National Trends in the Mortality of Children with Sickle Cell Disease, 1968 through 1992

ABSTRACT

Objectives. This paper describes national trends in mortality of children with sickle cell disease and the settings in which death occurred.

Methods. United States death certificate data from 1968 through 1992 were used to calculate mortality rates of Black children with sickle cell disease 1 to 14 years old. Deaths from trauma, congenital anomalies, and perinatal conditions were excluded.

Results. Between 1968 and 1992, mortality rates of Black children with sickle cell disease decreased 41% for 1- to 4-year-olds, 47% for 5- to 9-year-olds, and 53% for 10- to 14-year-olds. During 1986 through 1992, children who died before hospital admission accounted for 41% of deaths among 1- to 4-year-olds, 27% among 5- to 9-year-olds, and 12% among 10- to 14-year-olds.

Conclusions. Survival of Black children with sickle cell disease has improved markedly since 1968. A substantial proportion of deaths continue to occur prior to hospital admission. Trends in sickle cell mortality can be monitored inexpensively with death-certificate data. (*Am J Public Health.* 1997;87:1317–1322)

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Introduction

Since the late 1960s, several improvements in health care for children with sickle cell disease may have led to a decrease in these children's mortality. These improvements include comprehensive care for children with sickle cell disease (with parental education and antibiotic treatment for febrile episodes in young children[1]), penicillin prophylaxis of disease caused by *Streptococcus pneumoniae*,[2] newborn screening programs,[3–7] and pneumococcal vaccines. After a comprehensive care program was established at a medical center in Los Angeles, mortality rates for children with sickle cell disease receiving care there were lower but not significantly so.[1] In addition to being based on a small number of deaths, trends at a single center might not reflect trends nationwide. Mortality rates during 1979 through 1987 in the multicenter Cooperative Study of Sickle Cell Disease[8] appeared to indicate that survival of children with sickle cell disease had improved since previous studies.[9,10] However, the researchers stated that methodological differences between their study and previous ones weakened comparability between them. In addition, in some age groups (3- to 5-year-olds, 6- to 9-year-olds), mortality rates were based on small numbers of deaths, so potential error due to chance is a concern. The small numbers make it very difficult to use these rates as a baseline from which to monitor mortality trends.

To study national trends in mortality of children with sickle cell disease, we used national death certificate data from a 25-year period and estimates of the number of Black children born with the disease each year. This enabled us to examine national mortality with a single database containing information from many years on a large number of deaths of children with the disease. In contrast to previous studies, the large database allowed us to depict trends in sickle cell disease mortality and to do so for several childhood age groups. In addition, to assess whether death certificates provide an adequate source of data for periodically monitoring national mortality at much less expense than repeated multicenter studies, we used death certificate data to calculate rates readily comparable to rates obtained in the Cooperative Study of Sickle Cell Disease. We also determined the settings in which the deaths occurred so that we could assess the proportion of children who died before hospital admission.

Methods

Study Population

Information on deaths of 1- to 14-year-old Black children with sickle

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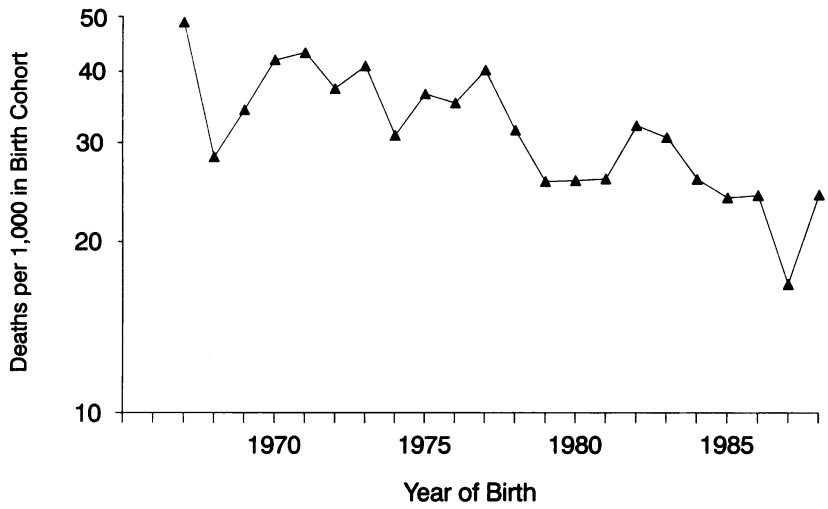
TABLE 1—Deaths of Black Children with Sickle Cell Disease by Age Group and Year of Birth: United States

Age Group, y	Cohort Group	Years of Birth	Deaths per Year of Birth, Mean No.	Deaths per 1000 Persons with Sickle Cell Disease in Birth Cohort, Rate (95% CI)
1–4	Early	1967–1969	55	37 (32, 43)
	Late	1986–1988	36	22 (18, 26)
5–9	Early	1963–1965	30	19 (15, 22)
	Late	1981–1983	15	10 (7, 12)
10–14	Early	1958–1960	29	17 (14, 21)
	Late	1976–1978	12	8 (6, 11)

Note. Deaths occurred in 1968 through 1992. Deaths due to trauma, congenital anomalies, or perinatal conditions were excluded. Sickle β-thalassemia is not included in the definition of the *International Classification of Diseases* codes for sickle cell disease used in this study. CI = confidence interval.



Note. All deaths occurred in 1968 through 1992. Rates represent deaths per 1000 children born with the disease in a given year; deaths due to trauma, perinatal conditions, or congenital anomalies are not included.

FIGURE 1—Mortality rates of 1- to 4-year-old Black children with sickle cell disease by year of birth, United States (log-linear graph).

cell disease for the period 1968 through 1992 was extracted from computer tapes containing death certificate data on all deaths in the United States.[11] These tapes include up to 20 causes of death coded from 1968 through 1978 with the *International Classification of Diseases,* Eighth Revision, Adapted for Use in the United States (ICDA-8), and from 1979 through 1992 with the *International Classification of Diseases,* Ninth Revision (ICD-9).

Deaths were included that had any cause coded for sickle cell disease (ICDA-8 code 282.5, ICD-9 code 282.6). Infants less than 1 year of age were not included because, prior to initiation of newborn screening, many probably died before sickle cell disease was diagnosed.[12,13]

A preliminary analysis compared the expected and observed number of deaths from trauma (ICDA-8 codes E800 through E845, E860 through E929, E940 through E999; ICD-9 codes E800 through E849, E860 through E869, E880 through E929, E950 through E999), congenital anomalies (ICDA-8 and ICD-9 codes 740 through 759), and perinatal conditions (ICDA-8 and ICD-9 codes 760 through 779), assuming that Black children with sickle cell disease had the same mortality rate from these causes as Black children without the disease. The analysis suggested that children with sickle cell disease who died of these causes often did not have sickle cell disease listed on their death certificates. For that reason, and to focus on deaths due to sickle cell disease, we excluded deaths having an underlying cause coded as trauma or any cause coded as congenital anomaly or perinatal condition. Among deaths coded for sickle cell disease, these exclusions accounted for 4.8% of deaths of 1- to 4-year-olds, 3.5% of deaths of 5- to 9-year-olds, and 4.1% of deaths of 10- to 14-year-olds.

In the ICDA-8 and the ICD-9, the sickle cell disease code included hemoglobin SS disease and hemoglobin SC disease but did not include sickle β-thalassemia. In the ICDA-8, the code also included sickle cell trait; this trait received its own code in the ICD-9 (282.5). To adjust for this change, we used ICD-9–coded data to determine that deaths coded for sickle cell trait represented 2% to 3% of deaths coded for sickle cell trait or disease, depending on the age group. The numbers of deaths coded as sickle cell disease when the ICDA-8 was used (1968 through 1978) were deflated accordingly to ensure comparability of mortality rates.

Deaths were included only for Black children 1 to 4 years old born in 1967 through 1988 (n = 1068), Black children 5 to 9 years old born in 1963 through 1983 (n = 388), and Black children 10 to 14 years old born in 1958 through 1978 (n = 349). This restriction was used because data often were analyzed by age group and year of birth, and it was necessary to ensure that children in an age group had the chance to live to the group's upper age limit. Year of birth was calculated as year of death minus age.

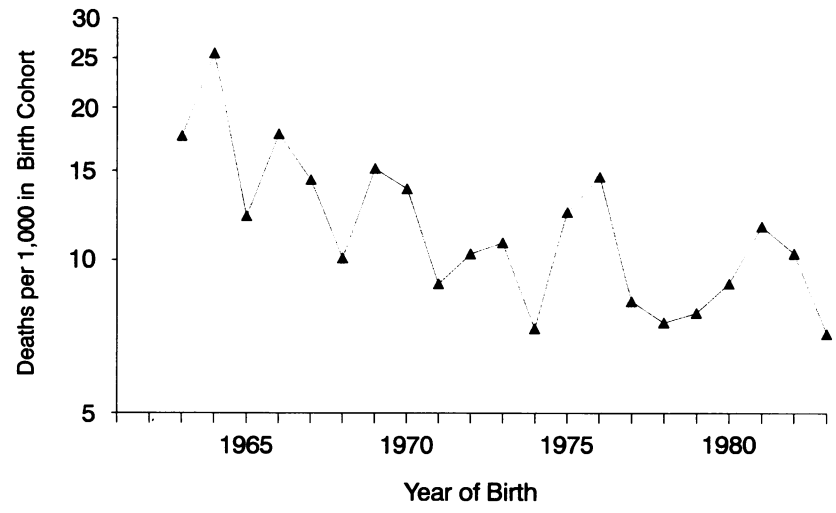
Definitions and Analyses

The number of Black infants born with hemoglobin SS disease or hemoglobin SC disease in a given year was estimated by multiplying the estimated number of births that year in which both parents were Black (National Center for Health Statistics, unpublished data, 1958 through 1988) by the sum of the national prevalences of hemoglobin SS disease and hemoglobin SC disease among Black newborns (1.6 cases of hemoglobin SS disease and 1.2 cases of hemoglobin SC disease per 1000 Black newborns).[14] The resulting number was used as the denominator in calculating mortality rates.

The sickle cell disease mortality rate was the number of deaths of Black children with sickle cell disease in a given age group and born in a given year per 1000 Black children with sickle cell disease born the same year. In some analyses, data from multiple years of birth were averaged to increase statistical stability. For each age group, we compared mortality rates for the group's earliest 3 and latest 3 years of birth in the study (e.g., mortality rates for 5- to 9-year-olds born in 1963 through 1965 vs 1981 through 1983).

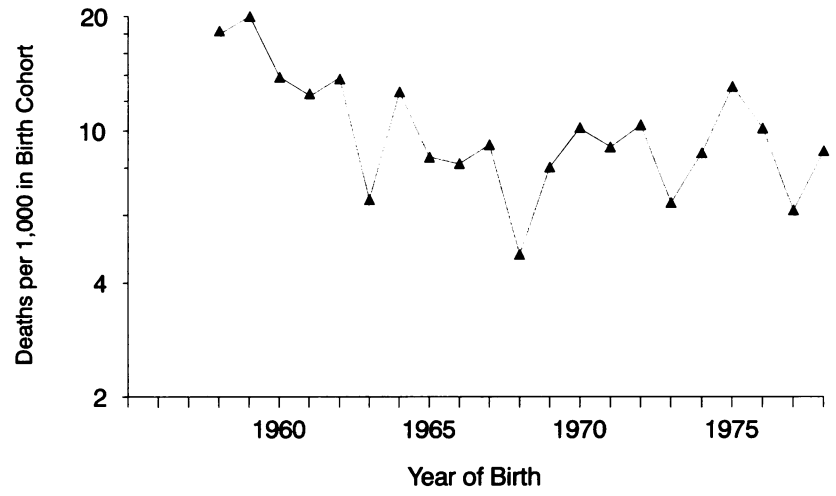
Data on the setting in which the death occurred (inpatient, emergency room or outpatient clinic, dead on arrival at the hospital) also were analyzed. These data were not recorded before 1979.

To compare rates in this study and the multicenter Cooperative Study of Sickle Cell Disease,[8] we calculated incidence–density rates using death certificate data for 1979 through 1987 and the estimated number of Black children born with sickle cell disease each year. We assumed that Black infants with sickle cell disease had a mortality rate of 22 deaths per 1000 live births (slightly higher than that of all Black infants in 1981[15]). We also assumed that Black children with and without sickle cell disease had the same mortality rate from trauma, congenital anomalies, and perinatal conditions; for these causes, mortality rates of Black children without an ICD code for sickle cell disease were calculated via death certificate data and natality data. Cooperative Study of Sickle Cell Disease rates were adjusted to reflect the relative frequency of hemoglobin SS disease and hemoglobin SC disease among Black newborns.[14] Rates from that study and the current study were significantly different if the 95% confidence interval (CI) (calculated with Fisher's Exact Test[16]) for the ratio of the rates did not include 1.0. A difference between two percentages was significant if the 95% confidence interval for the difference did not include zero.



Note. All deaths occurred in 1968 through 1992. Rates represent deaths per 1000 children born with the disease in a given year; deaths due to trauma, perinatal conditions, or congenital anomalies are not included.

FIGURE 2—Mortality rates of 5- to 9-year-old Black children with sickle cell disease by year of birth, United States (log-linear graph).



Note. All deaths occurred in 1968 through 1992. Rates represent deaths per 1000 children born with the disease in a given year; deaths due to trauma, perinatal conditions, or congenital anomalies are not included.

FIGURE 3—Mortality rates of 10- to 14-year-old Black children with sickle cell disease by year of birth, United States (log-linear graph).

Results

National Mortality Rates

The years 1967 through 1969 were the earliest 3 years of birth in this study for children who died when they were 1 to 4 years old. During each year in this period, an estimated 1482 US Black children, on average, were born with hemoglobin SS disease or hemoglobin SC disease. Of children in each annual birth cohort, an estimated average of 55 died when they were 1 to 4 years old (excluding deaths due to trauma, congenital anomalies, and perinatal conditions), a mortality rate of 37 deaths per 1000 Black children with sickle cell disease in the cohort (Table 1). By the time Black children with sickle cell disease born during 1986 through 1988 were 1 to 4 years old, each annual birth cohort had an average of 36 deaths in this age group, and the mortality rate had decreased 41% to 22 deaths per 1000 children with sickle cell disease in the cohort (see Table 1 and Figure 1).

In other age groups, children with sickle cell disease in the three most recent

TABLE 2—Incidence–Density Rate of Deaths of Children with Hemoglobin SS Disease and Hemoglobin SC Disease in the Current Study and in the Cooperative Study of Sickle Cell Disease (CSSCD), 1979 through 1987

Age Group, y	Deaths per 100 Person-Years		Rate Ratio (95% CI)
	CSSCD[a]	Current Study	
1–2	1.43	1.07	1.33 (0.82, 2.08)
3–5	0.17	0.43	0.38 (0.08, 1.14)
6–9	0.26	0.23	1.11 (0.52, 2.10)

Note. Rate ratios were calculated with rates that were not rounded. CI = confidence interval.
[a]Adjusted to reflect the distribution of hemoglobin SS disease and hemoglobin SC disease among Black newborns.

annual birth cohorts also had markedly lower mortality rates than those in the three earliest ones (Table 1). From the early-cohort to late-cohort group, the rate decreased 47% for 5- to 9-year-olds and 53% for 10- to 14-year-olds. Graphs suggest that for 5- to 9-year-olds and 10- to 14-year-olds with sickle cell disease, mortality rates leveled off during the study period's last half (Figures 2 and 3).

Table 2 compares incidence–density rates based on deaths in the Cooperative Study of Sickle Cell Disease in 1979 through 1987 and death certificate data during the same period. In each age group, the 95% confidence interval of the ratio of the rates included 1.0, indicating that the rates were not significantly different. Of note, however, is that for 1- to 2-year-olds, most of the confidence interval of the ratio was above 1.0.

In children with sickle cell disease who died, the percentages of boys were 58% (95% CI = 55%, 61%) among 1- to 4-year-olds, 54% (95% CI = 49%, 59%) among 5- to 9-year-olds, and 52% (95% CI = 47%, 58%) among 10- to 14-year-olds. These percentages did not differ significantly for children born in the first and second halves of each age group's study period.

Setting in Which Death Occurred

Of deaths that occurred in 1986 through 1992 and had data available on the setting in which the death occurred, children who died as outpatients or in an emergency room or who were dead on arrival at the hospital accounted for 41% of deaths for 1- to 4-year-olds, 27% for 5- to 9-year-olds, and 12% for 10- to 14-year-olds (Table 3). A comparison of deaths in 1979 through 1985 vs 1986 through 1992 revealed a significant decrease in the percentage of deaths in these settings among 5- to 9-year-olds (Table 3). When all age groups were combined, analysis showed that, of deaths in 1986 through 1992 with data available, the percentages that occurred prior to hospital admission were 30% (64 of 210 deaths) in counties in Metropolitan Statistical Areas and 37% (19 of 52 deaths) in other counties (95% CI of difference = −21%, 8%).

Discussion

Examination of national trends in mortality of children with sickle cell disease has previously been hampered by several factors. A lack of methodological comparability among studies in different time periods has impeded comparison of their mortality rates.[8–10] Although mortality has been studied for children followed longitudinally at a medical center in Los Angeles,[1] the experience at a single center might not reflect the experience nationwide. In addition, even in the multicenter Cooperative Study of Sickle Cell Disease, which spanned several years,[8] estimates of mortality rates in some childhood age groups (3- to 5-year-olds, 6- to 9-year-olds) were based on small numbers of deaths; as a result, errors due to chance are a concern. Furthermore, the resources required for multicenter studies limit how often such studies can be repeated to monitor national trends in mortality. In the current study, national trends in mortality were examined via a large national database. Using 25 years of national death certificate data on deaths other than those due to trauma, congenital anomalies, or perinatal conditions, the study demonstrated marked decreases in rates of death of Black children with sickle cell disease, with decreasing trends shown in all childhood age groups.

Mortality rates in this study and the Cooperative Study of Sickle Cell Disease did not differ significantly. Differences in the studies' rates might be due entirely to chance; for 1- to 2-year-olds, however, the point estimate and width of the confidence interval for the ratio of the rates suggest that part of the difference might have been due to chance and part due to underreporting of sickle cell disease on death certificates of young children.

We assumed that the prevalences of hemoglobin SS disease and hemoglobin SC disease among Black newborns were constant during the study period. We accounted for increasing interracial parentage by using the number of births for which both parents were Black to estimate the number of Black infants born with sickle cell disease. Although it is possible to diagnose hemoglobinopathies prenatally and then decide to terminate the pregnancy, prenatal diagnosis was not often used during the study period.[17]

Since the mid-1960s, young children with sickle cell disease have been known to have an increased risk of severe bacterial diseases, especially those resulting from *S pneumoniae.*[18–20] Consequently, parents and physicians began to aggressively manage febrile illnesses and thereby probably decreased the morbidity and mortality attributable to *S pneumoniae.* In Los Angeles, a decrease in the percentage of pneumococcal bacteremia episodes progressing to meningitis and/or death was attributed to the establishment, in 1972, of a program providing close medical supervision of febrile children with hemoglobin SS disease less than 6 years old and to the rapid institution of parenteral antibiotic therapy.[1]

Penicillin prophylaxis, as a means of preventing serious disease due to *S pneumoniae,* probably helped decrease mortality among children less than 5 years old. From 1980 through 1984, children less than 3 years old in the Cooperative Study of Sickle Cell Disease had a declining incidence of pneumococcal bacteremia that was associated with increased use of penicillin prophylaxis.[21] In 1986, a multicenter trial found that administration of oral penicillin twice a day to children less than 3 years of age with hemoglobin SS disease resulted in an 84% decrease in pneumococcal septicemia.[2] The decrease occurred despite problems with compliance (estimated in other studies at 55% to 66%).[22,23] Oral penicillin prophylaxis now is recommended for all children less than 5 years of age with hemoglobin SS

TABLE 3—Settings in Which Deaths Occurred: Black Children 1 to 14 Years Old with Sickle Cell Disease by Age Group and Year-of-Death Group, United States, 1979 through 1992

Setting in Which Death Occurred	Age Group and Year-of-Death Group					
	1–4 y		5–9 y		10–14 y	
	1979–1985 (n = 255[a]), %	1986–1992 (n = 152), %	1979–1985 (n = 75), %	1986–1992 (n = 61), %	1979–1985 (n = 71), %	1986–1992 (n = 49), %
Hospital or clinic						
Inpatient	52	54	47	69	68	82
Outpatient or in emergency room	27	33	30	20	13	12
Dead on arrival	14	8	14	7	10	0
Other	7	5	10	4	8	5

Note. The following were not included: deaths of 1- to 4-year-olds born after 1988, deaths of 5- to 9-year-olds born after 1983, deaths of 10- to 14-year-olds born after 1978, and deaths due to trauma, congenital anomalies, or perinatal conditions. Sickle β-thalassemia is not included in the definition of the *International Classification of Diseases* codes for sickle cell disease used in this study. Percentages do not add to 100 as a result of rounding.

[a]Not included because of unavailable data: 1- to 4-year-olds, 66 in 1979–1985, 30 in 1986–1992; 5- to 9-year-olds, 19 in 1979–1985, 8 in 1986–1992; 10- to 14-year-olds, 25 in 1979–1985, 9 in 1986–1992.

disease or hemoglobin S β°-thalassemia.[24]

Screening newborns for sickle cell disease has probably assisted in lowering mortality among younger children. In 1980, statewide newborn screening for sickle cell disease was done in only 5 states and included only 20% of Black newborns.[25] By 1988, statewide newborn screening was occurring in 22 states, covering 65% of Black newborns[25]; by 1992, it was occurring in 43 states, covering 99% of Black newborns.[26] Newborn screening enables affected infants to enter promptly into comprehensive care. Reports suggest that newborn screening, coupled with careful follow-up and extensive parental education, does lower mortality.[3–7]

Pneumococcal vaccine probably decreased mortality only modestly, if at all. The children with sickle cell disease at highest risk for pneumococcal bacteremia are less than 5 years old; children less than 2 years of age are particularly susceptible.[21] However, children less than 2 years of age have a poor immunologic response to the vaccine,[27] and therefore it is given after 2 years of age. A comparison of serotypes of *S pneumoniae* from vaccinated and unvaccinated persons suggested that among children 2 to 10 years old, the vaccine did not prevent disease.[28]

Some of the decreased mortality among children with sickle cell disease might have resulted from health care improvements not specific to the disease. Between 1970 and 1990, the number of pediatricians per population less than 18 years of age increased 107%, suggesting that access to pediatric care generally increased.[29] Care for critically ill children also might have improved and become more available; indicative of this is the increased number of fellowship programs in pediatric intensive care (3 programs in 1975,[30] 14 in 1980,[31] 30 in 1985,[32] and 49 in 1990[33]).

For sickle cell disease to be reported on a death certificate, the child's physician must know the child has the disease and must be careful enough to report it. Newborn screening increased the probability that a young child with sickle cell disease who died would have been diagnosed with the disease and therefore have it reported on a death certificate. In the current study, the years of birth for 1- to 4-year-olds were 1967 through 1988, and many statewide newborn screening programs were established in 1980 through 1990.[25] Therefore, reporting of deaths of young children with sickle cell disease probably improved in the second half of the study period. This change would tend to obscure a decrease in mortality. Consequently, the actual decrease in mortality of 1- to 4-year-old children with sickle cell disease probably was even steeper than estimated here. Because most (although not all) children with sickle cell disease will have developed symptoms by 5 years of age,[12,13] underreporting and changes in reporting completeness are smaller problems in older age groups.

By 1991, the vast majority of newborns with sickle cell disease were being diagnosed via screening programs within the first 6 months of life.[25,26] Therefore, for children with sickle cell disease born in 1991 or later, rates of reporting of the disease on death certificates may be very high and not expected to improve further. This suggests that for children born in 1991 or later, death certificate data will be an even more valuable tool for monitoring trends in mortality, particularly 5- to 10-year trends. The usefulness of these data for monitoring short-term trends will be limited by considerable year-to-year fluctuations in estimated rates.

A substantial proportion of deaths of children 1 to 9 years old occurred in an outpatient department or emergency room, or the child was dead on arrival at the hospital. Fulminant pneumococcemia and acute splenic sequestration can cause death within hours of the onset of symptoms.[20,34] Still, this high proportion raises concern about whether care for acute illnesses is sought promptly and is readily accessible. Research is warranted to confirm settings and to determine whether care was sought promptly and was readily accessible to children who died prior to hospital admission.

Much of the research on sickle cell disease done in the United States in the last 25 years has been a consequence of the 1972 National Sickle Cell Anemia Control Act,[35] which established a sickle cell disease research program organized and sponsored by the National Institutes of Health. Research conducted under this program resulted in an understanding of how to prevent deaths of children with sickle cell disease, and research findings subsequently were implemented. Consequently, the National Sickle Cell Anemia Control Act was a crucial step toward

decreasing mortality of children with the disease.

Further decreases in mortality of children with sickle cell disease might occur as benefits accrue from recently established newborn screening programs. Additional declines would occur if there were greater compliance with penicillin prophylaxis; thus, research on cost-effective ways to increase compliance should be a priority. Finally, this study has demonstrated that analysis of death certificate data is a useful, efficient method for surveillance of medium- and long-term trends in mortality among children with sickle cell disease, and future analyses of these data should be done periodically. □

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