Geographic Differences in Mortality of Young Children with Sickle Cell Disease in the United States

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SYNOPSIS

Objectives. Because geographic differences in health care have been found for many diseases, including those affecting children, there are probably geographic differences in the health care of young children with sickle cell disease. Consequently, survival of young children with sickle cell disease might differ among geographic areas. This study's objective was to identify areas in the United States where young children with sickle cell disease are at especially high and low risk of dying.
Methods. Using U.S. death certificate data from 1968 through 1992, the authors calculated the mortality rates of 1- through 4-year-old black children with sickle cell disease for states, counties, and cities. Deaths from trauma, congenital anomalies, and perinatal conditions were excluded.
Results. From 1968 through 1980 and from 1981 through 1992, 1- through 4-year-old black children with sickle cell disease in Florida had a markedly higher risk of dying, and those in Pennsylvania had a markedly lower risk of dying, than the average 1- through 4-year-old black child with the disease in the United States. From 1981 through 1992, 1- through 4-year-old black children with sickle cell disease in Maryland had the lowest mortality rate in the nation. During the same time period, 1- through 4-year-old black children with sickle cell disease in five counties in Florida were at especially high risk, while in Baltimore no young black children with the disease died. These geographic differences in mortality of black children with sickle cell disease greatly exceeded geographic differences in mortality of black children without the disease.
Conclusions. Marked differences exist across the United States in mortality of young black children with sickle cell disease. To improve survival for children with the disease in high mortality areas, evaluations should be made of the accessibility and quality of medical care, and of parents' health care seeking behavior and compliance with antibiotic prophylaxis. In addition, efforts should be made to understand and duplicate the success of treatment programs in low mortality areas.

Since the late 1960s, efforts have been made to decrease the mortality of young children with sickle cell disease. These include education of parents to recognize complications,[1] prompt parenteral antibiotic treatment during febrile illnesses,[2] penicillin prophylaxis of disease caused by *Streptococcus pneumoniae*,[3] and newborn screening.[4-6]

Geographic differences in health care have been found for many diseases, including those affecting children.[7,8] Although no studies have examined whether there are geographic differences in the health care of young children with sickle cell disease, such differences might exist because of several factors. These include possible differences in the accessibility and quality of medical care; in physicians' approach to treating sickle cell disease; in parents' compliance with antibiotic prophylaxis, recognition of complications, and health care seeking behavior; and in socioeconomic factors.

Geographic differences in the health care of young children with sickle cell disease might cause geographic differences in their survival. Potentially important benefits can result from identifying geographic differences in mortality of young children with sickle cell disease. Public health officials and clinicians will want to make special efforts to lower mortality in areas where it is much higher than in the nation overall. In addition, health care providers across the nation could learn from the experience of health care providers in low mortality areas.

Examining geographic differences in mortality of young children with sickle cell disease is possible only through the use of a national database that includes information from many years on a large number of deaths of young children with the disease. Therefore, to determine geographic differences in mortality of young children with sickle cell disease, we used United States death certificate data for a 25-year period to calculate state mortality rates. For those states with especially high or low mortality rates, we also calculated county and city mortality rates.

Methods

Study population. Using computer tapes of death certificate data on all deaths in the United States, we obtained information on deaths from 1968 through 1992 of 1- through 4-year-old children with sickle cell disease whose "race" was recorded as "black" on the death certificate. The computer tapes, which are produced annually by the National Center for Health Statistics (NCHS), list up to 20 causes of death for each person. From the multiple causes of death listed for a person, the states or NCHS select one as the underlying cause. This selection is made by using a standardized methodology.[9]

The states or NCHS assign a numerical code to each cause of death listed on the death certificate. From 1968 through 1978, they coded the causes of death using the *International Classification of Diseases, Eighth Revision, Adapted For Use In the United States (ICDA-8)*. From 1979 through 1992, they used the *International Classification of Diseases, Ninth Revision (ICD-9)*.

We included deaths for which sickle cell disease (*ICDA-8* 282.5, *ICD-9* 282.6) was listed as one of the causes, regardless of whether sickle cell disease was listed as the underlying cause. Infants under 1 year old were not included because prior to the widespread implementation of newborn screening programs, it is likely that many infants died before sickle cell disease was diagnosed.[10]

To focus on deaths due to complications of sickle cell disease, we excluded deaths for which the underlying cause was coded as trauma (*ICDA-8* E800-E845, E860-E929, and E940-E999; *ICD-9* E800-E849, E860-E869, and E880-E999) or for which the underlying cause or one of the other causes was coded as congenital anomalies (*ICDA-8* and *ICD-9* 740-759) or perinatal conditions (*ICDA-8* and *ICD-9* 760-779). These exclusions accounted for 4.8% of deaths for which sickle cell disease was listed as the underlying cause or one of the other causes of death.

In both *ICDA-8* and *ICD-9*, the sickle cell disease code included hemoglobin SS disease and hemoglobin SC disease but did not include sickle beta-thalassemia, which is coded with other thalassemias. However, some deaths of children with sickle beta-thalassemia might have been included in the study. This is because the death certificate might have listed a cause of death as sickle cell disease, without mention of sickle beta-thalassemia.

In *ICDA-8* the sickle cell disease code also included sickle cell trait, which received its own code in *ICD-9* (282.5). To adjust for this change, we analyzed *ICD-9*-coded data and determined that deaths coded as sickle cell trait comprised 2.2% of total deaths coded as either sickle cell trait or disease. The number of deaths coded as sickle cell disease for the years 1968 through 1978 were deflated by 2.2% for each geographic area to ensure comparability of mortality rates. An analysis revealed that if we had instead used state-specific deflation factors, mortality rates would have changed only slightly; therefore, for simplicity's sake, we used the 2.2% deflation factor for each geographic area.

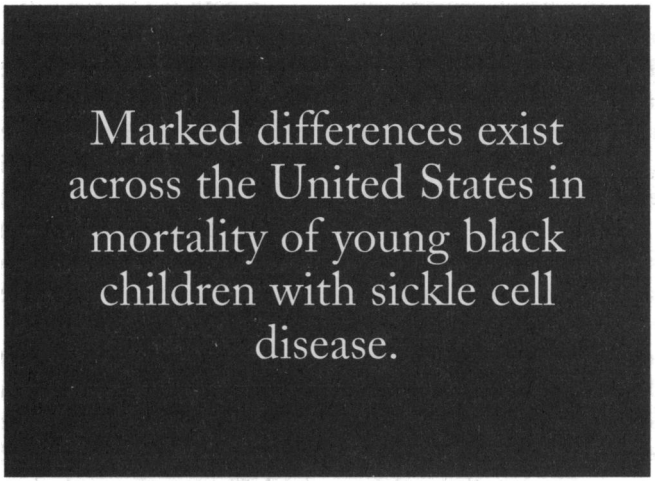
Definitions and analyses. The sickle cell disease mortality rate was the number of deaths of 1- through 4-year-old black children with sickle cell disease per 1000 person-years. Rates were calculated for two time periods: 1968 through 1980 and 1981 through 1992.

Sickle cell disease mortality rates were calculated for the entire United States and for selected states, counties, and cities. To try to ensure that mortality rates would not be markedly affected by random variation, we calculated state mortality rates only for states whose 1980 population of 1- through 4-year-old black children was more than 50,000, including children with and without sickle cell disease. For states whose mortality rates differed significantly from the national rate, we calculated mortality rates for counties or cities that from 1981 through 1992 had or (based on population and the U.S. mortality rate for black children with sickle cell disease) would have been expected to have five or more deaths of 1- through 4-year-old black children with sickle cell disease. When calculating rates, we used data on where the child resided rather than where the child died.

To calculate the denominator for a geographic area's sickle cell disease mortality rate during each time period, we

first interpolated counts from the 1970, 1980, and 1990 U.S. Censuses to estimate the number of 1- through 4-year-old black children in the geographic area in 1974 and 1986 (the mid-points of the two time periods). We then multiplied each of these two population estimates by the sum of the prevalences of hemoglobin SS disease and hemoglobin SC disease among black newborns: 2.8 cases per 1000 black newborns.[11] Then we multiplied by 0.98 because the prevalence of sickle cell disease among black children 1 through 4 years old is an estimated 2% lower than among black newborns, due to mortality for black children with sickle cell disease[12] being higher than for other black children.[13] Lastly, we multiplied by the number of years in the time period to estimate the number of person-years.

To calculate mortality rates for 1- through 4-year-old black children without sickle cell disease, we obtained from computer tapes information on the deaths of black children without a code for sickle cell disease. We applied the same exclusions of deaths from trauma, congenital anomalies, and perinatal conditions as were applied to deaths of black children with the disease.



The relative risk of death of black children with sickle cell disease in a geographic area was calculated as the area's mortality rate for black children with sickle cell disease divided by the overall U.S. mortality rate for black children with sickle cell disease. The relative risk of death of black children without sickle cell disease was calculated as the area's mortality rate for black children without the disease divided by the overall U.S. mortality rate for black children without the disease.

Statistical methods. To compare state, county, and city rates to the U.S. rate, we first calculated the ratio of an area's rate to the U.S. rate. We then used two-sided Fisher's exact probabilities to determine the probability that the difference between this ratio and 1.0 arose only by random chance.[14] This probability is the *P* value.

We calculated mortality rates for 18 states during two time periods; consequently, we compared 36 state:national rate ratios to 1.0. We also calculated mortality rates for seven counties or cities during two time periods; therefore we compared 14 county:national or city:national rate ratios to 1.0. If the state:national rate ratio differed from 1.0 at $P \leq 0.0014$, we considered the state rate and the national rate to be significantly different. At this *P* value there is a 5% probability that one or more state rates (of the 36 state rates evaluated) met the criterion for significance because of random chance alone.[15] For similar reasons, if the county:national or city:national rate ratio differed from 1.0 at $P \leq 0.0036$, we considered the county or city rate and the national rate to be significantly different.

In addition, we considered an area's rate to be significantly different from the national rate if during both time periods the rate ratio differed from 1.0 at $P \leq 0.05$; the ratio also had to be greater than 1.0 during both time periods or less than 1.0 during both time periods. Using the binomial distribution, we calculated that the probability was 2.2% that one or more states of the 18 in the study met this criterion because of chance alone. The probability was 0.9% that one or more counties or cities of the seven in the study met this criterion because of chance alone.

Results

National mortality rate. In the United States during the years 1968 through 1992, there were an estimated 1206 deaths of 1- through 4-year-old black children with sickle cell disease due to causes other than trauma, congenital anomalies, or perinatal conditions. Our data show that during this period, the mortality rate of 1- through 4-year-old black children with sickle cell disease decreased substantially; the rate for 1981–1992 was 35% lower than the rate for 1968–1980 (Table 1).

State mortality rates. During both time periods, 1- through 4-year-old black children with sickle cell disease in Florida had a markedly higher risk of dying, and those in Pennsylvania had a markedly lower risk of dying, than the average 1- through 4-year-old black child with the disease in the United States (Table 1). In each period, these two states had rates that differed from the U.S. rate at $P < 0.05$; the probability that one or more of the 18 states studied would have these results by random chance is 2.2%.

In Florida, black children 1 through 4 years old with sickle cell disease had a mortality rate that exceeded the national rate by 75% in 1968–1980, and by 140% in 1981–1992. By contrast, 1- through 4-year-old black children without sickle cell disease in Florida had a mortality rate that was 14% greater than the national rate during the earlier period and 27% greater during the later period.

In Pennsylvania, 1- through 4-year-old black children with sickle cell disease had a risk of dying that in 1968–1980 was 47% lower than the national risk and in 1981–1992 was 52% lower. In Pennsylvania, black children 1 through 4 years old without sickle cell disease had a risk of dying that in the earlier time period was 15% lower than the

national risk and in the later time period was 6% lower.

In Maryland, during the years 1981 through 1992, black children with sickle cell disease who were 1 through 4 years old had a mortality rate 88% lower than the U.S. rate ($P < 0.0002$); this difference met the study's criteria for statistical significance. In Maryland during the same time period, black children without sickle cell disease who were 1 through 4 years old had a mortality rate 8% lower than the national rate.

From 1968 through 1980, mortality rates for 1- through 4-year-old black children with sickle cell disease in Alabama and Illinois were higher and the rate in North Carolina was lower than the national rate, with $P \leq 0.05$ for each state (Table 1). For the years 1981 through 1992, the sickle cell disease mortality rate in Georgia was higher and the rate in Virginia was lower than the national rate, with $P \leq 0.05$ for each state. However, in some of these states, chance probably accounts for the difference found between the state rate and the U.S. rate. Using the binomial distribution, we calculated that the probability was 84% that random chance would cause one or more of the 36 state rates (18 states during two time periods) to differ from the U.S. rate at $P \leq 0.05$. For five or more state rates to differ at $P \leq 0.05$ because of random chance, the probability was 3.2%.

County and city mortality rates. In Florida from 1981 through 1992, five counties had five or more deaths of black children with sickle cell disease who were 1 through 4 years old (Table 2). Three of these counties (Dade, Broward, and Palm Beach) are contiguous and in the southern part of the state. Brevard County is in the middle of the state. Duval County is in the northern part.

From 1981 through 1992, in each of these five Florida counties, black children 1 through 4 years old with sickle cell disease had a mortality rate that exceeded the national rate by 175% or more. During this time period, sickle cell disease mortality rates in Brevard, Broward, and Dade Counties differed from the U.S. rate at $P < 0.003$; thus, these differences met the study's criteria for statistical significance. During the earlier period, 1968 through 1980, in each of these five Florida counties, black children 1 through 4 years old with sickle cell disease had a risk of death more

Table 1. Estimated state mortality rates of black children 1 through 4 years old with sickle cell disease, 1968–1980 and 1981–1992

	1968–1980			1981–1992		
State	Estimated no. of deaths	Estimated rate[a]	Relative risk[b]	Estimated no. of deaths	Estimated rate[a]	Relative risk[b]
United States	733	10.5	1.00	473	6.8	1.00
Alabama	41	15.2	1.44[c]	16	6.4	0.95
California	36	14.1	1.34	30	8.7	1.29
Florida	64	18.4	1.75[d]	71	16.2	2.40[d]
Georgia	45	11.8	1.13	44	10.5	1.56[e]
Illinois	68	15.1	1.44[e]	32	7.5	1.11
Louisiana	35	9.8	0.93	27	7.8	1.12
Maryland	23	10.8	1.04	2	0.8	0.12[d]
Michigan	25	8.0	0.75	16	5.1	0.76
Mississippi	24	8.8	0.83	15	6.2	0.91
New Jersey	30	12.4	1.19	14	6.2	0.91
New York	59	9.4	0.90	37	6.0	0.88
North Carolina	19	5.8	0.56[e]	19	5.8	0.86
Ohio	31	11.4	1.08	14	5.1	0.75
Pennsylvania	15	5.6	0.53[f]	8	3.2	0.48[c]
South Carolina	23	9.3	0.88	14	5.6	0.83
Tennessee	23	12.7	1.19	17	9.1	1.34
Texas	43	9.3	0.88	41	8.1	1.21
Virginia	17	7.2	0.69	8	3.2	0.48[c]

NOTE: Includes only states that in 1980 had more than 50,000 black children 1 through 4 years old.

[a]Rates are deaths of 1- through 4-year-old black children with sickle cell disease per 1000 person-years. The study does not include deaths due to trauma, congenital anomalies, or perinatal conditions. Sickle beta-thalassemia is not included in the definition of the *International Classification of Diseases* codes for sickle cell disease used in this study.

[b]Relative risks were calculated with rates that were not rounded.

[c]Differs from U.S. rate at $P<0.05$

[d]Differs from U.S. rate at $P<0.0002$

[e]Differs from U.S. rate at $P<0.01$

[f]Differs from U.S. rate at $P<0.02$

than 90% higher than the risk nationally. In Dade County and Palm Beach County, 1- through 4-year-old black children with sickle cell disease had mortality rates that differed from the national rate at $P < 0.05$ during both time periods, a statistically significant finding.

For black children without sickle cell disease who were 1 through 4 years old, we found the following: During the years 1981 through 1992, their mortality rate in Brevard County was 47% lower than the U.S. rate; in Broward County, their mortality rate was 39% higher than the U.S. rate; in Dade County, it was 68% higher; in Duval County, it was 14% lower; and in Palm Beach County, it was 95% higher.

In the city of Baltimore, Maryland, during the years 1981 through 1992, there were no deaths of 1- through 4-year-old black children with sickle cell disease (Table 2) even though six deaths would have been expected based on population and the national sickle cell disease mortality rate ($P < 0.003$). This difference met the study's criteria for statistical significance. In Baltimore during the same time period, 1- through 4-year-old black children without sickle cell disease had a mortality rate 2% lower than in the United States overall.

In Philadelphia, Pennsylvania, the sickle cell disease mortality rate among 1- through 4-year-old black children was 33% lower than the national rate in 1968–1980 and 59% lower in 1981–1992; however, these differences were not statistically significant.

Discussion

Using national death certificate data for a 25-year period, this study identified areas in the United States where 1- through 4-year-old black children with sickle cell disease have particularly high and low risks of dying. During both the 1970s and 1980s, young black children with sickle cell disease in Florida had a markedly higher risk of dying than the average young black child with the disease in the United States, and those in Pennsylvania had a markedly lower risk. During the years 1981 through 1992, the lowest risk of death for young black children with sickle cell disease was in Maryland. The study also identified five Florida counties where 1- through 4-year-old black children with the disease had especially high risks of dying.

These geographic differences in mortality of black children with sickle cell disease greatly exceeded geographic differences in mortality of black children without sickle cell disease. The findings should prompt special efforts to decrease mortality in high risk areas and to learn from the experience of low risk ones.

In estimating the denominator used to calculate sickle cell disease mortality rates, we assumed that the prevalences of hemoglobin SS disease and hemoglobin SC disease among black newborns were constant in all states and counties. Newborn screening data suggest that the prevalences of these hemoglobinopathies among black newborns in

Table 2. Estimated mortality rates in selected areas of Florida, Maryland, and Pennsylvania among black children 1 through 4 years old with sickle cell disease, 1968–1980 and 1981–1992

	1968–1980			1981–1992		
Area (Major city in area)	*Estimated no. of deaths*	*Estimated rate[a]*	*Relative risk[b]*	*Estimated no. of deaths*	*Estimated rate[a]*	*Relative risk[b]*
United States	733	10.5	1.00	473	6.8	1.00
Florida						
Brevard County (Cocoa, Melbourne, and Titusville)	2	26.7	2.54	5	62.8	9.24[c]
Broward County (Ft. Lauderdale and Hollywood)	6	20.5	1.94	11	23.6	3.49[c]
Dade County (Miami)	14	20.3	1.93[d]	18	18.6	2.75[c]
Duval County (Jacksonville)	8	22.3	2.11	8	19.4	2.87[d]
Palm Beach County (Palm Beach)	8	37.6	3.57[e]	7	24.8	3.67[e]
Baltimore city, Maryland	15	13.3	1.27	0	0.0	0.00[c]
Philadelphia, Pennsylvania	12	7.1	0.67	4	2.8	0.41

NOTE: Includes counties and cities in Florida, Maryland, and Pennsylvania that during 1981–1992 had or, based on population, would have been expected to have five or more deaths of black children 1 through 4 years old with sickle cell disease.

[a]Rates are deaths of 1- through 4-year-old black children with sickle cell disease per 1000 person-years. The study does not include deaths due to trauma, congenital anomalies, or perinatal conditions. Sickle beta-thalassemia is not included in the definition of the *International Classification of Diseases* codes for sickle cell disease used in this study.

[b]Relative risks were calculated with rates that were not rounded.

[c]Differs from U.S. rate at $P<0.003$

[d]Differs from U.S. rate at $P<0.05$

[e]Differs from U.S. rate at $P<0.01$

Florida,[16,17] Maryland,[16] and Pennsylvania (Unpublished data, Pennsylvania Department of Health, 1993 through 1995) are similar to the national prevalences.

Statewide newborn screening for hemoglobinopathies started in Maryland in 1985, in Florida in 1988, and in Pennsylvania in 1992.[16,17] Local screening programs began in Miami in 1979, in Jacksonville in 1983, and in Philadelphia in 1990.[17,18] Therefore, this study's sickle cell disease mortality rates for Maryland, Florida, and Pennsylvania reflect to only a limited extent the effects of newborn screening.

The probability of developing complications of sickle cell disease is affected by genetic factors. Genetic markers identify subgroups of patients with lower and higher risks of painful crisis, bone infarct, irreversible organ failure in soft tissue, and hospitalization.[19] Although the influence of genetic factors on the risk of death of young children with sickle cell disease is not known, such factors might account for some of the geographic differences in mortality rates.

Differences in state and county mortality rates during the 1980s might also arise from differences in physicians' use of penicillin prophylaxis and parents' compliance with it. In 1986, a multicenter trial found that prophylactic oral penicillin greatly decreased the incidence of pneumococcal septicemia among young children with hemoglobin SS disease.[3] By the early 1980s some centers, particularly in the northeastern United States, had already begun to routinely prescribe penicillin as prophylaxis.[20]

Geographic differences in mortality rates of young children with sickle cell disease might reflect differences in the accessibility and quality of medical care and in parents' health care-seeking behavior and compliance with antibiotic prophylaxis.

Geographic differences in mortality rates of young children with sickle cell disease might also reflect differences in the accessibility and quality of medical care and in parents' health care seeking behavior. In Los Angeles, decreased morbidity from pneumococcal bacteremia was attributed to the establishment in 1972 of a program providing rapid institution of parenteral antibiotic therapy to febrile children with sickle cell disease.[2] Comprehensive care programs also can teach parents to recognize symptoms of other potentially fatal complications, such as splenic sequestration and aplastic crisis, and to promptly seek care whenever these symptoms appear.

The study could not assess if failure to record sickle cell disease on death certificates accounts for the lower mortality rates found in Maryland and Pennsylvania. However, one can readily calculate how mortality rates would be affected by under-recording of the disease. For example, assume that for as many as 20% of the black children with sickle cell disease who died in Maryland and Pennsylvania, physicians did not record the disease on the death certificates (20% under-recording is a percentage that in the authors' judgment is not implausible). Under these circumstances, the estimated sickle cell disease mortality rates in Maryland and Pennsylvania during 1981–1992 would still be much lower than the national rate, 85% lower in Maryland and 40% lower in Pennsylvania.

The public use data tapes used in this study did not have information that could be used to identify the children who died. Therefore, the study did not confirm that black children whose death certificates listed sickle cell disease as a cause of death actually had the disease. One can calculate how mortality rates would be affected by over-recording of the disease. For example, assume that in Florida as many as 20% of the black children for whom sickle cell disease was listed on their death certificates did not have the disease. Under this circumstance, the estimated mortality rate in Florida during 1981–1992 still would be 90% higher than the national rate.

In areas in Florida identified as having high mortality rates, clinicians and health officials might want to collaborate with the state health department's epidemiology and vital statistics divisions to study the accuracy of the death certificates on which sickle cell disease was recorded. In high mortality areas, there should be evaluations of the health care for children with sickle cell disease. These evaluations should examine the accessibility and quality of medical care for children with sickle cell disease as well as parents' health care seeking behavior and compliance with antibiotic prophylaxis. In low mortality states (Pennsylvania and Maryland), managers of sickle cell disease treatment programs should describe their highly effective programs. This will enable health care providers in other geographic areas to learn from their successes. A study also should be done to determine if the health care for children with sickle cell disease during a fatal complication differs from the health care for children who had a similar complication but did not die. These efforts might lead to a better understanding of how to improve the care, and thereby the survival, of young children with sickle cell disease nationwide.

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