

# Evidence that childhood acute lymphoblastic leukemia is associated with an infectious agent linked to hygiene conditions

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**Objectives:** The incidence of acute lymphoblastic leukemia (ALL) in children has shown temporal and geographic variation during the 20th century, with higher rates in developed nations appearing in the first half of the century, but with persisting low rates in developing nations. We sought to assess the relation of childhood ALL with hygiene conditions, an aspect of socioeconomic development affecting rates of exposure to infectious agents.

**Methods:** Infection patterns for hepatitis A virus (HAV), an agent with a fecal-oral route of transmission, were used to indicate hygiene conditions in different populations, with emphasis on instructive United States and Japanese data. A catalytic model was fit to these data, estimating the HAV force of infection and age-specific seroprevalence rates over time. These analyses were used to assess the temporal relationship of changes in HAV infection rates to changes in childhood leukemia mortality and incidence rates.

**Results:** We observed an inverse relationship between HAV infection prevalence and rates of childhood leukemia. Further, decreases in the HAV force of infection in the United States and Japan appear to have preceded increases in childhood leukemia rates. We describe a model based on a putative leukemia-inducing agent with a change in infection rate over time correlated with that of HAV that describes well the temporal trends in childhood leukemia rates for White children in the US and for Japanese children.

**Conclusion:** The data suggest that improved public hygiene conditions, as measured by decreased prevalence of HAV infection, are associated with higher childhood ALL incidence rates. The model that we present supports the plausibility of the hypothesis that decreased childhood exposure to a leukemia-inducing agent associated with hygiene conditions leads to higher rates of ALL in children by increasing the frequency of *in utero* transmission caused by primary infection during pregnancy (or by increasing the number of individuals infected in early infancy because of lack of protective maternal antibodies). *Cancer Causes and Control* 1998, 9, 285-298

**Key words:** Acute lymphoblastic leukemia, hepatitis A virus, hygiene, Japan, socioeconomic status, United States.

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## Introduction

The incidence of acute lymphoblastic leukemia (ALL) in children has shown temporal and geographic variation during the 20th century. Rates have increased substantially in developed nations,<sup>1,2</sup> while in developing nations low ALL incidence rates have persisted until the present time.<sup>3,4</sup> This variation in rates is primarily accounted for by a sharp peak in the incidence of ALL at two to three years of age (see Figure 1) that appears to have been present in developed nations since at least the 1940s,<sup>2,5-8</sup> but which is diminished or absent in developing nations.<sup>9</sup> Notably, most of the cases comprising the peak are a specific type of B-precursor ALL ('common' ALL, *i.e.*, cALL) associated with expression of the CD10 surface antigen and B-cell surface antigens such as CD19.<sup>10,11</sup>

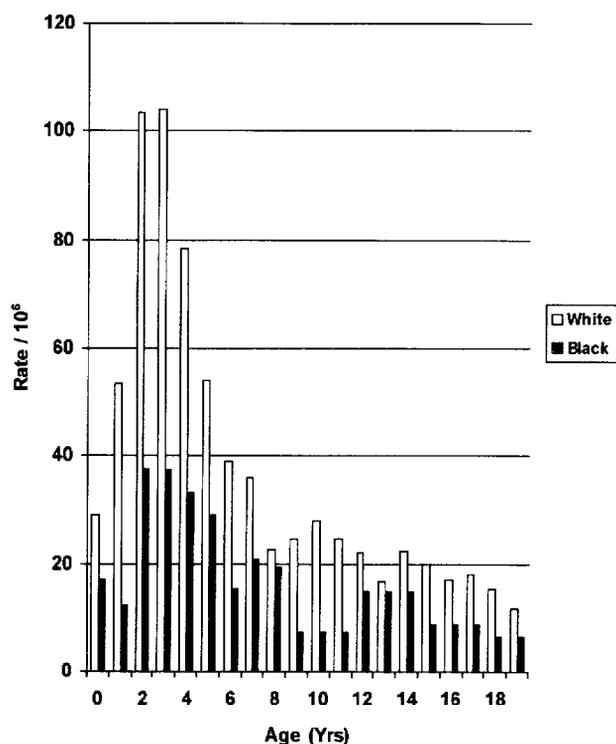
To explain differences in the age-specific rates of childhood ALL observed in developed compared with developing countries, an environmental factor associated with unknown aspects of improving socioeconomic status has been sought as a causative agent. However, studies of populations in western Europe, the United States, and Australia have yielded conflicting results

concerning the relationship of undefined elements of socioeconomic status with risk of childhood ALL. While many studies have noted positive associations between socioeconomic status and risk of childhood ALL,<sup>12-21</sup> others have not.<sup>22-25</sup> These discrepant results may reflect true differences in the effect of socioeconomic status in different regions at different times. However, they may also reflect the different measures employed in these studies to indicate the socioeconomic status of patient and control populations,<sup>26</sup> especially as the measures of socioeconomic status considered most commonly (*e.g.*, parental education, occupation, and family income) are likely to represent surrogates for some as yet undefined causal agent(s).

In this report, we address another aspect of socioeconomic development: the improved hygiene conditions in developed nations that result in decreased childhood exposure to infectious agents. While Greaves and others have called attention to the timing of early childhood infections as playing a possible etiologic role for ALL in children,<sup>27-33</sup> the approach that we take differs by focusing on the infection history of women of childbearing age. Specifically, we hypothesize that under the improved hygiene conditions that occur with increased socioeconomic status, more women of childbearing age are likely to be unexposed to a putative leukemia-inducing agent(s), leading to increased opportunity for *in utero* transmission due to primary infections during pregnancy or leading to a higher frequency of infections during early infancy due to the absence of protective maternal antibodies, and consequently resulting in more children at risk for developing ALL. Our interest in public hygiene as a factor possibly associated with childhood ALL was based in part on the recent consideration of 'JC virus' as a candidate etiologic agent for childhood ALL, specifically that *in utero* infection or infection in the first months of life increases the risk of subsequent development of ALL during childhood, while infections later in life are non-leukemogenic.<sup>34</sup> Although the route of JC virus spread is not known, one possibility is transmission *via* human waste, which is suggested by the persistence of the virus in renal tissues with shedding into the urine and by transmission of a related murine virus *via* urine.<sup>35,36</sup> However, a different infectious agent whose transmission is linked to hygiene conditions could similarly explain the changing incidence pattern for ALL during periods of dramatic alterations in social, economic, or demographic characteristics.

As one test of this hypothesis, we have used the prevalence of antibody to hepatitis A virus (HAV) and estimated rates of HAV infection as a marker of public hygiene conditions within specific populations. HAV is

**Figure 1.** Incidence of ALL Among Black and White Children – The incidence rates of ALL by year of age for White and Black children in the United States, are from the SEER registry for the period 1986 to 1994. Incidence rates are per 10<sup>6</sup>. A description of the SEER program can be found in the most recent volume of *SEER Cancer Statistics Review*.<sup>44</sup>



generally transmitted by the fecal-oral route, and childhood exposure to the virus is common where there is overcrowding, lack of clean water, or inadequate systems for removal and treatment of sewage.<sup>37</sup> Thus, HAV infection history can be used to indicate likely trends in the infection patterns of the postulated leukemogenic agent. The following specific predictions can be made:

- (i) Societies with less adequate public hygiene (as measured by a high prevalence of antibodies to HAV) should have low rates of childhood ALL, while societies with adequate public hygiene (as measured by a low rate of childhood exposure to HAV) should have higher rates of childhood ALL;
- (ii) Changes in public hygiene over time that decrease the exposure of children to infections (as estimated by changes in the HAV force of infection over time), should lead to an increased incidence of childhood ALL as the frequency of women susceptible to primary infection during pregnancy increases. The timing of the change in ALL rates will reflect the balance between seronegative females of childbearing age (*i.e.*, unexposed females) in the population and the likelihood that these females become infected during pregnancy (or that their offspring will be infected shortly following birth).

In the remainder of this paper, rates of occurrence of childhood ALL in populations are compared with estimates of exposure to HAV in these same populations, with particular attention to how changes in HAV infection rates over time relate to changes in the incidence of childhood ALL.

## Materials and methods

Data concerning the prevalence of antibody to HAV in the US are from the second National Health and Nutrition Examination Survey (NHANES II)<sup>38</sup> which was conducted by the National Center for Health Statistics (NCHS) from 1976 to 1980. The survey was designed to provide national statistics on the health and nutritional status of the civilian noninstitutionalized population through household interviews and standardized physical examinations conducted in special mobile examination centers. The total sample consisted of 27,802 participants of whom 20,322 (73 percent) were interviewed and examined.<sup>38</sup> For many analyses, the nonresponse and poststratification statistical adjustments performed by NCHS removed most sources of nonresponse bias.<sup>39</sup> The examination weights incorporated in the analyses adjusted for nonresponse and oversampling of certain populations. Sera from 9,516

persons who participated in the survey were available for anti-HAV testing. A commercially available enzyme immunoassay was used to test for anti-HAV (HAVAB, Abbott Diagnostics, Abbott Park, Illinois).

NHANES II data describing the age-specific prevalence of antibodies to HAV were analyzed using a catalytic epidemic model as previously described by Schenzle *et al*<sup>40</sup> for European countries and by Ike-matsu, *et al*<sup>41</sup> for Okinawa, Japan. Application of this model to cross-sectional, age-specific seroprevalence data allows estimates of the prevalence of infection during time periods in which the sampled population were living. In this catalytic model, the force of infection (*i.e.*, the probability of a non-immune individual being infected in a given year) is age-independent and is described by the function

$$\lambda(t) = \lambda_{\infty} \left\{ 1 - \frac{1}{1 + \exp[-\alpha(t - \theta)]} \right\} \quad (1).$$

This function has a value  $\lambda_{\infty}$  at  $t = -\infty$ , where the time of serum collection is considered  $t = 0$ . The variable  $\alpha$  can be considered a measure of the speed with which the force of infection decreased, with higher  $\alpha$  values indicating a more rapid reduction in the force of infection. The model was fit separately for Whites and Blacks. The data used were the number of seropositive individuals in each age range and the number of subjects tested within each age range. The midpoint of each age stratum was used for the modeling, with NHANES II serum collection approximated as occurring in 1978 for all subjects. Subjects over 70 years old were assumed to be 74 years of age. The method of maximum likelihood was used using the nlminb function of S-Plus (MathSoft Inc., Seattle).

The probability that a woman  $i$  years old at calendar year  $\tau$  is seronegative can be written

$$\left\{ \frac{1 + \exp[-\alpha(\tau - \tau_0 - \theta)]}{1 + \exp[-\alpha(\tau - \tau_0 - \theta - i)]} \right\}^{\frac{\lambda_{\infty}}{\alpha}} \quad (2).$$

where  $\tau_0$  is the year of sampling. This reduces to the formula of Schenzle, *et al* for the special case where  $\tau$  equals the year of sampling  $\tau_0$ .<sup>40</sup>

We also evaluated a model in which the force of infection of a putative leukemia-inducing agent is  $\lambda^*(t) = w\lambda_{\text{HAV}}(t) + (1 - w)\lambda_{\text{HAV}\infty}$  (*i.e.*, a weighted average of the HAV force of infection as given in expression (1) which changes over time and of the asymptotic HAV force of infection  $\lambda_{\infty}$ ). For this model the probability of seronegativity is:

$$\left\{ \frac{1 + \exp[-\alpha(\tau - \tau_0 - \theta)]}{1 + \exp[-\alpha(\tau - \tau_0 - \theta - i)]} \right\}^{\frac{\lambda_{\infty}}{\alpha} w} \exp\{-(1 - w)\lambda_{\infty} i\} \quad (3).$$

Direct comparison of rates of ALL for children less than five years of age for different time periods in the 20th century is problematic because of changes in reporting and diagnosis during this long period of interest.<sup>42,43</sup> To enable comparisons over time, we: (i) used mortality to approximate incidence before 1960 (and in Japan up until 1965), since childhood leukemia was invariably fatal before this time and since incidence data are not available;<sup>42</sup> (ii) focused on total leukemia rates within populations, since the criteria and methods for diagnosing ALL have changed markedly over time. For this reason and since ALL represents greater than 80 percent of leukemia cases for children less than five years of age,<sup>44</sup> we have used the term 'childhood leukemia' throughout the manuscript, with the understanding that changes in rates for

childhood leukemia primarily reflect changes in ALL rates; (iii) assessed the rate ratio of leukemia among children aged zero to four years to leukemia among young adults aged 15 to 24 or 20 to 24 years (a cancer of presumably different etiology) to estimate the magnitude of the peak among children aged two to four years as shown in Figure 1. The rate ratio was generally 2.0 to 2.5 for countries of the developing world, and approximately 4.0 for countries of the developed world (Tables 1 and 2).

## Results

### *United States and Japan*

We have focused on the US and Japan to examine the relationship between childhood leukemia rates and

**Table 1.** Leukemia incidence and mortality rates in the United States and Japan

Population Year(s) studied-outcome	Leukemia rates – child 0-1 to 4 yrs <sup>a</sup>	Leukemia rates – young adult 15-20 to 24 yrs <sup>a</sup>	Ratio child to young adult rates
United States – White			
1921-25 Mortality <sup>2</sup>	1.9	0.8	2.3
1926-30 Mortality <sup>2</sup>	2.5	1.0	2.4
1931-35 Mortality <sup>2</sup>	3.2	1.2	2.6
1936-40 Mortality <sup>2</sup>	4.4	1.5	3.0
1941-45 Mortality <sup>45</sup>	5.2	1.9	2.7
1946-50 Mortality <sup>45</sup>	5.8	1.9	3.0
1951-55 Mortality <sup>45</sup>	6.1	2.2	2.8
1956-60 Mortality <sup>45</sup>	5.9	2.1	2.8
1975-79 Incidence <sup>b</sup>	6.7	2.2	3.1
1980-84 Incidence <sup>b</sup>	6.5	2.1	3.1
1985-89 Incidence <sup>b</sup>	7.5	1.9	3.9
1990-94 Incidence <sup>b</sup>	7.2	2.4	3.0
United States – Non-White/Black			
1941-45 Non-white mortality <sup>c,45</sup>	1.6	1.1	1.4
1946-50 Non-white mortality <sup>45</sup>	2.0	1.5	1.4
1951-55 Non-white mortality <sup>45</sup>	2.6	1.7	1.5
1956-60 Non-white mortality <sup>45</sup>	2.6	1.8	1.5
1975-79 Black incidence <sup>b</sup>	2.8	1.9	1.5
1980-84 Black incidence <sup>b</sup>	3.9	2.3	1.7
1985-89 Black incidence <sup>b</sup>	3.9	1.6	2.5
1990-94 Black incidence <sup>b</sup>	3.5	1.8	2.0
Japan			
1950 Mortality <sup>115</sup>	2.3	1.1	2.0
1955 Mortality <sup>115</sup>	3.4	1.8	1.9
1960 Mortality <sup>115</sup>	4.1	2.3	1.8
1965 Mortality <sup>115</sup>	4.0	2.3	1.8
1975-79 Incidence <sup>115</sup>	6.1	1.8	3.4
1980-84 Incidence <sup>115</sup>	5.1	1.6	3.3
1988-92 Incidence <sup>d</sup>	5.4	1.8	3.0

<sup>a</sup> Age range for mortality data from 1921-60 is 1-4 years and for incidence data from 1975-94 is 0-4 years. For Japan, the lower age range for both mortality and incidence data is 0-4 yrs. For the older age group, the age range is 15-24 yrs for the US and 20-24 yrs for Japan. Incidence rates are per 100,000 and all values are rounded off to the nearest one-tenth.

<sup>b</sup> Incidence data for children in the United States are from the SEER Program (1975-94). A description of SEER procedures can be found in the most recent volume of SEER Cancer Statistics Review.<sup>44</sup>

<sup>c</sup> United States mortality rates were specified for whites and for non-whites (but not separately for blacks) during 1941-1960.<sup>45</sup>

<sup>d</sup> Incidence rates for 1988-92 are calculated from rates for 6 Japanese tumor registries that reported data for *Cancer Incidence in Five Continents*, Volume VII.<sup>46</sup>

**Table 2.** Leukemia incidence rates in South American and Asian countries<sup>a</sup>

Population (years studied)	Rate 0-4 yrs	Rate 20-24 yrs	Ratio <sup>b</sup>
Colombia, Cali (1987-91)	5.5	2.2	2.5
Ecuador, Quito (1988-92)	5.5	2.6	2.1
Peru, Lima (1990-91)	4.3	1.2	3.6
China, Shanghai (1988-92)	4.1	2.1	1.9
China, Tianjin (1988-92)	4.8	2.2	2.2
Hong Kong (1988-92)	7.4	2.9	2.6
India, Bangalore (1988-92)	3.0	1.9	1.6
India, Bombay (1988-92)	2.9	1.2	2.4
India, Madras (1988-92)	2.9	2.0	1.4
Philippines, Manila (1988-92)	5.8	3.4	1.7
Singapore: Chinese (1988-92)	7.9	2.3	3.5
Thailand, Chiang Mai (1988-92)	4.7	2.9	1.6
Thailand, Khon Kaen (1990-93)	4.0	3.1	1.3
Australia, New South Wales (1988-92)	8.2	1.9	4.4
Canada (1988-92)	8.0	1.9	4.2
Sweden (1988-92)	6.5	1.7	3.9
UK, England and Wales (1988-90)	6.9	1.8	3.8

<sup>a</sup> Leukemia incidence rates (ICD-9th Revision, 204-208) are from *Cancer Incidence in Five Continents*, Vol. VII.<sup>46</sup> To have sufficient cases for stable estimates of incidence, only those registries from South America and Asia with more than 20 cases during the reporting period in each age group were included. Incidence rates are per 100,000 and all values are rounded off to the nearest one-tenth. The last 4 countries in the table are provided to allow comparison with leukemia rates for young children in developed countries.

<sup>b</sup> Ratio of leukemia incidence rates for 0-4 of 20-24 year olds.

HAV exposure as a measure of public hygiene conditions. The US was selected because of the availability of HAV seroprevalence data from NHANES II and because of the availability of population-based mortality data for childhood leukemia during the first half of this century. The US appears typical of countries of the developed world in which childhood leukemia rates increased in the first half of the 20th century.<sup>7</sup> Japan, on the other hand, was of interest because it did not show an increase in childhood leukemia rates until the second half of the 20th century.<sup>47</sup> Additionally, published data on the HAV force of infection for a Japanese population were available.<sup>41</sup>

It is difficult to estimate precisely childhood leukemia mortality rates for the US during the period from 1900 to 1950. Reasons for this difficulty include limited mortality data for substantial geographic regions of the US prior to 1933, inclusion of Hodgkin's disease in the rubric for leukemia prior to 1920, and variation in the level of care and accuracy for medical certification of cause of death over time leading to different levels of completeness of case ascertainment.<sup>42</sup> These caveats must be considered when reviewing historical mortality rate data for children. Focusing on the one to four year age group, since this age group accounts for the largest percentage of childhood ALL cases among White children in the US (Figure 1), available data suggest that:

- The peak in childhood leukemia mortality at two to four years of age was barely discernible among White children in the US in 1929-31, was

clearly discernible by 1939-41, and was more pronounced in 1949-51;<sup>2</sup>

- Leukemia mortality rates among one year old White children in the US did not appreciably change between 1935 and 1955, whereas leukemia mortality rates for two, three, and four year old children increased appreciably during this period before reaching a plateau in the late 1940s and early 1950s;<sup>5</sup> and
- The ratio of the leukemia mortality rate for one- to four-year olds to that of 15- to 24-year olds increased from 2.3-2.4 in the 1920s to approximately 3.0 in the 1940s (Table 1).

These observations suggest that leukemia rates rose among White children in the one- to four-year age group during the period 1920-50, and stabilized thereafter.

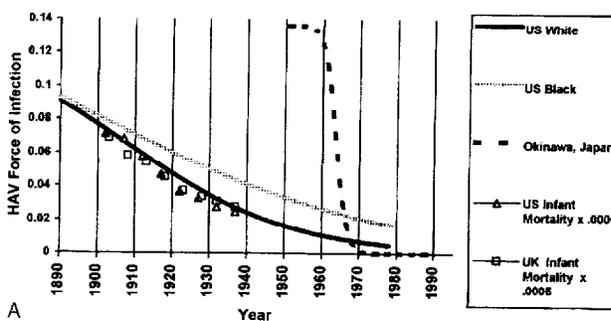
The temporal pattern of leukemia rates for Black children in the US is very different than that for White children. The peak in leukemia rate observed for White children at two to four years of age was not present among Black children in the 1950s.<sup>5</sup> Although the peak in ALL incidence for two- to four-year old Black children was present in the late 1980s, it was much smaller than that for White children (Figure 1). The ratio of leukemia rates for one- to four-year olds compared with 15- to 24-year olds for Blacks in the US remained at approximately 1.5 through the 1970s before increasing to approximately two after 1980 (Table 1).

Childhood leukemia mortality rates in Japan remained low through the early 1960s (Table 1), and the ratio of mortality rates for zero- to four-year old children compared with 20- to 24-year olds was approximately two or less from the 1950s through 1965 (Table 1). The sharp peak in mortality rates seen subsequent to the 1930s for two- to four-year old White children in the US was absent or greatly diminished among Japanese children in the 1950s.<sup>47</sup> In the last half of the 1970s and the first half of the 1980s, the childhood leukemia incidence rates for Japan were increased, as was the ratio of rates for zero- to four-year olds compared with 20- to 24-year olds (Table 1). Other published reports have also noted that the childhood leukemia rate in Japan in the 1950s and the early 1960s appeared to be substantially below that observed for the US and that the leukemia rate increased during the 1970s.<sup>47-49</sup>

To summarize the qualitative differences in the trends in leukemia rates over time for children less than five years of age observed in the US and in Japan: increasing rates of childhood leukemia for White children in the US appear to have occurred between 1920 and 1950, while increasing rates for Black children developed much later, with rates for Black children remaining substantially lower than for White children; an increasing rate of childhood leukemia in Japan appears to have been delayed until after the early 1960s and was clearly present by the late 1970s.

We turn now to the changes over time in exposure to HAV as a measure of public hygiene conditions for persons in the US and in Japan. The prevalence of antibodies to HAV in the US population was determined in the NHANES II study (1976-80), with an overall cross-sectional rate of seropositivity of 38 percent and with seroprevalence rates steadily increasing with age from 11 percent in children less than five years of age to 74 percent in those over 50 years of age.<sup>47,48</sup> In order to quantify the change in HAV force of infection over time, we applied a catalytic model to the cross-sectional NHANES II data (Figure 2A). Application of the model to HAV seroprevalence data for the US White population provided an excellent fit, with observed and predicted seroprevalence values for different age groups being almost superimposable. For Whites, the maximum likelihood parameter for  $\lambda_{\infty}$  was 0.129 (implying a maximum infection rate-for non-immune individuals of 129 per 1,000 person-years). Figure 2A also shows that the downward trend for infant mortality rate (another measure of the adequacy of public hygiene) in the US from 1900 to 1940 essentially paralleled the decreasing HAV force of infection. Comparison of the data of Table 1 and Figure 2A shows that the HAV

**Figure 2A.** Change in HAV Force of Infection over time for the United States and for Okinawa, Japan. Data for the United States are from NHANES II, with the HAV force of infection calculated as described in the Methods section. For Whites, the maximum likelihood parameters were  $\lambda_{\infty} = 0.129$ ,  $\alpha = 0.0462$ , and  $\Theta = -69.5$ . For Blacks, the parameters were  $\lambda_{\infty} = 0.156$ ,  $\alpha = 0.028$ , and  $\Theta = -74.5$ . The force of infection described for Japan uses parameters based on data from the Okinawa population, as reported by Ikematsu *et al.*<sup>41</sup> The open triangles indicate the infant mortality rate per 100,000 in the US from 1900 to 1940 (multiplied by 0.0005 in order to fit the scale of the graph), with total rates from 1900-15 from *Historical Statistics of the United States, 1789-1945*,<sup>52</sup> and rates for White infants from 1916-40 from *Vital Statistics Rates in the United States 1940-1960*.<sup>43</sup> Infant mortality rates for the United Kingdom are from *Infant and Perinatal Mortality in England and Wales*.<sup>53</sup>



force of infection decreased substantially before the increase in leukemia rates for US White children.

The HAV force of infection over time for Blacks in the US has been consistently greater than that for Whites during the 20th century (Figure 2A). For Blacks,  $\lambda_{\infty}$  was 0.156 (somewhat higher than that observed for Whites), and the rate of decrease in the force of infection has been slower than for Whites. This difference in the HAV force of infection is likely associated with socioeconomic status, since middle-class White and Black blood donors from the New York area had a similar prevalence of antibody to HAV.<sup>54</sup> Similar to the pattern seen for White children, the HAV force of infection in the Black population diminished substantially before an increase in the leukemia rate for Black children was observed (Table 1 and Figure 2A).

The temporal pattern of changes in HAV infection in Okinawa, Japan differed markedly from that observed for Whites in the US. Figure 2A shows application of a catalytic model to HAV seroprevalence data for persons living in Okinawa.<sup>41</sup> A rapid decrease in HAV force of infection began in the 1950s, with a 50 percent reduction in the force of infection occurring around 1963. The rapid decrease in HAV force of infection documented for the Okinawa population may well have occurred earlier for the larger Japanese population, based on a 90

percent drop in mortality due to gastroenteritis that occurred among Japanese children (ages one to 14 years) during the 1950s,<sup>55</sup> and on a report describing a low frequency of HAV infection for residents of a Japanese community born after 1960.<sup>56</sup> A substantial decrease in HAV force of infection appears to have preceded the time when leukemia rates were clearly increased among Japanese children (Table 1 and Figure 2A), and we use the Okinawa data subsequently to illustrate possible relationships between rapid changes in public hygiene and changes in leukemia rates.

#### *Populations of the developing world*

HAV infection patterns in countries of the developing world differ from those described above for the US and Japan. HAV infection continues to occur at an early age in most African populations and in other areas of the developing world, indicating a very high force of infection. For example, 50 percent of Black South African children are anti-HAV positive by two years of age and nearly all are positive by six years of age.<sup>57,58</sup> Similar results are reported for Somalia,<sup>59</sup> Nigeria,<sup>60</sup> Zaire,<sup>61</sup> Egypt,<sup>62</sup> Cambodia,<sup>63</sup> Brazil,<sup>64</sup> and India.<sup>65</sup>

As would be predicted by our hypothesis, ALL is uncommon among Black African children and the peak at two to three years of age seen in developed countries is absent or greatly reduced.<sup>4,66-68</sup> Published reports for non-African developing countries also describe low rates of ALL in children and/or the absence (or marked reduction) of the peak in ALL incidence at two to four years of age (e.g., in Papua New Guinea (1968-76),<sup>69</sup> China,<sup>70</sup> Cuba,<sup>71</sup> India,<sup>68,72</sup> Kuwait,<sup>68</sup> and Mexico<sup>73</sup>). While these data could be explained in some measure by under-reporting, the lower incidence of childhood ALL in these countries seems real based on the following evidence:

- the ratio of ALL to AML among these populations is lower than that in countries with higher economic standards (as would be expected if ALL cases were reduced while AML cases were constant);<sup>69,70,72,74-77</sup>
- the proportion of ALL cases represented by T-cell ALL (a distinctive type of ALL that does not appear to show the same geographic variation in incidence as the more common B-precursor ALL) is higher in these populations;<sup>13,66,67,78,79</sup>
- the ratios of leukemia rates for young children to young adults in developing countries are, in general, substantially lower than those for children in developed countries and are similar to those observed in Japan before 1965 and to

those observed in the United States before 1930 (Tables 1 and 2). In the absence of single year age-specific leukemia rates, this provides some measure of the diminished magnitude of the peak in leukemia rates for children less than five years of age in these countries (as shown in Figure 1).

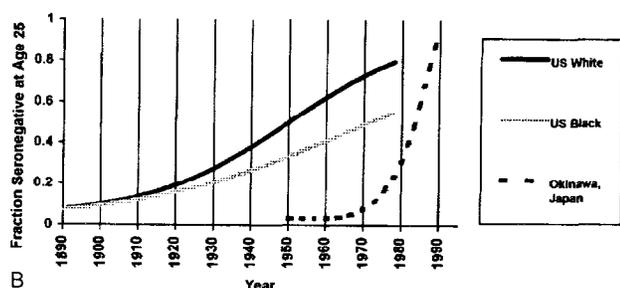
Within some countries of the developing world, there is wide disparity in living conditions, and both the prevalence of antibody to HAV and the rates of occurrence of childhood ALL vary accordingly. For example, by six years of age, the prevalence of anti-HAV was almost 100 percent among a group of Black children in South Africa, reflecting the poor socioeconomic and environmental conditions in which these children live.<sup>57</sup> The prevalence of antibodies to HAV among White South Africans appears to be much lower than for Blacks.<sup>80</sup> Consistent with the inverse relationship between anti-HAV prevalence and childhood ALL incidence rates, ALL is much more common in South African White children (zero to four years of age) compared with Black children of the same age.<sup>11</sup> Similarly, in a region in the Brazilian state of Sao Paulo that is characterized by striking differences in socioeconomic status between the White and non-White populations, the incidence of ALL is only 8.1 per million person-years for non-White children but is nearly 30 per million person-years for White children.<sup>81</sup> These examples suggest that when higher rates of ALL are observed for children under five years of age in developing countries, the increase is likely to be restricted to population subsets within these countries that have more 'developed' lifestyles.

#### *Models for childhood leukemia rates derived from HAV force of infection*

The inverse relationship in different populations between the prevalence of HAV infection and the rate of childhood leukemia as well as the finding that increases in childhood leukemia appear to be preceded by changes in HAV infection rates are consistent with the hypothesis described in the Introduction. This led us to consider whether a plausible quantitative relationship between HAV force of infection and childhood leukemia rates could be derived, assuming that a leukemia-inducing agent(s) has a force of infection that varies with time in a manner similar to that of HAV. To do so, we made the simplifying assumption that 25-year old women could be used to represent the overall group of childbearing women in the populations that we examined.

We began by calculating the model-predicted values for the percentage of HAV seronegative women 25 years old (Figure 2B). Assuming that the force of infection for

**Figure 2B.** Change over time in the frequency of HAV seronegative 25-year old women in the United States and Japan. The frequency of 25-year old HAV seronegative women was calculated as described in the Methods section based on the calculated force of infection in each of the populations.



the putative leukemia-inducing agent was identical to that of HAV, then the frequency of 25-year old women seronegative for the agent would be the same as the frequency of 25-year old women seronegative for HAV. The calculated frequency of seronegative 25-year old White women in the US increased from approximately 20 percent in 1920 to 50 percent in 1950. The percentage of seronegative Black women increased from approximately 15 to 33 during the same period. For Japan, we used the Okinawa data, recognizing (as noted previously) that changes in HAV force of infection may have occurred earlier in the overall Japanese population.<sup>55,56</sup> The frequency of seronegative 25-year olds in Okinawa was low until 1970 and then increased throughout the 1970s and into the early 1990s.

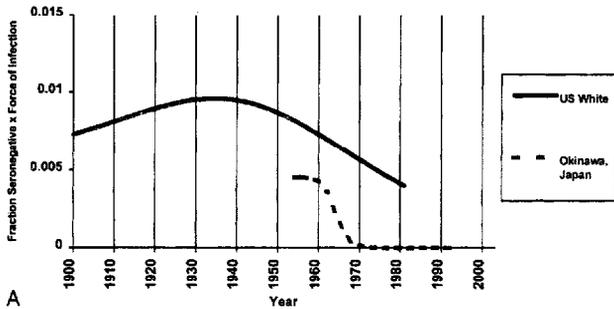
Under the hypothesis described in the Introduction, the likelihood of ALL developing should be proportional to the frequency of seronegative women of childbearing age in a population and to the likelihood that these women will become infected with the leukemia-inducing agent(s) during a pregnancy (or that their children will be infected with the agent shortly after birth).<sup>34</sup> We examined three models describing the likelihood of infection of seronegative women of childbearing age within a population. In the first model, we considered the likelihood of maternal infection during pregnancy (or infant infection shortly following birth) as being proportional to the force of infection of the agent (assumed to be equal to the HAV force of infection). The frequency with which pregnant seronegative women or their infants would be infected (and hence the likelihood of children of these pregnancies developing leukemia) would thus be proportional to the product of the frequency of seronegative women in the population and the force of infection during that year. Figure 3A shows the time trend for leukemia rates predicted by this model. The model predicts maximal leukemia rates for Japan in the 1950s and predicts

relatively constant rates of leukemia for Whites in the US from 1920 through 1940, with declining rates thereafter. This pattern is distinctly different from the time trend for leukemia rates for White children in the US and for Japanese children shown in Table 1.

The second model for the likelihood of infection of seronegative women during a pregnancy (or infection of their offspring shortly after birth) assumes that the likelihood of infection is proportional to the frequency of seropositive individuals within the population. This model was evaluated because of the possibility that the leukemia-inducing agent(s), unlike HAV, might persist in its host after primary infection, thereby leading to seropositive individuals being infective. The frequency with which infection of pregnant seronegative women (or their children shortly after birth) would occur under this model would be proportional to the product of the frequency of seronegative women in the population and the frequency of seropositive individuals. Under the simplifying assumption that seropositive individuals of the same age group (e.g., spouses) are most likely to be sources of infection, this model predicts higher leukemia rates among Whites in the US from 1900 through the 1940s, and predicts increasing leukemia rates in Japan beginning in the late 1960s and extending through the early 1980s (Figure 3B). However, the model-predicted rates of leukemia decrease for Whites in the US after 1950 and decrease rapidly for Japanese after 1980, which is not in concordance with the observed rates of leukemia in these populations.

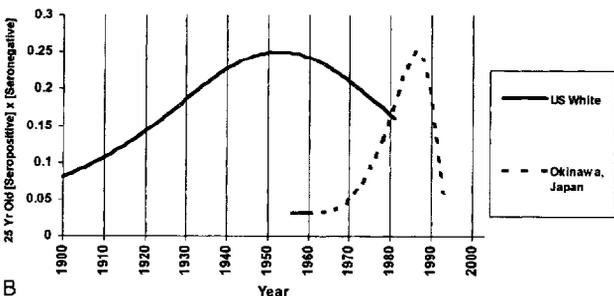
The third model is a variation of the second and assumes that the putative leukemia-inducing agent(s), unlike HAV, has a force of infection that does not approach zero following improvements in public hygiene, but rather decreases from an initial high value to a lower stable value. This implies that although the agent is transmitted in ways that are affected by improving public hygiene, the agent also has routes of transmission that are maintained despite high standards of public hygiene. Thus, we consider a certain proportion of the force of infection of the agent as being related to transmission pathways shared with HAV (and hence varying over time) and the remaining proportion of the force of infection being independent of the changes in public hygiene over time that have resulted in diminished HAV infection rates (see Methods section for details). Application of this 'weighted' force of infection model to White children in the US provides a plateau after 1960 with rates increasing most rapidly between 1920 and 1940 (Figure 3C). Applying a slightly larger  $\alpha$  value for the force of infection of the putative leukemia-inducing agent than that calculated for HAV (0.08 *cf* 0.046) increases the rapidity of the changes in its force of infection without altering the year of half-maximal force

**Figure 3A.** Model for the change over time in the likelihood of infection of women of childbearing age by a leukemia-inducing agent(s) based on the frequency of HAV seronegative women and the HAV force of infection. The model assumes that the leukemia-inducing agent has the same force of infection as HAV and that the likelihood of infection of a woman of typical childbearing age (*i.e.*, 25 years old) is proportional to the product of the frequency of seronegative women in the population and the force of infection for the agent.

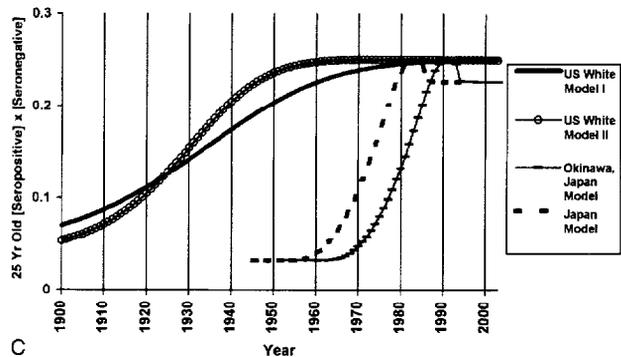


of infection. By using the larger  $\alpha$  value, the predicted rates of leukemia from this model more closely fit that shown for White children in the US, with rates rapidly increasing from 1920-40 and attaining near-maximal levels by 1950 (Figure 3C). Application of the 'weighted' force of infection model using the Okinawa HAV force of infection data predicts the rapid increase and subsequent plateau in leukemia rates suggested for Japan by Table 1, but the model-derived curve appears to plateau later than that observed for Japanese leukemia rates (Figure 3C). If the time for half-maximal force of infection for the leukemia-inducing agent for Japan as a whole occurred in the mid-1950s, rather than the early

**Figure 3B.** Model for childhood leukemia incidence based on the change over time in the likelihood of infection of women of childbearing age by a leukemia-inducing agent(s) assuming that this likelihood reflects the frequency of women who are seronegative for the agent and the frequency of seropositive persons of similar age in the population. The model assumes that the leukemia-inducing agent has the same force of infection as HAV and that the likelihood of infection of a woman of typical childbearing age (*i.e.*, 25 years old) is proportional to the product of the frequency of seronegative 25-year old women in the population and the frequency of seropositive 25-year olds in the population.



**Figure 3C.** 'Weighted' force of infection model for childhood leukemia. This model is the same as that described for Figure 3B, but assumes additionally that the leukemia-inducing agent has a force of infection that has the same time dependence as HAV, but approaches a constant lower value with increasing time instead of approaching zero ( $0.2\lambda_{\infty}$  for the US population and  $0.15\lambda_{\infty}$  for the Japanese population). The US model II assumes a slightly larger  $\alpha$  value (0.08) for the putative leukemia-inducing agent than that observed for HAV in the US (0.0462), which has the effect of shifting the plateau in predicted leukemia rates to an earlier time period (without changing the year of half-maximal force of infection for the agent). The 'Japan' model assumes that the half-maximal force of infection for the putative leukemia-inducing agent occurred in 1955 in Japan as a whole rather than in 1963 as estimated for HAV in the Okinawa population. Each of the above graphs is shifted by 3 years to account for the time from birth to development of leukemia among 0-4 year olds.



1960s as for HAV in Okinawa, then a reasonably good fit to the observed leukemia rates would be obtained as illustrated in Figure 3C.

We note two additional points about the models described above. First, it is obvious that under the assumption of a continuing high force of infection, such as that observed in developing countries, all of the models predict a constant low rate of childhood leukemia. Second, we tested whether applying the 'weighted' force of infection concept to our first model (*i.e.*, leukemia rate proportional to the product of the force of infection and the fraction of women seronegative) provided a good fit to observed leukemia rates in Japan and the US. While a plateau was obtained by using the 'weighted' force of infection in our first model, this plateau was delayed in comparison to that shown in Figure 3C for our third model, with the time to reaching a plateau in Japan delayed into the 1990s. Thus, of the models described, our third model provides the best fit to the observed leukemia rates.

## Discussion

An infectious etiology for childhood acute leukemia has been suspected for over 50 years.<sup>82-89</sup> While there is

currently considerable enthusiasm for hypotheses that associate childhood ALL with infection-related events (e.g., as presented by Greaves and by Kinlen and their colleagues),<sup>27-33</sup> the characteristics of the putative childhood ALL inducing agent(s) remain a mystery,<sup>90,91</sup> as does the timing of the infectious events that either result in or protect against leukemia.<sup>30,92,93</sup>

The main contribution of this report is to focus attention on particular characteristics of a putative leukemia-inducing agent. Specifically, the consistently observed inverse relationship between the age-specific prevalence of antibody to HAV and the incidence of childhood leukemia seen in different populations supports the possibility of a leukemia-associated agent whose transmission appears to be affected by changes in public hygiene conditions. Further, our analyses utilizing the change in HAV force of infection over time as a surrogate for the change in force of infection of an unknown leukemia-inducing agent demonstrate that the temporal relationship of these changes may be sufficient to support the hypothesis that rising ALL rates result from an increase in the frequency of women susceptible to primary infection by the agent during pregnancy and/or an increase in the frequency of infants unprotected by maternal antibody to the agent. The third model that we present, which is able to provide a reasonable fit for time trends for childhood leukemia rates for children in the US, suggests two other possible characteristics of the putative leukemia-inducing agent:

- (i) that the agent remains widespread in developed countries, with a force of infection that has been reduced by changes in public hygiene, but that has now reached a lower, stable value. In order for our third model to obtain a plateau in leukemia rates (rather than a decline in rates as force of infection diminishes with improving public hygiene), it is necessary for the leukemia-inducing agent to persist in populations with a lower, constant force of infection. For example, in the scenario illustrated in Figure 3C (which predicts a plateau rate of ALL in the US after 1950), approximately 50 percent of 25 year olds in the US have previous exposure to the agent under the new steady state conditions existing following improvements in public hygiene during the first half of the century. It is important to emphasize that the putative agent persists in developed countries in spite of high standards of hygiene, implying that the agent has transmission routes that are not dependent on poor hygiene conditions;
- (ii) that the agent may persist in infected individuals. This characteristic of causing persistent infection provides a reasonable explanation for the relatively

good concordance between childhood leukemia rates and the product of the frequencies of seronegative women and seropositive individuals as applied in our third model.

Members of the human herpesvirus and human polyomavirus families are examples of viruses that meet the criteria of being transmitted by bodily fluids, of showing infection patterns that are dependent upon socioeconomic status (with high rates of infection among children in developing countries), and of producing persistent infections with seropositive individuals being infective.<sup>94-101</sup>

Similar temporal trends to those described for the US appear to have occurred in some other developed countries in the first half of the 20th century. For example, the overall prevalence of anti-HAV in England appears to have been similar to that among Whites in the US, with the same association between age and seroprevalence.<sup>102-104</sup> The similar pattern of change in infant mortality rates during the early years of the 20th century for England and the US is further evidence that changes in public hygiene occurred at a comparable pace in the two countries (Figure 2A).<sup>52,53</sup> An increase in childhood leukemia mortality in England and Wales among two- to four-year olds compared with children less than two-years old was barely perceptible before 1930, but was apparent thereafter.<sup>1,7,8,105</sup> For both Norway and Sweden, the reported asymptotic HAV force of infection  $\lambda_\infty$  is substantially lower than that observed for the US (0.023-0.047 *cf* 0.129) with declining force of infection beginning around 1920 and continuing until 1960.<sup>40</sup> This lower force of HAV infection in the early 1900s (in comparison with that in the US) is consistent with the lower infant mortality rate for Norway during this period compared with that of the US.<sup>106</sup> In Norway, the peak in leukemia mortality among one- to four-year olds was observed after 1930, and the incidence rates of ALL for two- to three-year olds in Norway in the 1950s was of similar magnitude to those shown for White children in the US in Figure 1.<sup>107</sup> Leukemia incidence data for Sweden are more limited, since national registration of incident cancers did not begin until 1958, but by this time there was a clear peak in leukemia incidence among children zero-to-four years of age.<sup>108</sup> Available data for Australia are similar to those described above for the US and Western European countries, both in terms of the age dependence for HAV seroprevalence<sup>109-111</sup> and in terms of rates of occurrence of childhood ALL over time.<sup>8</sup>

The change in HAV force of infection for Greece differs from that described above for the countries of northern Europe, with a diminishing force of infection not being observed until the 1960s for urban Greek

populations and not occurring through 1976 for rural populations.<sup>40</sup> The rates of leukemia among zero- to four-year olds were higher in urban areas in Greece (approximately 70 per million person-years) compared with rural areas (approximately 45-50 per million person-years).<sup>112</sup> Thus, although the quantitative relationship between HAV force of infection and leukemia rate may differ in Greece from that described for the US, internally there appears to be the same inverse relationship between HAV force of infection and childhood leukemia rates.

The pattern of changing rates of childhood leukemia in Japan is especially instructive, as the situation in Japan differed markedly from that in northern Europe and the US. The early years following World War II in Japan were a period in which malnutrition and poor sanitary conditions were common.<sup>113</sup> Additionally, the agricultural tradition of using human waste as fertilizer continued in Japan into the postwar period.<sup>114</sup> A consequence of these conditions was an extremely high rate of parasitic infections among Japanese in the early to mid-1950s.<sup>113,114</sup> Thus, it is not surprising that the prevalence of HAV antibody was very high in Japan in the 1950s. Extensive public health measures initiated during the 1950s and improving economic conditions resulted in a sharp decrease in HAV force of infection with seroprevalence rates dropping to very low levels for persons born subsequent to 1960.<sup>41,56</sup> In essence, the prolonged period of improvements in public hygiene that occurred over the 20th century in northern Europe and the US was compressed into a relatively short period in Japan. Further investigation of the time course of the incidence trends for childhood ALL in Japan and in other countries with rapidly improving public hygiene conditions in the second half of this century may be particularly informative in defining the true extent of the lag between improving public hygiene and increasing childhood ALL incidence.

It is important to note *caveats* about the use of the HAV force of infection as a surrogate for changing patterns of infection for another agent transmitted in similar manner to define a temporal relationship between changing patterns of infection for the putative leukemia-inducing agent and changing rates of childhood ALL. First, while the catalytic model that we have applied fits the HAV seroprevalence data for Whites in the US very well, the changes in HAV force of infection during the 20th century are calculated from cross-sectional data obtained in the 1970s and there are no seroprevalence data prior to that time. However, the similar pattern of decline for the infant mortality rate in the US and the calculated HAV force of infection provides some reassurance about the appropriateness of using the HAV force of infection as a measure of changes in public

hygiene conditions for White children during the first half of the 20th century. Second, the putative infectious agent may have either an earlier change in infection rates or a later change in infection rates than HAV as a result of improved public hygiene conditions. Only by identifying the putative leukemia-inducing agent and defining its change in force of infection over time in various populations will it be possible to establish definitively the presence of a lag between changes in infection rates and childhood leukemia rates. It is also important to recognize that while the model that we present demonstrates the plausibility of our hypothesis relating childhood leukemia to maternal infection status, it does not preclude the possibility that other plausible models based on quite different hypotheses might also explain the observed time trends for childhood leukemia in different countries.

A strength of the approach that we have used is in showing the consistency of the inverse relationship between HAV exposure as a marker for an agent transmitted under poor hygiene conditions and childhood ALL incidence in multiple populations. However, these are ecologic comparisons, and the incidence of childhood ALL in each population reflects a summation of all protective and promoting factors that effect the development of ALL and not just the factors under investigation. Nonetheless, the hypothesis proposed in this paper may provide important leads towards identification of the etiologic agent(s) for childhood ALL by focusing attention on the infection history of women of reproductive age (e.g., as measured by prevalence of antibodies to specific infectious agents) and on candidate agents with particular routes of transmission.

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