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Patterns of infection and day care utilization and risk of childhood acute lymphoblastic leukaemia

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Summary To investigate if decreased exposure to common childhood infections is associated with risk of childhood acute lymphoblastic leukaemia (ALL) we conducted a case–control study of 1842 newly diagnosed and immunophenotypically defined cases of ALL under age 15, and 1986 matched controls in the US. Data regarding day care, sibship size and common childhood infections were obtained through parental interviews. Data were analysed stratified by leukaemia lineage and separately for 'common' childhood ALL (age 2–5 years, CD19, CD10-positive). Neither attendance at day care nor time at day care was associated with risk of ALL overall or 'common' ALL. Ear infections during infancy were less common among cases, with odds ratios of 0.86, 0.83, 0.71 and 0.69 for 1, 2–4, 5+ episodes, and continuous infections respectively (trend $P = 0.026$). No effect of sibship size or birth interval was seen. With one exception (ear infections), these data do not support the hypothesis that a decrease in the occurrence of common childhood infection increases risk of ALL. © 2000 Cancer Research Campaign

Keywords: childhood acute lymphoblastic leukaemia; infections; day care

Acute lymphoblastic leukaemia (ALL), the most common childhood cancer worldwide, occurs at annual rates of between three and four cases per 100 000 children under age 15 in most developed countries (Gurney, 1995; Parkin et al, 1998). Apart from genetic disorders and ionizing radiation, there are no clear aetiological risk factors for ALL (Ross et al, 1994; Pui, 1995; Greaves, 1997; Sandler and Ross, 1997). Investigations of more ubiquitous exposures, including low frequency electromagnetic radiation, have been inconsistent (Savitz et al, 1988; Feychting and Ahlbom, 1993; Linet et al, 1997). ALL is a heterogeneous disorder; however, the majority of cases arise from cells which express CD10 and CD19 cell-surface proteins consistent with B-lineage differentiation (Pui et al, 1993; Kersey, 1997). This phenotype is most common among children diagnosed with ALL between ages 2 and 5, corresponding to the observed age-specific incidence peak (Gurney, 1995; Sandler and Ross, 1997). Greaves hypothesized that the pathogenesis of 'common' B-lineage childhood ALL is a two-step process (Greaves, 1988). In the first step, the developmentally driven proliferation of B-precursor cells results in spontaneous mutation of a small population of cells. In the second event, additional mutation or proliferation of the initially mutated cells results from infectious exposures. In this model, *delayed* exposure to common childhood infections leads to a leukaemic outcome in a small number of children as a result of stimulation of an expanded population of pre-leukaemic cells by virtue of later infection. International and regional patterns of ALL incidence demonstrating lower rates in developing countries support this hypothesis (Greaves and Chan, 1986; Greaves, 1988, 1993).

In a large case–control study, the Children's Cancer Group (CCG) and the National Cancer Institute investigated patterns of infection, surrogates of infection and risk of childhood ALL within immunophenotypic subgroups. We hypothesized that children with ALL would have had fewer childhood infections or have been less likely to be in high-exposure environments (i.e. day care) than controls.

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METHODS

Case ascertainment

Cases of newly diagnosed ALL in children under 15 years of age were ascertained from CCG member institutions throughout the USA. To be eligible, cases had to be newly diagnosed with ALL between 1 January 1989 and 15 June 1993, and the biological mother had to be available for interview, speak English and have a telephone in the household. Submission of a diagnostic bone marrow specimen for immunophenotyping was required. A total of 2081 eligible cases were identified during the study period and a telephone interview completed for 1914 (92.1% of eligible cases). The reasons for non-participation of 167 eligible cases are shown in Table 1.

Control selection

Controls were randomly selected using a random digit-dialling methodology previously described (Robison and Daigle, 1984) and individually matched to cases on age (within 25% of age at diagnosis of the case, with a maximum difference of ± 2 years), race (white, black, or other, although this match was relaxed if a

Table 1 Characteristics of cases and controls

	Cases	Controls	*P*-value
Maternal interview			
Eligible	2081	2597	
Completed interview	1914 (92.1%)	1987 (76.5%)	
Matched set	1842 (88.6%)	1986 (76.5%)	
Non-response	167 (7.9%)	610 (23.5%)	
Physician refusal	41 (2.0%)	–	
Parental refusal	70 (3.4%)	457 (17.6%)	
Lost to follow-up	18 (0.9%)	17 (0.7%)	
Other	38 (1.8%)	136 (5.2%)	
Gender – male	1018 (55.2%)	1076 (54.2%)	0.54
Age			
<12 months	64 (3.5%)	81 (4.1%)	0.07
12–23 months	138 (7.5%)	189 (9.5%)	
2–5 years	1020 (55.4%)	1038 (52.3%)	
6–10 years	408 (22.2%)	466 (23.5%)	
11–15 years	212 (11.5%)	212 (10.7%)	
Race			
White	1492 (81.0%)	1720 (86.6%)	<0.01
Black	109 (5.9%)	94 (4.7%)	
Hispanic	153 (8.3%)	121 (6.1%)	
Other	88 (4.8%)	51 (2.6%)	
Maternal education			
= High school	797 (43.3%)	762 (38.4%)	<0.01
Some post high school	592 (32.1%)	701 (35.3%)	
College +	453 (24.6%)	523 (26.3%)	
Paternal education[a]			
≤ High school	676 (41.8%)	638 (37.1%)	<0.01
Some post high school	480 (29.7%)	510 (29.6%)	
College +	462 (28.6%)	574 (33.4%)	
Income			
<10 000	217 (11.8%)	176 (8.9%)	<0.01
10 000–19 999	390 (21.2%)	370 (18.6%)	
20 000–29 999	433 (23.5%)	475 (23.9%)	
30 000–39 999	334 (18.1%)	369 (18.6%)	
40 000–49 999	204 (11.1%)	221 (11.1%)	
50 000+	250 (13.6%)	357 (18.0%)	
Unknown	14 (0.8%)	18 (0.9%)	
Immunophenotype			
T-cell	183 (9.9%)		
Early pre-B-cell	893 (48.5%)		
Pre-B-cell	233 (12.6%)		
B not specified	231 (12.5%)		
Unknown	302 (16.4%)		

[a]Based on 1618 cases and 1722 matched controls who responded to paternal interview.

control was not obtainable for a given case) and telephone area code and exchange. T-cell case–controls were also matched for gender. A total of 2597 eligible controls were identified, of whom 1987 (76.5%) participated. One control was excluded because the case was later found to be ineligible for the study. Reasons for non-participation are shown in Table 1. Matched controls were not found for 72 (3.6%) interviewed cases, resulting in 1842 case–control pairs (1704 sets of 1:1 match, 132 sets of 1:2 match and 6 sets of 1:3 match).

Interview

The structured interview included questions about the subject's and mother's health history, details of pregnancy and birth, childhood illnesses, illnesses of siblings and parental occupation. The maternal interview included details of day care and pre-school attendance (whether or not the index child ever attended day care or pre-school, approximate dates of attendance, and average number of hours per day). Day care or pre-school attendance in the year prior to the ALL diagnosis (cases) or index date (controls) was excluded to eliminate the possibility that symptoms of ALL itself decreased attendance at day care or pre-school. There was considerable overlap in day care and pre-school attendance times, thus total time spent by a child in these activities were pooled for analysis and is referred to as 'day care'.

Mothers of cases and controls residing in a nine-state region of the northeastern USA participated in an additional in-home interview (Kleinerman et al, 1997; Hatch et al, 1998), which included more detailed information on the childhood health history and several common childhood illnesses.

Immunophenotype determinations

A standard panel of monoclonal antibodies was applied to all diagnostic bone marrow specimens to determine B- or T-lineage. A subset of B-lineage leukaemias was further classified by the determination of cytoplasmic immunoglobulin. Cases were assigned to one of the following mutually exclusive groups: T-cell ALL, early pre-B ALL (B-lineage markers and cytoplasmic immunoglobulin negative), pre-B ALL (B-lineage markers and cytoplasmic immunoglobulin positive), B-lineage ALL – not otherwise specified (NOS) (B-lineage markers but cytoplasmic immunoglobulin not performed), or unclassifiable. 'Common' childhood ALL was defined as those cases determined to be of B-lineage expressing both the CD10 and CD19 surface antigens, and diagnosed in children aged 2–5 years.

Statistical analysis

Data were analysed for all types of ALL as a group and within strata defined by age or immunophenotypic subtype. Conditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (CI) as an approximation of relative risk with control for potential confounders. Tests for trend were performed by treating levels of categorical data as continuous variables in the logistic model. Analyses were adjusted for maternal education, family income and race.

RESULTS

Study participants

The characteristics of 1842 cases and 1986 controls are shown in Table 1. Cases were predominately male, white and between the ages of 2 and 5 years. As compared to the cases, controls were more often white, and were of higher socio-economic status as evidenced by differences in income, and maternal and paternal education (Table 1). Phenotypically, 9.9% of ALL cases were T-lineage, 73.7% B-lineage, and no clear lineage could be assigned in 16.4%. Among 1357 B-lineage cases, 633 (46.6%) were designated 'common' childhood ALL.

Day care and pre-school (Table 2)

The likelihood of ever attending day care was similar among cases and controls (OR 0.96; 95% CI 0.82–1.12). No inverse association (protective effect) of day care attendance (vs no day care attendance) was seen among children with 'common' ALL (OR 0.96,

Table 2 Day care[a] and risk of childhood ALL

	Total ALL			'Common' ALL CD10+, CD19+, Age 2–5			All other ALL		
	Cases n = 1744	Controls n = 1879	OR (95% CI)	Cases n = 633	Controls n = 687	OR (95% CI)	Cases n = 1111	Controls n = 1192	OR (95% CI)
Any day care									
No	914	949	1.00	413	429	1.00	501	520	1.00
Yes	830	930	0.96 (0.82–1.12)	220	258	0.96 (0.75–1.24)	610	672	0.95 (0.78–1.16)
Age at start of day care									
No day care	914	949	1.00	413	429	1.00	501	520	1.00
≤ 6 months	165	201	0.91 (0.72–1.15)	67	78	1.02 (0.70–1.48)	98	123	0.85 (0.62–1.16)
7–12 months	66	76	0.99 (0.70–1.41)	27	28	1.23 (0.70–2.15)	39	48	0.90 (0.57–1.41)
13–24 months	114	113	1.06 (0.79–1.41)	41	49	0.88 (0.56–1.38)	73	64	1.18 (0.80–1.73)
> 24 months	185	540	0.94 (0.77–1.14)	85	103	0.84 (0.57–1.23)	400	437	0.96 (0.77–1.21)
Test for trend			P = 0.712			P = 0.423			P = 0.995
Time in day care (days in day care, regardless how many hours/day)									
No day care	914	949	1.00	413	429	1.00	501	520	1.00
<3 months	78	73	1.07 (0.77–1.50)	33	30	1.08 (0.64–1.83)	45	43	1.05 (0.67–1.62)
3–6 months	74	68	1.09 (0.76–1.55)	35	26	1.31 (0.75–2.30)	39	42	0.92 (0.58–1.48)
7–12 months	218	266	0.88 (0.71–1.10)	47	71	0.74 (0.48–1.12)	171	195	0.93 (0.72–1.22)
> 12 months	460	523	0.94 (0.78–1.13)	105	131	0.96 (0.70–1.32)	355	392	0.95 (0.75–1.20)
Test for trend			P = 0.407			P = 0.560			P = 0.597
Day care before age 2									
No	1399	1489	1.00	498	532	1.00	901	957	1.00
Yes	345	390	0.99 (0.84–1.17)	135	155	1.05 (0.80–1.37)	210	235	0.97 (0.78–1.20)
Time in day care before age 2									
No	1399	1489	1.00	498	532	1.00	901	957	1.00
< 3 months	63	54	1.23 (0.84–1.80)	22	16	1.43 (0.73–2.79)	41	38	1.12 (0.70–1.79)
3–6 months	51	40	1.30 (0.85–1.99)	25	11	2.33 (1.08–5.01)	26	29	0.96 (0.56–1.65)
7–12 months	71	95	0.87 (0.63–1.20)	25	51	0.61 (0.37–1.00)	46	44	1.17 (0.76–1.79)
> 12 months	160	201	0.91 (0.73–1.15)	63	77	1.09 (0.76–1.57)	97	124	0.83 (0.62–1.13)
Test for trend			P = 0.461			P = 0.949			P = 0.458

[a]Excluding day care within 1 year before the diagnostic date (case) or reference date (control). Excluding subjects who were less than 1-year-old at diagnostic date (case) or reference date (control). Odds ratios were derived from conditional logistic model adjusted for maternal race, education, and family income.

Table 3 Siblings and risk of childhood ALL

	Total ALL			'Common' ALL CD10+, CD19+, Age 2–5			All other ALL		
	Cases n = 1744	Controls n = 1879	OR (95% CI)	Cases n = 633	Controls n = 687	OR (95% CI)	Cases n = 1111	Controls n = 1192	OR (95% CI)
Number of older siblings									
None	730	813	1.00	258	287	1.00	472	526	1.00
1	634	659	1.08 (0.93–1.26)	236	234	1.11 (0.86–1.43)	398	425	1.06 (0.87–1.28)
≥2	380	407	1.05 (0.88–1.26)	139	166	0.94 (0.70–1.26)	241	241	1.13 (0.90–1.41)
Test for trend			P = 0.447			P = 0.842			P = 0.279
Interval to birth of next older sibling									
No older sibling	730	813	1.00	258	287	1.00	472	526	1.00
≤5 years	855	911	1.05 (0.92–1.21)	314	333	1.03 (0.81–1.30)	541	578	1.03 (0.89–1.27)
> 5 years	159	155	1.18 (0.92–1.51)	61	67	1.08 (0.72–1.63)	98	88	1.23 (0.89–1.69)
Test for trend			P = 0.200			P = 0.692			P = 0.219

Excluding subjects < 1 year old. Odds ratio were derived from conditional logistic model, adjusted for maternal race, education and family income.

95% CI 0.75–1.24). Detailed analysis by immunophenotypic category revealed no additional associations with ORs of 1.00, 0.90, 0.86 and 0.75 for early pre-B ALL, pre-B ALL, B-cell NOS, and T-cell ALL respectively (data not shown).

No significant associations were present for age at start of day care or time in day care, defined as the total number of days that the subject attended day care. Children with 'common' ALL were as likely to have started day care before 6 months of age as were controls. No effect was seen for starting day care later in childhood.

Table 4 Infection during infancy and risk of childhood ALL*

	Total ALL			'Common' ALL CD10+, CD19+, Age 2–5			All other ALL		
	Cases *n* = 727	Controls *n* = 637	OR (95% CI)	Cases *n* = 299	Controls *n* = 270	OR (95% CI)	Cases *n* = 428	Controls *n* = 367	OR (95% CI)
Ear infection									
None	386	302	1.00	150	111	1.00	236	191	1.00
Once	88	81	0.86 (0.61–1.22)	37	36	0.83 (0.49–1.40)	51	45	0.92 (0.58–1.45)
2–4	161	152	0.83 (0.63–1.09)	72	76	0.65 (0.43–1.00)	89	76	0.99 (0.69–1.43)
5 or more	75	83	0.71 (0.50–1.01)	36	40	0.64 (0.38–1.08)	39	43	0.75 (0.46–1.22)
Continuous	17	19	0.69 (0.35–1.37)	4	7	0.47 (0.13–1.67)	13	12	0.79 (0.35–1.79)
Test for trend			*P* = 0.026			*P* = 0.016			*P* = 0.326
Lung infection									
None	575	523	1.00	237	224	1.00	338	299	1.00
Once	80	58	1.32 (0.92–1.89)	33	25	1.32 (0.76–2.32)	47	33	1.33 (0.82–2.14)
2–4	56	36	1.48 (0.95–2.29)	24	14	1.79 (0.89–2.58)	32	22	1.28 (0.72–2.27)
5 or more	16	19	0.70 (0.35–1.40)	5	7	0.51 (0.15–1.74)	11	12	0.79 (0.34–1.86)
Test for trend			*P* = 0.330			*P* = 0.403			*P* = 0.595
Vomiting or diarrhoea									
None	545	192	1.00	222	213	1.00	323	279	1.00
Once	85	62	1.26 (0.89–1.80)	31	30	1.06 (0.62–1.84)	54	32	1.55 (0.96–2.49)
2 or more	97	83	1.07 (0.78–1.48)	46	27	1.57 (0.93–2.66)	51	56	0.78 (0.51–1.19)
Test for trend			*P* = 0.428			*P* = 0.108			*P* = 0.622
Pressure equalization (PE) tubes									
No	649	565	1.00	269	241	1.00	380	324	1.00
Yes	77	71	0.97 (0.69–1.37)	30	29	0.94 (0.54–1.63)	47	42	0.96 (0.61–1.51)
Age at PE tubes									
No	649	565	1.00	269	241	1.00	380	324	1.00
0–1 years	30	35	0.78 (0.47–1.30)	14	15	0.86 (0.40–1.85)	16	20	0.68 (0.34–1.34)
≥2 years	47	35	1.18 (0.75–1.88)	16	14	1.01 (0.48–2.15)	31	21	1.28 (0.72–2.31)

[a]Participants in the expanded in-person interview, excluding cases and controls under age of 18 months. Odds ratios derived from unconditional logistic model, adjusted for maternal race, education, age and sex of index child and family income

Examination of day care within strata defined by age at diagnosis of ALL revealed that among children under age 5, any attendance at day care was associated with ALL risks similar to those for children never attending day care (OR 0.90, 95% CI 0.75–1.09); risks were similarly close to unity among children aged 6–10 years (OR –1.00, 95% CI 0.70–1.42), and for children aged 11 and older (OR 1.20, 95% CI 0.78–1.87). Among these age groups, no significant associations were seen between age at starting day care or total number of day care visits and risk of childhood ALL (data not shown). Similar results were obtained when the analysis was restricted to day care attendance prior to 2 or 1 years of age.

Sibship characteristics (Table 3)

No differences between cases and controls were seen in the number of older siblings. The time interval between the birth of children with ALL and the birth of their next older sibling was similar to that of their controls. No significant difference in sibship size or interval were seen within B-lineage groups (data not shown); however, children with T-lineage ALL were somewhat more likely to have two or more older siblings than were their controls (OR 1.88, 95% CI 1.05–3.36).

Health history, reported infections (Table 4)

Additional data on the occurrence of infections were available for subjects participating in the in-home interview (see Methods). No differences in reported lung infections or instances of gastroenteritis (vomiting and diarrhoea) were evident for the entire group, among cases of 'common' ALL, or within B-lineage or T-lineage ALL subsets (data not shown). Cases were no more likely to have ever had pressure equalization (PE) tubes placed in the ears (OR 0.97, 95% CI 0.69–1.37). Additionally, no significant differences in ALL risk were found for age at, or occurrence of, tonsillectomy, adenoidectomy, or appendectomy (data not shown).

The risk of ALL was reduced in those who experienced one or more ear infections during the first year of life. Risk of ALL decreased with increasing numbers of reported ear infections during the first year of life with ORs of 0.86, 0.83, 0.71 and 0.69 for 1 episode, 2–4 episodes, 5+ episodes and continuous infections respectively (trend $P = 0.026$). This significant inverse association with ear infections in infancy was most evident in children with 'common' ALL (test of trend $P = 0.016$). Cases and controls were equally as likely to report a history of varicella (OR 1.10, 95% CI 0.84–1.45) among all children with ALL and among 'common' ALL cases and controls (OR 0.96, 95% CI 0.56–1.51).

Infectous exposures in aggregate

An attempt was made to evaluate infectious exposure in aggregate by the creation of a summary variable including day care data, reported infections and sibship characteristics (Table 5, see footnote of the Table for grouping information). No clear trend was evident when comparing the 'intermediate' or 'most' exposed

Table 5 Summarized infections exposure level and risk of childhood ALL[a]

	Total ALL			'Common' ALL CD10+, CD19+, Age 2–5			All other ALL		
	Cases *n* = 727	Controls *n* = 637	OR (95% CI)	Cases *n* = 299	Controls *n* = 270	OR (95% CI)	Cases *n* = 428	Controls *n* = 367	OR (95% CI)
Least exposed group[b]	110	101	1.00	44	36	1.00	66	65	1.00
Intermediate exposed group[b]	519	450	1.06 (0.78–1.43)	207	193	0.87 (0.53–1.42)	312	257	1.21 (0.83–1.78)
Most exposed group[b]	98	86	1.13 (0.76–1.70)	48	41	1.07 (0.58–1.99)	50	45	1.16 (0.68–2.00)
Test for trend			*P* = 0.541			*P* = 0.790			*P* = 0.511

[a]Participants in the expanded in-person interview, excluding cases and controls under age of 18 months. [b]Least exposed group: no day care prior to age of 2; no older sibling; no ear infection, no lung infection during infancy, no history of PE tubes prior to age of 2. Most exposed group: had at least two of the following conditions: had 7 or more months of day care before age of 2; had an older sibling within 5 years; had five or more ear infections or PE tubes prior to age of 2. Intermediate exposed group: all children who did not fall into least or most exposed groups. Odds ratios were derived from unconditional logistic model, adjusted for maternal race, education, the age and sex of index child and family income

groups to the 'least' exposed group for all children with ALL or the subset of children with 'common' ALL.

DISCUSSION

Three separate, but not exclusive, hypotheses of ALL pathogenesis and infection deserve consideration. Citing the international variations in ALL rates, the development of the ALL 'peak' at different times in different populations, and the higher rates of 'common' childhood ALL among more developed populations, Greaves (1988) has suggested that delaying the occurrence of childhood infections may, in some susceptible children, have an aetiological role in the leukaemogenic process. Kinlen has suggested that childhood ALL occurs as a rare response to a specific viral agent or agents and that excesses of childhood leukaemia are promoted by marked urban–rural population mixing, as a result of an increased level of contacts between susceptible and infected individuals. Studies describing an increased occurrence of ALL in British 'New Towns' and other areas of population mixing support this theory (Kinlen, 1988, 1995; Kinlen et al, 1990; Alexander et al, 1997). Smith (1997) has suggested an aetiological role for a viral agent infecting a susceptible mother during pregnancy. JC virus, a polyoma virus, has been proposed as a candidate virus, but there are no data testing this hypothesis in childhood ALL. As part of a large study of childhood ALL undertaken to evaluate risk factors within biologically defined subgroups, we sought to test the hypothesis that fewer infections during early childhood increase the risk of ALL through the use of surrogate indicators of infection including day care, sibship distribution and size, and maternal reporting of her child's illnesses.

Studies of children attending day care in the USA have shown a higher frequency of upper respiratory infections, otitis media, and gastroenteritis compared to children not attending day care (Haskins and Kotch, 1986; Wald et al, 1991; Hansen, 1993; Reeves et al, 1993). Therefore, we postulated that children with ALL would attend day care less often and/or for shorter duration than controls. Overall, and among children with 'common' ALL, we found no protective effect. Moreover, examination of day care 'exposure' variables, including age at initiation of day care and time in day care revealed no evidence for an association. No 'threshold' of day care exposure (time in day care) was present as was reported for 'creche' attendance in Athens (Petridou et al, 1993).

In our study, mothers of children with 'common' ALL reported fewer ear infections than control mothers. This association was confined to the 'common' ALL group. We observed no differences for reported episodes of colds, lung infections, or gastroenteritis between the cases and controls. The reason for this apparent discrepancy is unclear, although maternal recollection of ear infections may be more accurate than recall of the other infectious diseases investigated, as the diagnosis of otitis media is virtually always made by a physician and usually results in treatment with a course of antibiotics. Infections less likely to result in a visit to the physician or treatment with antibiotics may be less reliably recalled. Nevertheless, it is noteworthy that no difference was noted for the frequency of PE tubes (often placed for recurrent ear infections) for the group overall or any of the leukaemia subsets.

The number of, and interval between, the birth of the index child and older siblings were also investigated as a surrogate of exposure to infection, based on the hypothesis that firstborn children or those children whose siblings are much older are less likely to be exposed to infection and thus at an increased risk of ALL (James, 1990). In contrast to our previous data showing an elevated risk of ALL with longer birth intervals (> 5 years) (Kaye et al, 1991), no evidence of an effect of birth order or interval was evident in this investigation.

Given the breadth of interactions that determine any child's frequency or timing of infections, we attempted to create a summary variable that would define the most and least infection exposed groups. This variable, composed of day care attendance, reported episodes of otitis media in infancy, sibship characteristics and need for PE tubes did not support the hypothesis that the 'most exposed' subset of children may be at decreased risk of ALL. Analysis within the immunophenotypically defined ALL strata and the 'common' ALL subset did not reveal any additional associations.

Overall, the results of this analysis provide little support for a relationship between early childhood infections and the risk of childhood ALL. The data reported for ear infections in infancy suggest a protective effect of early, repeated, non-specific

infection, as most episodes of otitis are initiated by viral upper respiratory infection. The specificity of this finding to the 'common' ALL subset provides additional support for this hypothesis. In contrast, the results of the data reported on attendance at day care and sibship characteristics do not.

It is possible that infections do impact on childhood ALL risk and that the limitations of our study precluded ascertainment of some of these relationships. Among worldwide populations there may be significantly more heterogeneity of childhood infectious exposures than within our study population. Thus, actual differences in occurrence and/or timing of infections may not have been great enough within our population to identify small increases (or decreases) in ALL risk. Another potential limitation is the absence of data on the size of the day care facility the study children attended. Thus, we were unable to stratify by day care size, which may impact on the exposures a child has. Nevertheless, day care visits, hours of attendance and age at first attendance of day care provided little evidence of any effect, either among the group overall or the 'common' ALL subset.

Similar investigations of childhood ALL aetiology currently are underway in the UK and Canada. Results from these studies and other hypothesis-directed investigations combining suspected epidemiological and biological determinants for childhood ALL should hopefully clarify any relationship between infection very early in life and the subsequent risk of childhood ALL.

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APPENDIX

Participating principal investigators – children's cancer group

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