Community Clusters of Childhood Leukemia and Lymphoma: Evidence of Infection?

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Information suggesting that infection may be an underlying cause of childhood leukemia and lymphoma includes the occasional appearance of cases in time-space clusters within communities and increased incidence after communities experience marked population influxes (population mixing). Among 50 clusters involving cases of childhood leukemia and lymphoma investigated in the United States in 1961–1977, eight showed suggestive evidence of underlying infectious causation. In seven of the eight communities, case occurrence was associated with the attendance of patients or their siblings at particular schools or with family participation in particular church groups. In five, rapid population growth had occurred. Other findings included the possible association of cases with unusual patterns of infectious disease (rheumatic illness in one community, chickenpox in another) and with other childhood diseases, including other forms of childhood cancer. In one community, two cases of Burkitt’s lymphoma occurred at the same time, and a third case arose 3 years later in boys living in a newly developing neighborhood. Such community observations support the need for continued biologic research regarding the possible role of infectious agents in childhood leukemia and lymphoma.

child; cluster analysis; infection; leukemia; lymphoma

Editor’s note: An invited commentary on this article appears on page 823, and the author’s response appears on page 825.

No infectious agents have yet been identified that cause childhood leukemia and lymphoma, aside from Epstein-Barr virus, which causes Burkitt’s lymphoma in Africa (1). The possibility, however, has long received epidemiologic attention. Initially, attention came largely from studies of case clusters identified within residential communities (2–12) and from population-based statistical analyses that supported a modest tendency for time-space clustering to occur beyond what chance might predict (13–19).

Since the late 1980s, interest has been heightened by repeated observations, first in the United Kingdom (20, 21) and then elsewhere (12, 22–25), that local rates of childhood leukemia or lymphoma increase when local populations rise abruptly, especially in sparsely settled areas. It is thought that such local population increases can involve population mixing that may promote the exposure of immunologically vulnerable children to persons carrying infectious agents capable of inducing leukemia or lymphoma. Rapid recent population growth was clearly evident in Niles, Illinois, where a leukemia case cluster was investigated in 1961 (2), and it is a striking feature of a case cluster currently under study in Fallon, Nevada (12).

Increasing knowledge regarding genetic and molecular markers has encouraged efforts to discover specific biologic events underlying these findings. Two models by which infection might result in childhood leukemia or lymphoma have been suggested. One proposes that common childhood infections, under conditions of population mixing, may induce leukemia or lymphoma in immunologically inexperienced children (21). The other postulates heightened vulnerability of some children, unexposed in utero or in early life, to later exposure to infectious agents (26, 27)—vulnerability being enhanced by chromosomal translocations in utero (28).
TABLE 1. Epidemiologic features of eight community clusters of childhood leukemia and lymphoma, United States, 1961–1977

<table>
<thead>
<tr>
<th>Feature</th>
<th>Niles, Illinois</th>
<th>Kendall Park, New Jersey</th>
<th>Middletown, Connecticut</th>
<th>Niles, Michigan</th>
<th>Milpitas, California</th>
<th>Cranston, Rhode Island</th>
<th>Dubois, Pennsylvania</th>
<th>Winchester, Virginia</th>
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<tbody>
<tr>
<td>Unusual case distribution by school attendance</td>
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<td>Unusual case distribution by church affiliation</td>
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<td>Recent influx of population</td>
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<tr>
<td>Possible links with childhood infection</td>
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<tr>
<td>Association with other childhood illness or cancer</td>
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Given these thoughts regarding infection as a possible cause of childhood leukemia and lymphoma, this paper reviews eight community case clusters that were investigated by the US Centers for Disease Control and Prevention in 1961–1977. In each investigation, epidemiologic or clinical features linked cases in ways that suggested infectious etiology (table 1). In seven communities, case occurrence was focused in particular school and church groups; in five, considerable population growth had recently occurred; in three, case occurrence seemed linked to common childhood infections; and in three, possible associations existed with other childhood illness, including other cancers. In none were there unusual environmental exposures or familial illness.

These eight investigations were drawn from a total of 50 case clusters involving childhood (under age 15 years) leukemia or lymphoma in US communities that were studied by the Centers for Disease Control and Prevention in cooperation with state and local health agencies and the National Cancer Institute. Limited laboratory studies were conducted (4, 29, 30), but none produced useful leads. Aside from the eight communities described here, little was found to link individual cases beyond increased case frequencies.

LEUKEMIA/LYMPHOMA CLUSTERS

Niles, Illinois

In 1956–1960, eight cases of acute leukemia occurred among children (one boy, seven girls) in the town of Niles, Illinois (expected incidence for children under age 15 years, 1.6 cases; \( p = 0.007 \)) (2, 10). Niles adjoins the north side of Chicago. Its total population in 1960 was 20,393, a sixfold increase since 1950. Nearly all of the growth occurred in the northern part of town, which had earlier been rural countryside. All eight patients lived in that new section and had moved to Niles 1–10 years prior to case onset from communities in the northern or western parts of Chicago.

The north section of Niles corresponded with the Catholic parish of St. John Brebeuf. Seven of the eight affected families both belonged to the parish and had children attending the St. John Brebeuf parish elementary school at the time of case onset. Three patients attended the school at onset, and four were of preschool age.

Approximately 60 percent of families in the parish area belonged to the parish, and approximately 70 percent of those families had children attending the St. John Brebeuf school. The school first opened in 1955. Its enrollment in 1960 was 1,430 (grades 1–8), about twice the size of the largest public school. Five public schools served the parish area.

In addition, during 1957–1960, eight cases of rheumatic illness occurred among children from families using the St. John Brebeuf school—four times the frequency reported for parish-area families using the public schools. Illnesses consisted of fever, joint symptoms, pharyngitis, and elevated antistreptolysin titers. Seven patients were attending the St. John Brebeuf school at the time of onset. One was the older sister of a leukemia patient. Another developed Hodgkin’s lymphoma in 1961, 3½ years after onset of rheumatic illness.

Two cases of adult acute leukemia and three cases of childhood cancer other than leukemia or lymphoma (Ewing’s sarcoma, vaginal sarcoma, and thyroid adenocarcinoma) were identified in parish-area residents with onsets in 1956–1961. All five patients were in families belonging to the St. John Brebeuf parish, four with children attending the St. John Brebeuf school at the time of illness onset.

Review of childhood mortality in 1956–1960 revealed an unusual pattern of neonatal cardiac birth defects (seven of eight fatal neonatal malformations as compared with 19 of 61 in neighboring towns). Four of the seven cardiac deaths occurred in families that lived in the parish area. Each of the four families attended the St. John Brebeuf church, but none had children enrolled in the St. John Brebeuf school.

A community survey conducted in 1961 collected data regarding the occurrence of common childhood infections in parish-area children (10). While patterns were similar among children in families attending the St. John Brebeuf church and children in other families, cases of chickenpox, measles, and rubella were more common in the St. John Brebeuf group in 1956–1957.

Follow-up studies carried out in 1969 indicated that the frequency of childhood leukemia and lymphoma declined appreciably after 1960 (10), although four further cases (two acute leukemias and two Hodgkin’s lymphomas) occurred in parish families that used the St. John Brebeuf school.

Kendall Park, New Jersey

During 1957–1969, six cases of acute leukemia occurred in young persons (two male, four female; five under age 15 years, one aged 19 years) in Kendall Park, New Jersey.
(expected incidence for youths under age 25 years, 2.3 cases; \( p = 0.03 \)) (10). Kendall Park, which had a total population of 10,400 in 1968, is 20 miles (32 km) southeast of New York City. At the time, it was a new residential community in a rural area where development began in 1957. Residents were mostly young families. Residential turnover was about 20 percent each year. Approximately one half of all employed residents commuted to the city.

The four most recent cases (1965–1969; expected incidence, 0.9 case) all occurred in families that belonged to the Catholic parish of St. Augustine. The same was true of two additional acute leukemia cases (one in a 5-year-old boy and one in a 6-year-old girl) occurring in families that had lived in the town since 1957 but had moved away 2–3 years before illness onset in 1968–1969. The four resident families had been living in Kendall Park for 4–11 years before onset. The families in which the two earliest cases occurred (onsets in 1959 and 1961) did not belong to the parish.

Although the St. Augustine parish covered an area greater than the town itself, residents of Kendall Park accounted for approximately 80 percent of parish members. In turn, parish members represented less than 40 percent of the town’s total population. No cases of childhood leukemia were identified among residents of the St. Augustine parish area outside of Kendall Park.

In 1963, the St. Augustine parish established a parochial elementary school (grades 1–8) adjoining the parish church. Children from all six families in which recent cases occurred (1965–1969) were enrolled in that school. While the six children in whom leukemia developed did not themselves attend the St. Augustine school at the time of onset (two families had moved away, and, of the four resident patients, two were of preschool age and two were older), siblings in all four resident families (eight children in all) were attending the school at onset (1968–1969). In 1969, the St. Augustine school enrolled 521 children. Kendall Park contained three public elementary schools (grades 1–6) with a total combined enrollment of 1,503.

In 1950–1969, eight cases of acute leukemia occurred among children in Middletown, Connecticut (expected incidence for children under age 15 years, 9.6 cases) (10). However, the six most recent cases (three in boys, three in girls; expected incidence for 1957–1969, 1.1 cases; \( p = 0.01 \)) arose in families living in a newly developing section of town where total population grew from 2,300 in 1957 to 10,500 in 1969. All six families belonged to the Catholic parish of St. Pius, which was established in 1957. Approximately 45 percent of the population living in the parish area belonged to the parish. In 1969, Middletown’s total population was approximately 32,000, equally divided among three geographically based parishes, St. Pius and two older parishes. The two earliest cases, diagnosed in 1950 and 1951, arose in children from families (one Catholic and one Protestant) living in an older parish.

The three most recent cases occurred within a 7-month period in 1968–1969. All three patients were students at the same public elementary school but were in different grades. The school was located near the St. Augustine church and was the site of parish activities before parish facilities were built in 1959.

One further case of childhood leukemia (in a 2-year-old girl, diagnosed in 1963) was identified in a family that had lived in the parish area until 1959. The family had moved to a nearby town but continued to attend the St. Pius church. The child’s father was a physician who continued his practice in Middletown.

Two cases of childhood cancer other than leukemia or lymphoma had been diagnosed in residents of the St. Pius parish area since 1950, one in 1967 (hepatoblastoma in a 6-year-old boy with congenital heart disease), the other in 1969 (Wilms’ tumor in a 2-year-old girl). Both patients belonged to families that attended the St. Pius church. Adult leukemia incidence was not increased; cases occurred widely over time in all three parish areas.

Niles, Michigan

In 1960–1970, nine cases of leukemia or lymphoma (five acute leukemias, one chronic granulocytic leukemia, and three Hodgkin’s lymphomas) occurred among children aged 3–17 years (seven boys, two girls) in the school district serving Niles, Michigan (expected incidence for youths under age 20 years, 3.7 cases; \( p = 0.01 \)) (31). In 1970, the population of youths under age 20 years was approximately 9,000. The district included the town and parts of two adjoining rural counties. The town’s population in 1969 was 16,400, an increase of 3,000 since 1960.

The situation came to public health attention in 1970 because of two leukemia cases diagnosed in teenage males who were next-door neighbors. Upon inquiry, it became apparent that an unusual number of bone cancer cases (three osteogenic sarcomas, one Ewing’s sarcoma) had occurred in teenage males during that same time period (expected incidence for youths under age 20 years, 0.4 case; \( p = 0.0008 \)). Therefore, investigation focused on these 13 cases (six leukemias, three lymphomas, and four bone sarcomas) in relation to possible associations within the school district.

All but the earliest case occurred in children who were attending school at the time of onset. Although they were scattered by time of illness, their distribution by school was unusual. Of the 17 schools in the district, four had two or more cases. In three of the four schools, pairs of cases occurred during a single school year: acute leukemia and Hodgkin’s lymphoma in 1962–1963 in one elementary school; acute leukemia and Hodgkin’s lymphoma in 1968–1969 in another elementary school; and acute leukemia and osteogenic sarcoma in 1969–1970 in the high school.

Nine of the 13 cases occurred in families living in the town; six occurred in families living in the town’s western third, including the two next-door neighbors. Two other cases occurred in that same neighborhood: a case of Ewing’s sarcoma diagnosed in 1968 in a 13-year-old boy who lived on the same block, and a case of acute leukemia diagnosed in a 3-year-old boy in 1960.

Of the nine leukemia or lymphoma cases, five occurred in families belonging to the St. Mary’s Catholic parish. Parish members represented 10 percent of the school district population of youths under age 20 years was approximately 45 percent of the population living in the parish area belonging to the parish. In 1969, Middletown’s total population was approximately 32,000, equally divided among three geographically based parishes, St. Pius and two older parishes. The two earliest cases, diagnosed in 1950 and 1951, arose in children from families (one Catholic and one Protestant) living in an older parish.

The three most recent cases occurred within a 7-month period in 1968–1969. All three patients were students at the same public elementary school but were in different grades.
population and approximately half of the district’s entire Catholic population (expected incidence for youths under age 20 years in parish families in 1960–1970, approximately 0.4 case; \( p = 0.0001 \)). None of the other eight patients in the district were from Catholic families. The St. Mary’s parish, including the St. Mary’s school (the elementary school where two cases occurred during the 1962–1963 school year), was located in the western part of the town, near the neighborhood where six of the 13 patients lived.

**Milpitas, California**

In 1967–1970, eight cases of acute childhood leukemia (five in boys, three in girls; ages 1–9 years) occurred in Milpitas, California (expected incidence for youths under age 20 years, 1.2 cases; \( p = 0.0001 \)) (31). No cases had occurred in the prior 7 years. The town, located south of San Francisco, adjoined two freeways and had grown rapidly. Its total population in 1970 was 27,149 (approximately 12,000 youths under age 20 years), more than four times its size in 1960. It was a residential community consisting mostly of young families and was subject to rapid population turnover.

The situation came to public health attention when two cases were diagnosed in one neighborhood 3 months apart. Four cases were diagnosed in 1967, two in 1968, and two in 1970. Five of the eight patients were from families belonging to the town’s principal Catholic parish. Some members of a sixth family also belonged to that parish. Parish membership included approximately 15 percent of the town’s population under age 20 years.

The town contained 11 public elementary schools in 1970 (no parochial schools), increasing from three in 1960. Seven of the eight families had children attending elementary school at the time of case onset. Five patients were of school age. They attended four different schools. All five had siblings attending the same schools at the same time. Three patients were of preschool age, two with older siblings attending elementary school at the time of onset. Two patients attended the same school during 1968, the year in which both became ill. At another school, a third patient at the time of diagnosis (1967) was attending school with the older sibling of a preschool child who developed leukemia in 1970. Both schools were located in the western portion of the town where the families of five patients lived. Three of those families belonged to the Catholic parish.

The families of three patients had moved to Milpitas approximately 1 year before diagnosis. The family of a fourth patient, diagnosed in 1970 at age 15 months, moved to the town during the second trimester of the mother’s pregnancy with the child. The other four families had been living in the town for 2–8 years before diagnosis.

**Cranston, Rhode Island**

In 1966–1971, eight cases of leukemia or lymphoma (four acute leukemias, one Hodgkin’s lymphoma, and three lymphosarcomas) occurred among children (four boys and four girls, ages 2–14 years) living or attending elementary school in Cranston, Rhode Island (31). Cranston’s population in 1970 was 74,287, an 11 percent increase since 1960. Five patients lived in Cranston, and six, including three from two adjoining communities, attended school in the town. While these numbers of cases did not greatly exceed the expected incidence for children under age 15 years, either for town residents (5 vs. 3.5) or for children attending the town’s schools (grades 1–8; 6 vs. 4.6), the occurrence in 1971 of acute leukemia in two children attending the same school attracted public health attention.

The six school students attended four different schools at the time of onset. Two cases were diagnosed during the 1968–1969 school year, one in 1969–1970, and three in 1970–1971. The two children whose cancers were diagnosed in 1968–1969 were in the same school and grade. Two of the three children diagnosed in 1971 were in the same school, grade, and class and were close friends. The town contained 26 elementary schools (21 public and five Catholic parochial), each enrolling approximately 500 students.

Three of the four schools attended by the six patients were parochial schools, including the two in which pairs of cases occurred in single school years. All six cases occurred in Catholic families. These six families belonged to three of the town’s six parishes, five of which operated elementary schools. Since the population of Cranston and neighboring communities was approximately 60 percent Catholic, the expected incidence of leukemia and lymphoma among parish children under age 15 years was about 2.8 cases for the 6-year period.

**Dubois, Pennsylvania**

Over a 6-month period in 1969–1970, three cases of lymphoma were diagnosed in boys in Dubois, Pennsylvania (expected annual incidence of childhood leukemia and lymphoma, 0.1 case) (10, 31). One was a case of reticulum cell sarcoma in a boy aged 14 years and two were lymphosarcomas in boys aged 7 and 11 years, the first progressing to acute lymphocytic leukemia. The only other childhood case in the town and in nearby rural areas served by the town’s school system was a case of acute leukemia that was diagnosed in a 14-year-old girl in 1965 (expected incidence among youths under age 20 years in 1960–1970, 4.7 cases). The town was located in a rural setting adjoining an interstate highway. Its population, which was 10,667 in 1960, did not change appreciably over the following decade.

All three cases diagnosed in 1969–1970 occurred in families belonging to the Catholic parish of St. Catherine, one of three parishes in the area. Approximately 25 percent of the town’s population was Catholic, and approximately 60 percent belonged to the St. Catherine parish. At the time of diagnosis, two of the 1969–1970 patients were attending the St. Catherine parochial school (grades 2 and 6). The third child was in public school but had attended the St. Catherine school 3 years before. The patient whose cancer was diagnosed in 1965 was from a Lutheran family, lived outside the town, and attended public school. None of the patients were closely acquainted.

The St. Catherine school (grades 1–8) was one of 20 elementary and junior high schools in the area. During the winter and spring of the 1969–1970 school year, an
Winchester, Virginia

In September 1971, two cases of Burkitt’s lymphoma were diagnosed in boys aged 9 and 15 years living two houses apart in a new residential neighborhood just outside Winchester, Virginia (6). Development of the neighborhood had begun 7 years before and was not yet complete. The town’s population, 14,643 in 1970, had not changed appreciably since 1960. It was located in a largely rural agricultural area.

One family had been living in the neighborhood for 7 years, the other for 2 years. Epstein-Barr virus-associated antigen was detected in one case. The frequency of heterogeneous-positive infectious mononucleosis in the area was not unusual.

In 1967–1971, six cases of childhood leukemia or lymphoma were diagnosed within the town. While incidence was greater than expected (1.4 cases for youths under age 20 years), the cases were widely scattered. The two Burkitt’s lymphoma cases were the only cases of childhood leukemia or lymphoma diagnosed in 1967–1971 in the postal rural-route area outside the town (expected incidence for youths under age 20 years, 1.2 cases). Twenty cases of adult leukemia or lymphoma occurred in the town and its vicinity in 1967–1971 (expected incidence, 23.4 cases).

In September 1976, 5 years later, a third case of Burkitt’s lymphoma was diagnosed in an 8-year-old boy living in the same neighborhood, approximately a half mile from the first two patients (7, 10). All three had attended the same public school but at different times. Religious affiliations differed, and their families were not acquainted. Further review of leukemia and lymphoma incidence among children and adults in the area (1972–1975) was unremarkable.

DISCUSSION

The findings of these eight investigations (table 1) suggest that the spread of infectious agents through interpersonal contacts may underlie the etiology of some forms of childhood leukemia and lymphoma. The principal recurring observation suggests the importance of contacts occurring among children in school and church settings. Often, churches serve populations that live largely within specific geographic parish areas. Considerable attention in such areas is given to group activities for young people, and in many Catholic parishes the parish may also operate a parochial school.

While no specific infectious agents could be identified in any of the above eight communities, two investigations suggest that herpesviruses might be involved (chickenpox in Dubois and, by clinical inference, Epstein-Barr virus in Winchester). Three investigations raised the possibility that childhood cancers other than leukemia and lymphoma might also result from the same kinds of exposure. Additionally, in Niles, Illinois, incidence of congenital heart disease was increased, an observation also suggested in two other towns where the Centers for Disease Control and Prevention conducted studies of childhood leukemia clusters (3–5, 10).

The recent population increases in five of the eight communities are in accord with evidence found elsewhere that links population mixing with increased incidence of childhood leukemia and lymphoma (12, 20–25). Such mixing is thought to mingle people carrying particular infectious agents with childhood populations not previously exposed. Perhaps the most obvious setting for such mingling involves newly created communities in rural areas, a definition that fits the five communities described here. Under this hypothesis, however, any community with considerable movement of families in and out of neighborhoods but without striking population growth might well experience a similar increase in childhood leukemia and lymphoma, as long as the necessary mix of infected and susceptible persons were present. While such population dynamics might have existed in the other three communities described here, it would have been hard to document.

Always, when time-space clustering is considered, there is concern about where one should set the boundaries of time and space. Narrow bounds maximize statistical significance, while wide bounds do the opposite. Although such statistical considerations are important in evaluating individual case cluster reports, decisions to conduct investigations should also consider both clinical data and information from community sources regarding possible links among cases or potential risk factors. It was in this context that Alexander Langmuir, in 1965, commented that, instead of relying fully on statistical testing, one should “investigate each cluster as it is reported and see if additional associations of possible interest can be found. If none turn up, there is obviously a cold trail... If the scent strengthens, then hot pursuit is in order” (32, p. 1386).

Evaluation of individual case clusters is difficult. The overall experience of the Centers for Disease Control and Prevention (33, 34) shows that only rarely do investigations find biologic explanations, whether concern rests with infectious causation or environmental exposures (8, 9, 11, 35–37). Only in occasional workplace situations has it been possible to confirm significant exposures and establish cause-effect relations (38). Small case numbers, uncertain illness latencies, and lack of cause-specific clinical features all limit biologic interpretation (39). Nonetheless, prompt investigation of community cluster reports is an important public health responsibility (40). The productivity of such investigations may improve as new methods become available for detecting infectious exposures and measuring immune susceptibility in individual children.
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REFERENCES


