i>n</i> = 760 <i>n</i> (%)	Adjusted ^a OR [95% CI]	Cases <i>n</i> = 167 <i>n</i>	Controls <i>n</i> = 432 <i>n</i>	Adjusted ^a OR [95% CI]	Cases <i>n</i> = 86 <i>n</i>	Controls <i>n</i> = 323 <i>n</i>	Adjusted ^a OR [95% CI]
Positive history									
Colds	195 (83)	605 (85)	0.97 [0.64, 1.45]	126	334	1.09 [0.66, 1.81]	69	271	0.72 [0.36, 1.44]
Otitis media	145 (60)	402 (56)	1.23 [0.90, 1.67]	91	207	1.36 [0.94, 1.99]	54	195	0.99 [0.59, 1.66]
Strep infection	24 (10)	76 (10)	1.02 [0.62, 1.66]	14	34	1.14 [0.60, 2.20]	10	42	0.88 [0.42, 1.87]
Influenza	27 (11)	72 (10)	1.18 [0.73, 1.89]	16	30	1.46 [0.77, 2.78]	11	42	0.88 [0.42, 1.81]
Croup	32 (13)	85 (12)	1.20 [0.77, 1.87]	16	43	0.98 [0.54, 1.80]	16	42	1.49 [0.78, 2.85]
Bronchiolitis	20 (8)	79 (11)	0.77 [0.45, 1.29]	9	30	0.75 [0.35, 1.63]	11	49	0.76 [0.37, 1.56]
Pneumonia	7 (3)	38 (5)	0.55 [0.24, 1.27]	5	15	0.83 [0.30, 2.34]	2	23	0.33 [0.08, 1.46]
Vomiting	69 (29)	214 (30)	0.99 [0.72, 1.38]	42	102	1.14 [0.75, 1.73]	27	112	0.78 [0.46, 1.32]
Diarrhoea	89 (37)	321 (45)	0.76 [0.56, 1.03]	53	162	0.81 [0.55, 1.19]	36	159	0.64 [0.39, 1.05]

Infections censored at the age of leukaemia diagnosis for cases and reference age for controls. Reference category in each analysis was a negative history for that particular infection.

^aOdds ratios adjusted for maternal education (years), birth year, smoking (yes/no), ever breast fed (yes/no). Total sample models also adjusted for ever child allergy history.

OR, odds ratio; CI, confidence interval.

before 13 months of age were also associated with reduced risk estimates, while the ORs associated with a first occurrence during the second year of life were greater than one; in each of these analyses the CIs included one and were overlapping for a given infection. Otitis media was the only illness associated with an increased risk of ALL during both the first and second years of life.

Subgroup analyses restricting the case group to B-lineage derived ALLs 2–14 years of age at diagnosis (Table 5) or to cases diagnosed between 2 and 5 years of age regardless of immunophenotype (also Table 5), generally resulted in increased point estimates and wider confidence intervals than the total sample analyses; results remained non-significant. The decreased risk associated with a first episode of diarrhoea during the first year of life was not observed in either of these subgroup analyses while the increased risk for a first episode of otitis media in the second year of life was strengthened, particularly among children diagnosed with ALL between 2 and 5 years of age.

In the total sample analyses, the ORs associated with chickenpox infection during the first to second years of life and between the third and sixth years of life were reduced but the confidence intervals included one. The reduced risk of ALL was strengthened in the

subgroup analysis of cases 2–5 years of age at diagnosis and may reflect the fact that exposure to chickenpox is frequent in this age group and that children with leukaemia, exposed to the chickenpox virus, were often administered varicella zoster immune globulin to prevent a severe or fatal chickenpox infection.

Among the serious infections reported by cases and controls before leukaemia diagnosis or reference date were: meningitis, reported by three controls (no cases), and septicaemia, reported by two cases and one control (unadjusted OR [95% CI] of 6.0 [0.5,66.4]). Several infections listed anecdotally in the 'other' category, also before leukaemia diagnosis or referent date were: fever of unknown origin (8 cases/1 control; unadjusted OR = 25, approximate 95% CI = [3.1, 196.2]); roseola (4 cases/3 controls unadjusted OR = 4, approximate 95% CI = [0.9, 17.9]); Kawasaki syndrome (1 case), scarlet fever (1 case), septic arthritis (1 control) and whooping cough (1 control).⁶⁶

Discussion

A positive personal history of any allergy before leukaemia diagnosis was associated with a significantly decreased risk of ALL as were allergies to inhaled allergens and food-drug-bees. Inverse associations were

Table 5. Age at first occurrence of common infections and the risk of childhood ALL. Total sample, and age and immunophenotype-specific case subgroups and controls, Western and Central New York Acute Lymphoblastic Leukaemia Study – logistic regression

Infection	Total sample			B-lineage ^a cases 2–14 years at DX and controls			Cases 2–5 years ^b at DX and controls		
	Cases	Controls	Adjusted ^c OR [95% CI]	Cases	Controls	Adjusted ^c OR [95% CI]	Cases	Controls	Adjusted ^c OR [95% CI]
	<i>n</i> = 255 <i>n</i>	<i>n</i> = 760 <i>n</i>		<i>n</i> = 195 <i>n</i>	<i>n</i> = 760 <i>n</i>		<i>n</i> = 155 <i>n</i>	<i>n</i> = 760 <i>n</i>	
Colds									
First year of life	135	408	1.00 [0.65,1.52]	107	408	1.24 [0.75,2.05]	88	408	1.57 [0.87,2.84]
Second	60	197	0.91 [0.57,1.46]	50	197	1.19 [0.69,2.06]	38	197	1.56 [0.82,3.00]
None or later	39	107	1.00 Reference	24	107	1.00 Reference	16	107	1.00 Reference
Otitis									
First year of life	87	264	1.12 [0.79,1.58]	66	264	1.13 [0.77,1.65]	61	264	1.44 [0.93,2.24]
Second	58	138	1.42 [0.96,2.08]	48	138	1.56 [1.02,2.37]	41	138	2.12 [1.31,3.44]
None or later	97	321	1.00 Reference	72	321	1.00 Reference	44	321	1.00 Reference
Strep infection									
First year of life	6	25	0.81 [0.32,2.02]	6	25	1.07 [0.43,2.69]	5	25	1.27 [0.46,3.53]
Second	18	51	1.11 [0.63,1.96]	17	51	1.41 [0.79,2.52]	13	51	1.46 [0.76,2.82]
None or later	214	651	1.00 Reference	160	651	1.00 Reference	124	651	1.00 Reference
Influenza									
First year of life	3	23	0.44 [0.13,1.50]	3	23	0.59 [0.17,2.01]	0	23	–
Second	24	49	1.50 [0.89,2.51]	21	49	1.71 [0.99,2.95]	19	49	1.71 [0.96,3.05]
None or later	214	653	1.00 Reference	160	653	1.00 Reference	127	653	1.00 Reference
Croup									
First year of life	12	45	0.82 [0.42,1.59]	9	45	0.77 [0.37,1.62]	10	45	1.08 [0.52,2.25]
Second	20	40	1.66 [0.94,2.92]	12	40	1.21 [0.61,2.37]	13	40	1.84 [0.93,3.66]
None or later	213	646	1.00 Reference	167	646	1.00 Reference	124	646	1.00 Reference
Bronchiolitis									
First year of life	12	39	0.87 [0.45,1.71]	11	39	1.02 [0.51,2.06]	7	39	0.72 [0.31,1.68]
Second	8	40	0.65 [0.30,1.42]	4	40	0.39 [0.14,1.12]	6	40	0.75 [0.30,1.85]
None or later	224	654	1.00 Reference	171	654	1.00 Reference	133	654	1.00 Reference
Pneumonia									
First year of life	5	19	0.70 [0.26,1.91]	4	19	0.72 [0.24,2.17]	4	19	0.81 [0.26,2.50]
Second	2	19	0.37 [0.09,1.62]	1	19	0.24 [0.03,1.86]	2	19	0.76 [0.17,3.45]
None or later	239	698	1.00 Reference	183	698	1.00 Reference	141	698	1.00 Reference
Diarrhoea									
First year of life	52	202	0.69 [0.48,0.99]	46	202	0.88 [0.60,1.30]	32	202	0.71 [0.46,1.13]
Second	37	119	0.85 [0.56,1.29]	32	119	1.05 [0.66,1.65]	27	119	1.07 [0.65,1.76]
None or later	150	396	1.00 Reference	105	396	1.00 Reference	85	396	1.00 Reference
Vomiting									
First year of life	30	101	0.91 [0.58,1.42]	29	101	1.20 [0.75,1.90]	21	101	1.05 [0.62,1.79]
Second	39	113	1.07 [0.71,1.61]	32	113	1.19 [0.76,1.86]	27	113	1.24 [0.76,2.02]
None or later	170	507	1.00 Reference	122	507	1.00 Reference	96	507	1.00 Reference
Chickenpox									
1st to 2nd year of life	39	121	0.90 [0.60,1.35]	33	121	1.03 [0.67,1.59]	22	121	0.83 [0.50,1.38]
3rd to 6th year of life	30	119	0.73 [0.47,1.15]	24	119	0.77 [0.47,1.26]	11	119	0.54 [0.28,1.06]
None or later	177	489	1.00 Reference	132	489	1.00 Reference	116	489	1.00 Reference

Infections censored at age of leukaemia diagnosis for cases and reference age for controls.

^aB-lineage cases include early pre-B, pre-B and B-cell not otherwise specified.

^bCases 2–5 years at diagnosis include both B-lineage and T-cell ALL.

^cTotal sample odds ratios adjusted for maternal smoking, ever breast fed, index child allergy history (ever), maternal education (years) and birth year. Odds ratios in models of case subgroups and controls also adjusted for sex and race.

OR, odds ratio; CI, confidence interval; DX, diagnosis.

also observed for a prior history of asthma or eczema, consistent with the results from three studies;^{28,38,39} however, our findings for asthma and eczema were not statistically significant. Our results are also consistent with three studies of adult lymphatic-haematopoietic malignancies in which inverse associations between a positive allergy history (defined as one or more of the following: food, drug, insect stings, animal dander, pollen, dust, feathers, asthma, hives, allergy inoculations) and adult acute myeloid leukaemia,⁴¹ non-Hodgkin's lymphoma,⁴³ and chronic lymphocytic leukaemia⁴⁰ were observed. Positive associations between allergy history (variously defined) and childhood ALL²⁹ and adult leukaemia, lymphoma or myeloma have been observed,^{44-46,51} as well as null associations.^{42,47-50}

Although our case-control study was population-based, cases were residents of the 31-county area when diagnosed with ALL while controls were born in the same region. Allergy prevalence varies by geographic location.⁶⁷ However, it is unlikely that our observed associations between allergies and ALL were due to residency differences during early childhood. Ninety per cent of responding cases were also born in New York State, of whom, 99% listed their place of birth in the 31-county area. In addition, over 90% of parents of potential participants were still residents of New York State at the time of the mailings in late 1995.

While the ORs associated with the several of the common infections evaluated for the total sample were below one and 'consistent' with the delayed infection hypothesis, the CIs were wide and included the null. Only the point estimates for pneumonia were below one for a first episode during both the first and second years of life for the total sample and for the two case subgroups. Otitis media before 25 months of age was associated with an increased risk, particularly a first episode during the second year of life. This observation was strengthened in both subgroup analyses but is contrary to expectation for the delayed infection hypothesis. Consequently, our findings provide little direct support for the hypothesis that delays in infection acquisition during the first 2 years of life are associated with an increased risk of ALL.

In the aggregate, our findings regarding infectious diseases are similar to results from many of the studies published to date, in that both weak positive and weak inverse associations compatible with the null hypothesis for a variety of viral and bacterial illnesses have been observed.^{1-7,29-33} However, the specific infec-

tions showing an association and/or the direction of the associations differ. Significantly increased frequencies of acute pulmonary episodes in leukaemia cases as compared with controls were observed in one study,¹ with a fourfold ($P=0.001$) increase in risk of childhood leukaemia or lymphoma associated with viral infections (e.g. rubella, chickenpox) prior to 6 months of age in another.⁴ An increased risk associated with influenza in the first year of life (OR = 6.8 [95% CI = 1.81, 25.66]) was observed in another study.³¹ Roseola and/or fever and rash in the first year of life decreased the risk of ALL (OR = 0.33 [95% CI = 0.16, 0.68]) in a recent study in Hong Kong.³³ Measles or measles vaccination prior to leukaemia diagnosis was associated with a significantly reduced risk of ALL in a Japanese study.²⁸ In our study, measles, mumps and rubella were not associated with ALL but were reported in <5% of cases and controls, perhaps due the presence of effective vaccines for these childhood diseases during much of the study period. In addition, bronchiolitis and pneumonia were associated with non-significant decreased risks of ALL as was influenza during the first year of life. Our observation of an increased risk of ALL associated with otitis media is in contrast to that of the Children's Cancer Group (CCG);⁷ they observed a reduced risk of ALL in children with one or more episodes of otitis media during the first year of life (P for trend = 0.026). Our observation of a reduced risk associated with early diarrhoeal episodes in the total sample was not observed in the more specific subgroup analyses and may be a chance finding.

In addition to evaluating individual infections, some investigators have employed summary measures of infection (e.g. any infection, four or more infections/year)³¹⁻³³ also with contradictory and inconclusive findings. While a reasonable strategy in principle, determination of 'which' infections to include in such a measure or 'how many' infections is complex and difficult to interpret, particularly since consistency across studies with regard to individual infections of interest has not been attained.

Although the child's personal allergy history was not a significant effect modifier of the infection-ALL associations in this study, the inter-relationships between allergy and infection⁵³⁻⁶¹ provide a biological rationale for assessing personal and family allergy histories in conjunction with infection in early life. Moreover, the observed associations between personal allergy history, family allergy history and childhood

ALL in this study and others^{38,39} support the view that personal and family allergy histories have the potential to confound early infection-ALL associations.

Limitations of our study include the fact that allergy and infectious disease histories were self-reported by case and control parents and are possibly subject to some misclassification. The time frame from birth to completion of the questionnaire was >10 years for approximately 75% of both case and control parents and probably contributed to the misclassification of these exposures as well. The prevalence of specific allergy types reported in our study are comparable to those from other surveys, although allergy prevalence remains difficult to ascertain because of differing definitions employed, differing rates by geographical location and an apparent increase in certain allergy types such as eczema in recent years.⁶⁷⁻⁷⁰

Under-reporting of infections by parents in our study appears likely based on prevalence figures from cohort studies,⁷¹⁻⁷³ reliability studies of parental reports of infections,^{74,75} findings from mailed surveys,^{76,77} and data from the National Health Interview Survey (NHIS).^{78,79} Even so, evaluations of the accuracy of self-reports in NHIS have indicated that under-reporting appears independent of population or socio-economic characteristics.⁷⁷ Under-reporting also may be more frequent for conditions lacking clear and unambiguous diagnostic criteria such as upper respiratory infections,⁸⁰ a common early childhood complaint. Non-differential bias towards the null due to the under-reporting of infections by case and control parents may account for the absence of observed effects for one or more illnesses in this study.

The frequencies of infections listed by name in the questionnaire were similar for cases and controls in almost all instances, yet case parents reported 'other' infections more frequently than controls (13% vs. 5%, $P < 0.0001$), even after censoring for age at diagnosis. Some of the 'other' infections listed were unusual or serious (e.g. Kawasaki syndrome, fever of unknown origin) while others were not (e.g. conjunctivitis, yeast infections). Leukaemia is often diagnosed in conjunction with a lingering infection, which may have sensitised case parents to a role for infection in ALL. Consequently, recall bias among case parents (less under-reporting by case parents in this study) would drive the ORs toward the null for 'true' inverse associations and away from the null for any positive associations. Alternatively, unusual illnesses such as fever of unknown origin may be associated

with ALL; the retrospective nature of this study and the lack of confirmatory laboratory data for infection histories makes it impossible to further characterise these associations.

Responding case and control parents were significantly more likely to be white than non-respondents and non-whites were more difficult to locate than whites (data not shown). Nonetheless, mean educational levels and ages at birth were similar for responding white and non-white mothers while non-white family incomes were lower than those of whites; these patterns were similar for both cases and controls. Overall, respondents in our study were well educated with 38% reporting family incomes of >US\$35 000 in 1994. These characteristics are similar to those observed among respondents in another childhood ALL study.⁸¹

Response bias could impact our findings if allergy or infection prevalence varied differentially by response status. Child allergy frequencies were similar for responding white and non-white parents, with the exception of an increased prevalence of asthma among non-whites (data not shown), an observation consistent with findings from a national sample of US children.⁷⁰ The frequencies of specific infections such as colds, otitis media, vomiting and lower respiratory tract illnesses did vary by race; however, these differences were similar for cases and controls (data not shown). While response bias may have resulted in a more homogeneous sample than the population from which it was drawn, case and control families appear to have been affected similarly.

In conclusion, a positive index child allergy history before leukaemia diagnosis was associated with a significantly reduced risk of ALL. Additionally, children with positive personal allergy histories reported more frequent infections in our study than those with negative histories, an observation consistent with findings from a large retrospective cohort study assessing risk factors for allergy development in British school children.⁶² Nonetheless, effect modification of the infection-ALL associations was not observed in our study, perhaps due in part to our relatively small sample size. Personal atopy or a high-risk of atopy based on family history, may influence the occurrence of infectious diseases during early childhood in a manner which complicates the interpretation of the role of infection in ALL. Additional evaluations of the role of childhood infectious disease histories in conjunction with both personal and family allergy history would perhaps

clarify the role of these factors in the development of childhood ALL.

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