
Neonatal screening for sickle cell disease: A cost-effectiveness analysis

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Purpose: To determine the cost-effectiveness of screening newborn infants for sickle cell disease.

Design: We developed a decision model that examined two strategies: (1) screening neonates and administering penicillin to infants found to have sickle cell disease in the hope of preventing pneumococcal sepsis, and (2) not screening but administering penicillin to infants after symptoms of sickle cell disease develop. The model calculates the cost-effectiveness of these strategies during the first 3 years of life. We applied the model to three prototypic populations of neonates—black, nonblack with a relatively high prevalence of hemoglobin S genes, and nonblack with a low prevalence of hemoglobin S genes.

Data identification: We obtained from the published literature the effectiveness and risk of penicillin prophylaxis, the risk of pneumococcal sepsis, and the probability that in infants not screened the development of symptoms would lead to the discovery of sickle cell disease within the first 3 years of life; we used the published literature and the Hardy-Weinberg law to determine the prevalence of sickle cell disease. We used actual variable costs of screening, antibiotic prophylaxis, and hospitalization for pneumococcal sepsis or anaphylaxis.

Results: Screening and then treating affected black infants costs only \$3400 more per life saved than not screening. Screening nonblack populations with a high prevalence of hemoglobin S genes would cost \$1.4 million per life saved, and screening low prevalence populations would cost \$450 billion per life saved.

Conclusions: Screening black infants is very worthwhile, but screening populations in which the hemoglobin S gene is rare is unjustified. (J PEDIATR 1994;118:546-54)

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A sound rationale underlies the belief that neonatal screening for sickle cell anemia and other severe sickling hemoglobinopathies may save the lives of affected infants. In the first 3 years of life, children with sickle cell disease are at great risk of infection with *Streptococcus pneumoniae*, which has a case-fatality rate as high as 30%.¹⁻¹³ Recent trials of prophylactic use of penicillin, though, have demonstrated reductions in the incidence of *S. pneumoniae* sepsis and in the associated mortality rate in patients less than 3

HbAA	Homozygosity for normal adult hemoglobin
HbAS	Heterozygosity for hemoglobins A and S
HbS	Sickle cell hemoglobin
HbSC	Sickle cell hemoglobin C disease
HbSS	Homozygosity for hemoglobin S

years of age.^{13,14} Furthermore, an inexpensive, sensitive, and specific test to identify affected neonates is available,¹⁵⁻¹⁷ and programs geared to the care of affected infants can reduce the morbidity and mortality rates associated with events such as splenic sequestration.¹⁸

On the basis of these advances, a recent National Institutes of Health Consensus Conference recommended universal screening of newborn infants for hemoglobinopathies.¹⁹ By late 1989, more than half of the states in the United States had initiated universal screening programs,²⁰ and by late 1990, approximately three fourths of the states were screening on some level (J. S. Lin-Fu, MD, Genetic Services Branch, Maternal and Child Health Bureau, Department of Health and Human Services: personal communication, October 1990).

We developed a decision model to examine the cost-effectiveness of such programs.

METHODS

Assumptions

Assumptions for populations. Although the incidence of hemoglobin SS and hemoglobin SC among black persons is well defined, the incidence among nonblack subjects is difficult to ascertain because the beta S and beta C genes are rare and vary in frequency from one population to another.²¹⁻²³ We thus examined two "prototypic" nonblack populations, one having a higher prevalence of HbSS than the other (see the discussion of probabilities, below). We assumed that the prevalence of HbSC relative to HbSS is similar to that in the black population.²⁴

Assumptions for screening

1. Screening would be done as an adjunct to screening for hypothyroidism and phenylketonuria. Thus no additional shipping and notification costs would be incurred.

2. Hemoglobin type would be determined by standard methods¹⁵⁻¹⁷; a positive screening test result would be followed by a confirmatory electrophoresis on a new sample.

3. The sensitivity and specificity of screening are both 100%. To account for laboratory errors, we relaxed these assumptions in a sensitivity analysis.

4. If the screening test result is negative, the baby would not be retested for sickle cell disease. Any unscreened infant with later development of sepsis or another manifestation of sickle cell disease would be tested for hemoglobinopathy. If the baby were found to have HbSS or HbSC, penicillin prophylaxis would be administered.

Assumptions for prophylaxis

1. Prophylaxis would consist of 125 mg of penicillin given orally twice a day, beginning at age 3 months (or as soon as sickle cell disease is discovered, whichever comes first) and continuing until age 3 years 3 months.

2. Compliance would be equivalent to that achieved in the prophylactic penicillin trial.¹³ Because this assumption may result in an overestimate of compliance, we performed a sensitivity analysis on the effectiveness of prophylaxis; effectiveness, as opposed to efficacy, encompasses compliance.

3. Although anaphylactic reactions should not occur in infants continually treated with penicillin, previous studies have indicated that therapy is often interrupted for brief periods. These lapses would be sufficient to allow a cutaneous or anaphylactic reaction to develop in a susceptible infant; the risk of reaction would be highest in the first few months of exposure and decline exponentially at a rate of 50% every 6 months.

4. Serious delayed hypersensitivity reactions rarely occur in young children and rarely, if ever, are fatal.²⁵⁻²⁷ Nevertheless, penicillin would be stopped in children with either an anaphylactic or a cutaneous reaction. Thereafter they would be subject to the same risk of sepsis as patients not given prophylaxis.

5. A separate analysis of patients allergic to penicillin considered prophylaxis with erythromycin, 200 mg twice a day, and assumed that erythromycin had the same effectiveness as penicillin. In that analysis, side effects would neither incur monetary cost nor necessitate discontinuing erythromycin therapy.

Assumptions for pneumococcal sepsis. One episode of sepsis would not make a subsequent episode more likely.¹³ We relaxed this assumption in a sensitivity analysis.

Cost assumptions

1. We considered the costs of screening and antibiotic prophylaxis but ignored the costs of counseling parents (see the Discussion section, below). We considered the variable hospitalization costs of anaphylaxis and sepsis. In a sensitivity analysis, we included estimated costs of physician visits.

2. The cost of the confirmatory hemoglobin electrophoresis would be the same as that of the screening test. We relaxed this assumption in a sensitivity analysis.

3. A cutaneous reaction to penicillin would not incur any monetary cost.

4. All cases of anaphylaxis and sepsis would be managed in the hospital. We used average variable costs, combining fatal and nonfatal cases.

Decision model. We applied a single decision model (Fig. 1, *A* and *B*) to three populations, each with unique data: black, nonblack with a high prevalence of HbS genes, and nonblack with a low prevalence. We considered two strat-

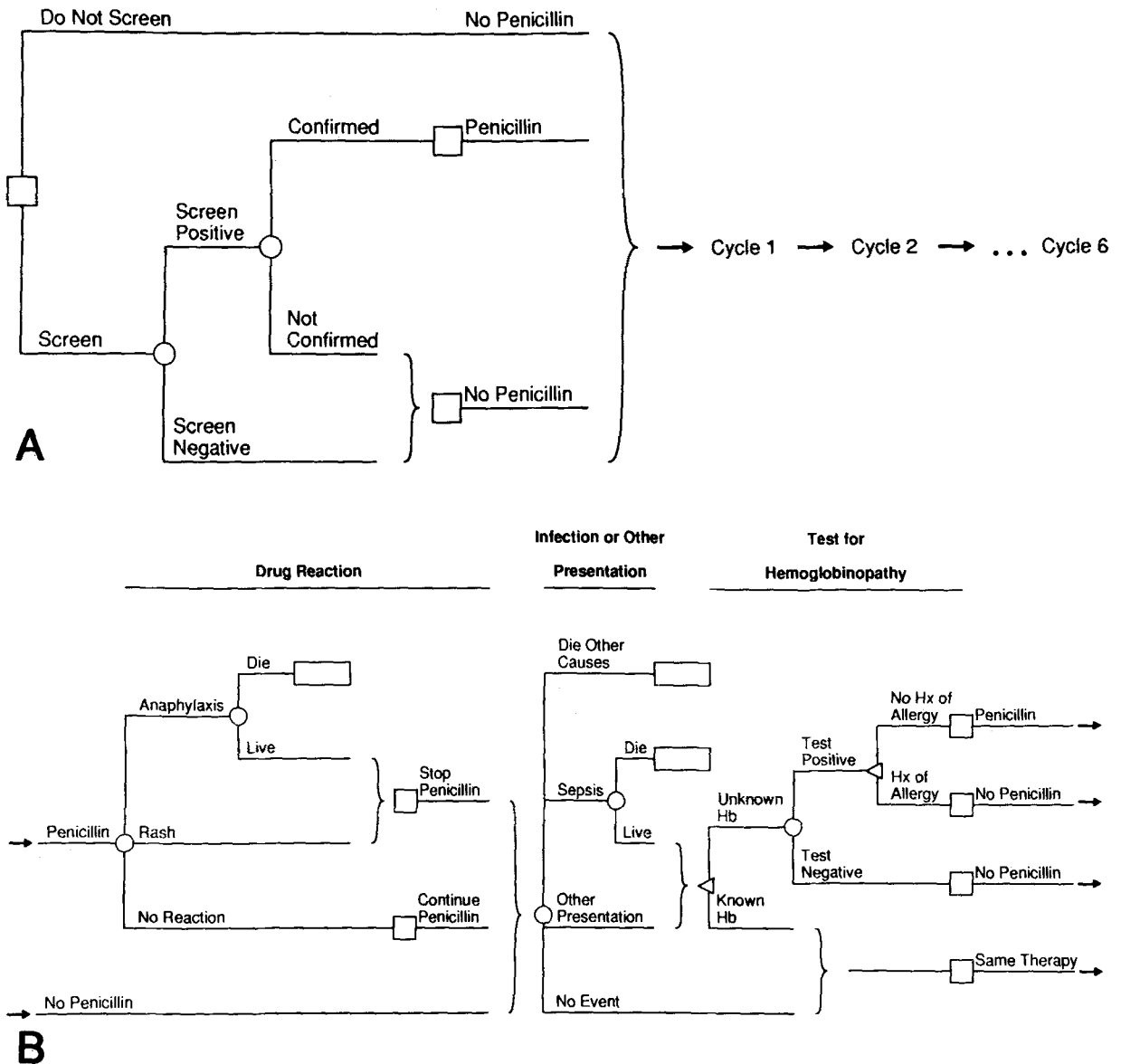


Fig. 4. A, Decision model. Node types are represented as follows: *square* = decision node; *circle* = chance node; *rectangle* = terminal (outcome) node; and *triangle* = Boolean (logic) node. *Bracket* denotes that all branches proceed to recursive subtree shown in **B**. See text and appendix for details. **B**, Recursive decision subtree modeling potential drug reactions, infection, other presentations of sickle cell disease, and testing. After sepsis or another presentation of sickle cell disease, patients are tested only if their hemoglobin (*Hb*) type is unknown. Node types are as in **A**. *Hx*, History.

egies: (1) do not screen and do not institute therapy unless the infant later had symptoms of HbSS or HbSC disease; and (2) screen and start penicillin prophylaxis if the infant is found to have HbSS or HbSC (for details of the model, see the Appendix, below).

The principal measures of outcome are the number of children alive at age 3 years 3 months and the costs incurred; we thus express outcomes as additional cost per additional

life saved. We also calculated the incidence of anaphylaxis, fatal anaphylaxis, sepsis, and fatal sepsis that would occur under each strategy.

Probabilities

Hemoglobinopathy. Prevalences of hemoglobin types among black populations are well known,^{21, 22, 24} but estimates for nonblack populations are less firm. For nonblack populations, we calculated the prevalence of HbSS by us-

Table 1. Baseline results

Infant population	Strategy	Cost per million babies (\$)	Anaphylaxis		Sepsis		Total deaths per million babies in first 3 yr	Incremental cost-effectiveness (additional \$ per additional life saved)
			Cases per million babies	Deaths per million babies	Cases per million babies	Deaths per million babies		
Black	Do not screen	2.44 million	0.15	0.016	872	210	10,493	—
	Screen	2.72 million	0.55	0.057	531	119	10,402	3100
Nonblack/ high admixture	Do not screen	1.71 million	0.00077	0.000084	446	96.0	7,904*	—
	Screen	2.36 million	0.0029	0.00030	444	95.5	7,904*	1.4 million
Nonblack/ low admixture	Do not screen	1.71 million	2.3×10^{-9}	2.5×10^{-10}	445*	95.6*	5,425*	—
	Screen	2.35 million	8.7×10^{-9}	9.0×10^{-10}	445*,†	95.6*	5,425*	450 billion

*Differences between "Screen" and "Do not screen" are inapparent because of rounding of figures.

†Cases exceed those for the nonblack-high admixture population because the lower infant mortality rate in the low-admixture population exposes more babies to the risk of sepsis.

ing the Hardy-Weinberg law and set the prevalence of HbSC at 75% of that of HbSS.²⁴ For the hypothetical non-black population having a high admixture of HbS genes, we used the average HbAS genotype frequency of white and Hispanic infants tested in a large municipal hospital screening program (average = 0.0058).²³ For a hypothetical nonblack population with a low admixture of HbS genes, we used a HbS heterozygote (HbAS) frequency of 1 in 100,000.^{21, 22} In all populations, we calculated the prevalence of HbAA by subtracting the sum of the other three genotypes from one.

Penicillin allergy. Because penicillin allergies of all types are less common in children than adults, we used the lower range of the published adult data.²⁵⁻²⁷

Sepsis. Infants with HbSS have a 9% annual risk of having pneumococcal sepsis; penicillin prophylaxis reduces this risk by 84%.¹³ For infants with HbSC, the risk is approximately 44% of that for those with HbSS,¹¹ or 4% per year without prophylaxis. The risk for patients with HbSC disease is derived from a study of *bacteremia* in sickle hemoglobinopathies¹¹; to the extent that the risk of *septicemia* may be somewhat lower, our analysis may be biased in favor of screening. For infants without hemoglobinopathy, we estimated the annual incidence of septicemia to be 0.016%.²⁸

Mortality rate. In the prophylactic penicillin trial, the two patients who received prophylaxis but nevertheless acquired sepsis survived.¹³ We hypothesized that a case-fatality rate of zero would be unlikely if larger numbers of patients were studied. We conservatively assigned the same case-fatality rate for sepsis (25%) in patients with HbSS or HbSC regardless of whether the patient was taking pro-

phylactic penicillin. Again, if the actual case-fatality rate among patients with HbSC is lower than our estimate, our analysis would be biased in favor of screening. For patients with HbAA or HbAS, we used a sepsis case-fatality rate of 20%.²⁸ We varied all case-fatality rates over a wide range in a sensitivity analysis.

The probability of dying from natural causes was based on 1981 U.S. Life Tables.²⁹

Other presentations of sickle cell disease. Patients with HbSS and HbSC in whom sepsis does not develop may come to medical attention for other reasons. We estimated that by age 3 years, approximately 50% of patients with HbSS who were not screened would come to medical attention for problems other than infection.³⁰ Among those patients, none would be identified before age 6 months, 30% during the second 6 months, and 5% during each of the subsequent four 6-month periods. We then estimated that patients with HbSC would be one tenth as likely to be identified as those with HbSS.

Costs. We used actual variable costs rather than charges.³¹ The costs of both anaphylaxis and sepsis represent the mean costs of hospitalization during fiscal year 1987 in a large metropolitan hospital and were obtained by using the Transition I—Clinical Cost Manager cost-accounting software program (Transition Systems, Inc., Boston, Mass.).

Screening. The variable cost of screening was estimated to be 64 cents per screening battery: 22 cents for consumable supplies³² and 42 cents for technician time, based on a conservative assumption that a technician earns \$12 per hour and can process 28 specimens an hour.

In our model, infants who on initial screening have HbSS,

Table II. Sensitivity analysis

Variable	Value	Incremental cost-effectiveness of screening compared with not screening (\$/life saved)		
		Black infants	Nonblack infants, HA (million)	Nonblack infants, LA (billion)
Probabilities				
Sensitivity and specificity of screening	0.99	9,900	5.0	"Do not screen" dominates
	1.0*	3,100	1.4	
Annual probability of sepsis in patient with HbSS with no prophylaxis	0.05	10,000	2.4	780
	0.094*	3,100	1.4	450
Annual probability of sepsis in patient with HbSC with no prophylaxis	0.15	"Screen" dominates	0.85	280
	0	7,200	2.0	650
Sepsis case-fatality rate in patient with HbSS or HbSC with no prophylaxis	0.018	4,900	1.6	540
	0.041*	3,100	1.4	450
	0.094	750	1.0	330
	0.1	7,700	3.4	1100
Costs (dollars) screening test	0.25*	3,100	1.4	450
	0.4	2,000	0.85	280
Confirmatory hemoglobin electrophoresis	0.30	"Screen" dominates	0.64	210
	0.64*	3,100	1.4	450
	1.00	7,400	2.1	700
	2.00	19,000	4.3	1400
	3.00	31,000	6.4	2100
	4.00	43,000	8.5	2800
Sepsis	0.64*	3,100	1.4	450
	6.40	8,300	1.4	450
	12.80	14,000	1.5	450
Physician fees†	0	9,200	1.4	450
	1,600*	3,100	1.4	450
	2,500	"Screen" dominates	1.4	450
	10,000	"Screen" dominates	1.3	450
\$50 first visit, then \$25/yr		7,200	1.4	450
\$500 first visit, then \$250/yr		23,000	1.4	450

HA, High admixture of HbS genes; LA, low admixture of HbS genes.

*Baseline value for all three populations.

†Not considered in baseline analysis.

HbSC, or HbAS are retested to confirm the diagnosis; in their cases the total testing costs in the baseline analysis were assumed to be doubled, or \$1.28.

Penicillin prophylaxis. The outpatient pharmacy acquisition cost of penicillin, 125 mg twice a day, is 2.3 cents per day, or \$8.40 per year (E. Anderson, Jr., MS, Associate Director of Pharmacy, New England Medical Center: personal communication, June 1989). To this we added a dispensing cost of \$3.30³³ once every 3 months. Thus the total variable cost of penicillin prophylaxis equaled \$21.60 per year.

Erythromycin prophylaxis. The acquisition cost of erythromycin elixir, 200 mg twice a day, is 31 cents per day, or \$113.50 per year (E. Anderson, Jr.: personal communication, June 1989). Because it has a 10-day shelf life, we added

the \$3.30 dispensing cost every 10 days, yielding a total variable cost for erythromycin of \$233.60 per year.

Anaphylaxis. The average variable cost of managing an episode of anaphylaxis in patients aged 40 days to 3 years is \$900, rounded to the nearest \$100.

Sepsis. The average variable cost of hospitalization for sepsis in this age group is \$1600.

Discounting. In the baseline analysis, we discounted future costs at a rate of 5% per year. We varied this rate from zero to 10% in a sensitivity analysis.

RESULTS

Baseline analysis (Table I). The incremental cost-effectiveness ratio for screening black neonates is \$3100 per life saved. For nonblack newborn populations with a relatively

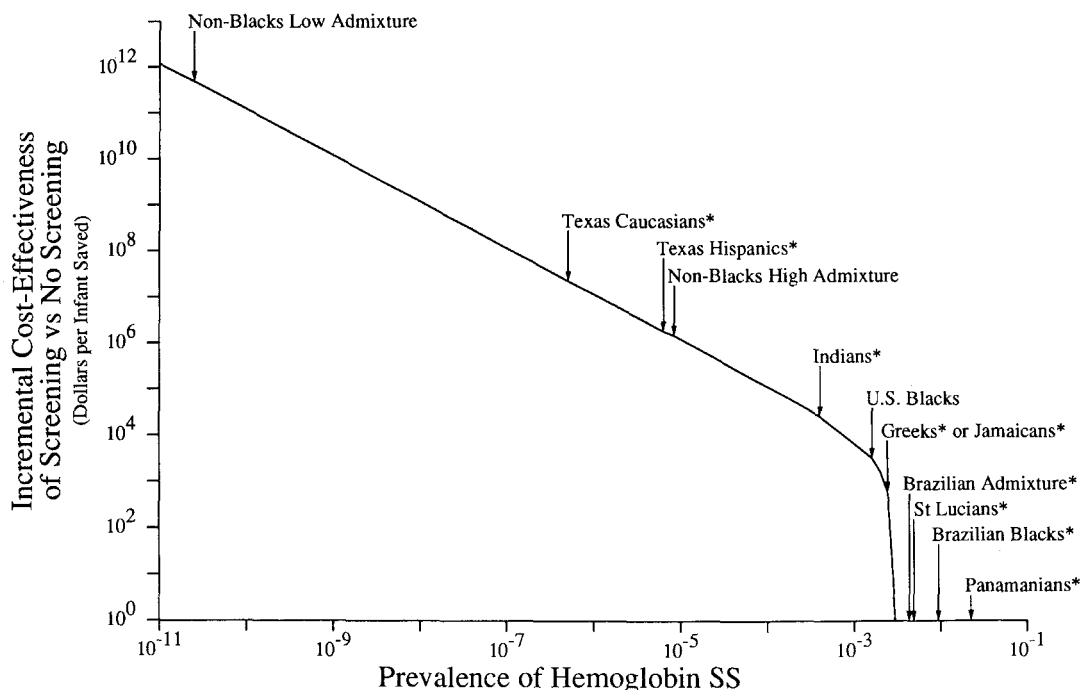


Fig. 2. Incremental cost-effectiveness of screening compared with no screening for varying prevalences of HbSS. Log of incremental cost-effectiveness (*y*-axis) is plotted against log of prevalence of HbSS in neonatal population (*x*-axis). Three populations considered in baseline analysis, as well as several other selected populations (denoted by *asterisk*), are illustrated. Prevalences of HbSS and HbSC in “Non-Blacks Low Admixture,” “Non-Blacks High Admixture,” “Texas Caucasians,” and “Texas Hispanics” were calculated (see also text and Table III).

high prevalence of HbS genes, the incremental cost-effectiveness is approximately \$1.4 million per life saved. For nonblack newborn populations with a low prevalence of HbS genes, the incremental cost-effectiveness is \$450 billion per life saved.

The strategy of administering erythromycin if penicillin allergy develops costs \$2200, \$640,000, and \$210 billion, respectively, per additional life saved compared with not screening for each of the three populations. These cost-effectiveness ratios are more favorable than the base case because they allow for full advantage to be taken of the information provided by screening. The strategy of using erythromycin prophylaxis for all patients with positive screening results, however, would cost more than \$850 million per additional life saved compared with using penicillin for each of the three populations; the higher cost of erythromycin overwhelms the small benefit of avoiding allergic reactions to penicillin.

Screening black infants would prevent 91 deaths per million infants during the first 3 years of life (Table I). In 1986, there were 621,221 black babies born.³⁴ Thus our model projects that screening all black neonates in a given year could potentially prevent approximately 57 deaths by the

time the cohort reaches age 3 years, at an incremental cost of \$176,700.

Sensitivity analysis (Table II). To determine whether changes in our assumed probabilities or costs affected the outcome of the analysis, we performed sensitivity analyses on each variable.

The results are not sensitive to wide changes in most variables. As expected, the analysis is most sensitive to the prevalence of HbSS. The relationship between incremental cost-effectiveness and the prevalence of HbSS^{21, 22, 32, 35} can be shown graphically (Fig. 2). Screening becomes the dominant (i.e., less costly and more effective) strategy when the prevalence of HbSS exceeds 0.0027. Prevalences of this order are found among black populations in Texas³⁵ and in Los Angeles County.³⁶

The analysis is sensitive to the annual probability of sepsis. For black populations, screening becomes the dominant strategy when the annual probability of infection exceeds 15%.

For black populations the results are also relatively sensitive to the cost of the initial screening test (but not to the cost of the confirmatory test) and to the cost of treating sepsis, but not to most other variables. If the cost of the ini-

Table III. Cost-effectiveness of screening in Texas

Race	% Newborn population*†	Prevalence of HbSS*‡	Incremental cost-effectiveness of screening vs not screening (\$/life saved)
Black	13	0.0023	1,600
Hispanic	26	6.2×10^{-6}	2.2 million
White	51	5.1×10^{-7}	26 million
Other, unspecified	9	1.0×10^{-5}	1.3 million
Entire state	100	3.2×10^{-4}	38,000

*Data from Therrell BL Jr, Simmank JL, Wilborn M. *Pediatrics* 1989;83(suppl):864-7.

†Rounded to nearest whole percent.

‡For Hispanic, white, and other races, the prevalence of HbSS was calculated by using the Hardy-Weinberg law, and the prevalence of HbSC was determined by using the statewide average ratio of HbSC to HbSS (0.35).

tial screening test falls to less than \$0.38, then screening becomes the dominant strategy for black populations. For nonblack populations the cost of screening would have to be less than 1 cent before screening could be considered as the dominant strategy. For black populations, if the cost of treating sepsis exceeds \$2400 (baseline cost \$1600), then screening becomes the dominant strategy. For the other two newborn groups, screening remains more expensive than not screening for all hospitalization costs for sepsis less than \$100,000.

DISCUSSION

Previous cost-benefit analyses of newborn screening programs have found that screening for phenylketonuria,³⁷ hypothyroidism,³⁸ and other metabolic diseases^{39, 40} conserves society's resources. We performed a cost-effectiveness analysis of neonatal screening for sickle cell disease to allow selective administration of prophylactic penicillin. Screening might involve cohorts of newborn infants at varying risks for sickle hemoglobinopathies. We found that screening black populations would incur a cost of only \$3100 per baby's life saved, whereas screening nonblack populations with a low prevalence of HbS genes would require a tremendous expense. In a nonblack population with a high degree of HbS gene admixture, as in certain areas of the world, the cost-effectiveness of screening is intermediate and depends on the prevalence of sickle cell disease in the specific population.

When considering whether to screen infants in a particular state or region, one should distinguish between the cost-effectiveness of screening specific racial groups and the cost-effectiveness of screening the entire population, as is now the practice in many states. As an illustration, in Texas the apparent incremental cost-effectiveness of screening all newborn infants compared with not screening is \$38,000 per life saved (Table III). This overall analysis conceals the much higher incremental cost-effectiveness ratios of screening certain subgroups. Although it costs only \$1600 per life saved to screen black infants, it costs \$26 million per life

saved to screen white babies. A more focused program might allow limited resources to be applied to other, more effective programs.

The results of the analysis did not change substantially when most of the probabilities and costs in the baseline analysis were varied over wide ranges, except for the prevalence of sickle cell disease, the risk of sepsis, the cost of screening, and the cost of treating sepsis (Fig. 2; Table II). The costs of screening used in the baseline analysis were derived from a large state health department³² and may be higher in smaller laboratories. The costs may also be higher if much time is required to sort samples for screening. In addition, we probably underestimated the costs of the confirmatory test. Yet even if a confirmatory test were 20 times as expensive as we assumed, the incremental cost-effectiveness of screening black infants would be favorable (approximately \$14,000 per life saved).

More interesting is how the cost of treating sepsis affects the analysis (baseline value \$1600). We used costs rather than charges for hospitalization. When the cost of hospitalization for sepsis exceeds \$2400, screening black newborn infants becomes both less expensive and more effective than not screening them, but this effect is not seen in either of the nonblack populations.

We did not model the cost of counseling parents of children with sickle cell disease or trait. These costs would make screening less cost-effective, unless counseling has a net societal benefit. On the other hand, we also ignored several benefits of screening. Our model applies only to HbAA, HbAS, HbSS, and HbSC. Because patients with HbS- β -thalassemia may have similar risks of sepsis, identifying these patients would enhance the effectiveness of screening. Potential additional benefits that may make screening even more cost-effective include reducing the number of deaths from sepsis by administering pneumococcal vaccine at age 2 years and reducing the number of deaths caused by acute splenic sequestration crisis.

The recommendation that all newborn infants be screened for sickle cell disease, except in populations with few infants

at risk, is based on five premises: (1) determining race may be arbitrary¹⁹ (e.g., in Georgia the mother identifies her own race and the infant is screened or not screened accordingly [J. Eckman, MD: personal communication, October 1990]); (2) often, sepsis occurs very early in life¹⁹; (3) its effects are frequently devastating¹⁹; (4) missing any infants at risk is unacceptable¹⁹; and (5) eliminating universal screening could result in decreased institutional compliance with other screening strategies. On the other hand, because sickle cell disease is so rare among most nonblack populations, screening those populations would require tremendous outlays of resources for each case found and life saved. Few would disagree that spending \$3100 to save a baby's life is very worthwhile, but the enormous additional cost per life saved for screening nonblack populations with a low prevalence of HbS genes should be carefully considered. More problematic is the situation in which there is a higher prevalence of HbS genes in the nonblack population. Here it seems most worthwhile to base the screening decision on the prevalence of HbSS in the specific population at hand.

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APPENDIX

In Fig. 1, *A*, the square decision node at the *left* shows the two strategies: "Do Not Screen" and "Screen." Following the Screen branch is a circular chance node representing the probabilities of a positive and a negative screening test result for hemoglobinopathy (based on the test characteristics and the prevalence of the different hemoglobin genes). If the screening test result is positive, a confirmatory test is performed, and if the result of the confirmatory test is also positive, penicillin therapy is begun. If the result of either the screening test or the confirmatory test is negative, prophylaxis is not given.

All branches proceed to a common subtree (Fig. 1, *B*). To simulate the 3 years that patients are at continuous risk for the devel-

opment of complications, we used a recursive model. Time is divided into slices called cycles, each lasting 6 months. Survivors go through the subtree six times in 3 years. Each "event"—drug reaction, sepsis, and "other presentation"—can occur once at most in each cycle. Patients receiving penicillin may have a drug reaction, which may be fatal. Patients may die of natural causes; acquire pneumococcal sepsis, which may be fatal; have another manifestation of sickle cell disease; or have no "event." At the triangular (Boolean) node, patients who survive sepsis or are seen for other reasons and who have not yet had hemoglobin electrophoresis performed are tested. If the test result is positive and there is no history of an allergic reaction to penicillin, prophylactic therapy is started. Otherwise, penicillin is not given.

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