



A cost-effectiveness evaluation of newborn hemoglobinopathy screening from the perspective of state health care systems

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Abstract

Objective: To determine the most cost-effective strategy for newborn hemoglobinopathy screening from the perspective of state health care systems. *Study design:* Using Alaska as an example, we used decision analysis to compare a policy of no screening to universal or targeted screening with selective follow-up only of infants who are homozygous or compound heterozygous for an abnormal hemoglobin variant and to universal or targeted screening with complete follow-up, including follow-up of infants with clinically insignificant traits. Probabilities and costs were varied over values that might be expected for other states. *Results:* Among the selective follow-up options, targeted screening would be the most cost-effective strategy for Alaska at a cost of \$206 192 per death averted; by contrast, universal screening would prevent 50% more deaths at an incremental cost of \$2 040 000 per death averted. Universal would be more cost-effective than targeted screening for several scenarios expected to occur in other states, including a high sickle cell disease prevalence, a low screening test cost, and a high cost per screen associated with racial targeting. Among the complete follow-up options, both targeted and universal screening would cost at least \$200 000 per death averted over the range of all variables tested during sensitivity analysis; the incremental cost of universal versus targeted screening would be at least \$600 000 per death averted. *Conclusions:* Our data suggest each state should determine the most cost-effective option based on state-specific values for sickle cell disease prevalence, test costs and racial targeting costs.

Keywords: Hemoglobinopathies; Neonatal screening; Cost-effectiveness; Sickle cell anemia

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1. Introduction

The National Institutes of Health Consensus Development Panel [1,2] has recommended universal newborn hemoglobinopathy screening, a policy which has been adopted by most states. The most cost-effective screening strategy, however, has not been adequately discussed. One previous report concluded that screening targeted to high-risk populations would be more cost-effective than universal screening in areas of low sickle cell disease prevalence [3]. A subsequent report concluded that all states should adopt universal screening [4]. Neither of these reports, however, considered all of the relevant immediate and long-term clinical benefits that would result from, as well as the cost to state health departments of operating, a hemoglobinopathy screening program.

The decision to implement newborn hemoglobinopathy screening has been based on evidence that some adverse outcomes of sickle cell disease are potentially preventable through early diagnosis and treatment. Sickle cell disease can lead to increased morbidity and mortality from splenic sequestration and pneumococcal sepsis and meningitis; pneumococcal meningitis may lead in turn to hearing loss, deafness, seizures and mental retardation. A landmark study demonstrated that penicillin prophylaxis can decrease mortality from pneumococcal infections among children < 3 years of age who have sickle cell anemia [5] and other reports have suggested that the complications of splenic sequestration are potentially preventable through parental education [6,7]. Using Alaska as an example, we sought to determine the most cost-effective screening strategy from the perspective of state health-care systems; additionally, we examined how the cost-effectiveness of different screening and follow-up strategies varied for states with other prevalences of hemoglobinopathies and costs of testing.

2. Methods

2.1. Definitions

We identified the direct costs and health outcomes of no screening compared with four different hemoglobinopathy screening and follow-up options: complete follow-up of persons with an abnormal screen using universal or targeted screening and selective follow-up of persons with an abnormal screen using universal or targeted screening. Universal screening would involve testing all newborns while targeted screening would involve testing newborns racially identified as black.

Follow-up was defined as tracking and contacting the families of affected infants and providing counseling, education, further hemoglobinopathy testing and, if appropriate, medical intervention. With complete follow-up, all newborns with an abnormal test result would receive follow-up, including those with clinically insignificant hemoglobin traits. With selective follow-up, only infants found to have a homozygous or compound heterozygous hemoglobinopathy, including hemoglobin CC, EE, SS and the thalassemias, would receive follow-up; for infants with a

clinically insignificant trait, physicians and the Alaska Department of Health and Social Services (ADHSS) would not receive test results and families would not be contacted or offered counseling, education or further testing.

We believe most states evaluating newborn hemoglobinopathy screening will decide whether to pursue a policy of complete or selective follow-up based primarily on ethical and legal (rather than cost) considerations and we did not account for these variables during our evaluation. Because of this, we present results for both complete and selective follow-up despite our finding that the complete follow-up options would always be less cost-effective than the selective follow-up options.

For this evaluation, sickle cell anemia was defined as a clinical condition caused by homozygous hemoglobin S (HbSS), whereas sickle cell disease (SCD) referred to a clinical condition caused by either HbSS, hemoglobin SC (HbSC) or hemoglobin S β -thalassemia. Sickle cell trait (HbAS) referred to the presence of a single hemoglobin S gene.

2.2. Model structure

We constructed a decision tree with branches representing each screening option. Probabilities were assigned to each node and outcomes assigned to each terminal node. The decision tree was based on evidence that suggests that the only adverse outcomes of hemoglobinopathies preventable by newborn screening are pneumococcal sepsis, splenic sequestration and their complications. Because outcomes occurred over only 1.75 years (the average age at which a child with HbSS was diagnosed if he or she did not have a newborn screen [6,8]), we did not discount outcomes.

Costs were divided into two areas: (a) potential savings resulting from the prevention of adverse outcomes of pneumococcal sepsis and splenic sequestration; and (b) costs resulting from administering a hemoglobinopathy screening program, including test, programmatic and medicine costs. Because the savings from prevention of an adverse outcome occasionally continued for as long as 45 years, the average life expectancy of a person with HbSS [9], costs were discounted. Primary and sensitivity analysis were conducted with Lotus 1-2-3 spreadsheet software [10]. For the base case analysis, we present the cost-effectiveness of all screening options compared to no screening. For the base case and sensitivity analysis we present, for each follow-up option, the incremental cost-effectiveness of universal versus targeted screening.

2.3. Probabilities

In the decision tree, we included hemoglobinopathy prevalence; pneumococcal sepsis, with or without survival; meningitis as a sequela of sepsis; mental retardation, deafness, hearing loss, or seizures as sequelae of meningitis; splenic sequestration, with or without survival; the preventability of sepsis and splenic sequestration with early diagnosis of SCD through newborn screening; and, for targeted screening, the proportion of all instances of SCD or HbAS which would be detected by testing only

Table 1
 Probabilities and other values, with ranges for sensitivity analysis, for a cost-effectiveness study of newborn hemoglobinopathy screening, Alaska, 1995

Factor	Value	Sensitivity analysis range	Reference
No. of births per year	11 676	—	ADHSS*
% white	67.4	—	ADHSS*
% Alaska Native	23.9	—	ADHSS*
% black	4.4	—	ADHSS*
% other	4.3	—	ADHSS*
Prevalence of SCD (per 100 000 persons)	14	1.8-282 ^a	[11]
Prevalence of homo-or compound heterozygous hemoglobinopathy other than SCD (per 100 000 persons)	15	—	[11]
Prevalence of HbAS (per 100 000 persons)	530	^b	[11]
Prevalence of hemoglobin trait other than HbAS (per 100 000 persons)	240	---	[11]
Sepsis rate (per 100 person years)	8.2	5-15	[5,50]
Proportion of sepsis cases that progress to death	0.15	0.05-0.25	[5,51]
Proportion of sepsis cases that progress to meningitis	0.18	0.1-0.3	[5,6,50]
Proportion of sepsis deaths with concurrent meningitis	0.31	0.2-0.4	[52,53]
Proportion of long-term sequelae among survivors of pneumococcal meningitis:			
Deafness	0.06	0.0-0.2	[54-56]
Hearing loss other than deafness	0.15	0.05-0.25	[54,55]
Mental retardation	0.05	0.01-0.15	[46,57-60]
Seizures	0.08	0.01-0.2	[46,61]
Proportion of pneumococcal episodes preventable with antibiotic prophylaxis	0.81	0.5-1.0	[5]
Rate of splenic sequestration (per 100 person years)	5	1-10	[7,62-64]

Proportion of splenic sequestration cases that progress to death	0.14	0.05-0.25	[62]
Proportion of splenic sequestration deaths preventable by newborn screening	0.5	0-1.0	[6,7]
Proportion of all instances of SCD and HbAS detected by targeting only black infants	0.75	0.5-1.0	[31,65]
Average age at which a child with SCD is diagnosed in the absence of newborn screening (in years)	1.75	1-4	[6,8]
Life expectancy of a person with SCD (in years)	45	5-75	[10]
Life expectancy of a person with SCD and either mental retardation or seizures (in years)	30	5-75	[26,27]
Number of relatives of an infant with an abnormal newborn screen who will request testing for themselves	0.5	0.1-2.0	[66]

*Alaska Department of Health and Social Services.^a 1.8 and 282/100,000 persons are the expected prevalences of SCD among an all-white and an all-black population, respectively.^b During sensitivity analysis, the relative ratio of SCD to HbAS was held constant.

black infants (because of racial misclassification and because not only black infants are at risk of hemoglobinopathies, a targeted screening program would fail to detect a certain proportion of all cases) (Table 1). We determined the overall expected prevalences of SCD, HbAS, homozygous or compound heterozygous hemoglobinopathies other than SCD, and hemoglobinopathy traits other than HbAS by applying national estimates of these conditions for different races [11] to the racial distribution of births in Alaska. All outcomes that were not logically mutually exclusive were considered independently (e.g. hearing loss and deafness were mutually exclusive outcomes but hearing loss and seizures were independent outcomes). The estimated age at which a child with SCD not diagnosed by newborn screening would be diagnosed in another setting was used as the follow-up period. The life expectancy of a person with SCD, with or without mental retardation or seizures, was used as the period over which costs from adverse sequelae of meningitis would accrue. Finally, we included the probability that a relative of an infant with a positive newborn screen would request testing for themselves solely because they learned of a positive result in the newborn; as suggested by probability assumption number 5 below, no obvious benefits would accrue to these people from this testing.

2.3.1. Data sources for probabilities

For the data on probabilities, we reviewed relevant literature through the National Library of Medicine data-base. Because of rapidly changing medical knowledge and practice, we used, with two exceptions, only manuscripts published after 1980. Where sufficient data existed, we included only studies from developed countries where clinical outcomes may be similar to those expected in Alaska. Previous cost-effectiveness analyses have relied on expert opinion; because of the extensive literature published on hemoglobinopathies and pneumococcal illness, we did not use this method to estimate probabilities.

2.3.2. Assumptions for probabilities

Table 1 contains data based on these assumptions.

1. Race recorded on birth certificates included white, black, Alaska Native and other. We assumed that all births with race recorded as other were Asian.
2. Because data on hemoglobinopathies among Alaska Natives were not available, infants with race listed as Alaska Native on the birth certificate had the same estimated prevalence of abnormal hemoglobins as those listed as white.
3. Among different hemoglobinopathies which neonatal screening might detect, clinical benefits resulted only from the early diagnosis of SCD [12].
4. The field sensitivity and specificity of the monoclonal immunoassay for identification of hemoglobin variants used for screening by OPHL both equalled 100% [13].
5. No clinical benefits resulted from decreased child bearing among people who know they carry a hemoglobinopathy trait [14–20].
6. All children identified by a screening program with SCD were located and given

- appropriate antibiotic prophylaxis at 2 months of age [20], a conservative assumption [21,22] that favors all screening strategies over no screening.
7. Patients had a compliance to prophylactic penicillin therapy similar to that achieved by Gaston et al. [5], a conservative assumption [23,24] that favored all screening strategies over no screening. This assumption was relaxed during sensitivity analysis by varying the proportion of pneumococcal episodes that were preventable through antibiotic prophylaxis.
 8. Children with SCD were not at greater risk of long-term neurologic sequelae from pneumococcal meningitis than other children with pneumococcal meningitis [25].
 9. Other than for treatment of pneumococcal illness, children with SCD who were diagnosed through newborn screening experienced hospitalization rates similar to children diagnosed later. This was a conservative assumption since the available data suggests children may be hospitalized more frequently if their hemoglobin status is known [7,14].
 10. Although estimates of life expectancy vary for persons with mental retardation [26,27], we estimated that persons with SCD and either mental retardation or seizures (most of whom would have mental retardation) would live 2/3 as long as other persons with SCD; this assumption was relaxed during sensitivity analysis.

2.4. Costs

Table 2 lists the cost considerations. The costs of newborn screening included the screen itself; penicillin prophylaxis; hemoglobin electrophoresis for relatives requesting testing, including test, phlebotomy and physician costs; determining the race of newborn infants for targeted screening, including additional time and equipment used for sorting specimens, billing and notification of results; and the yearly programmatic costs for operating a hemoglobinopathy screening program. For targeted screening, we combined the personnel costs of determining race in the hospital and the laboratory costs of only testing black infants under the heading racial ascertainment costs. Potential savings through prevention of adverse sequelae of SCD included hospitalization for sepsis or meningitis; medical care for seizures, deafness or hearing loss; additional education costs for persons with mental retardation, deafness or hearing loss; additional home-care costs for persons with deafness or hearing loss; and additional medical and institutional or home-care costs for persons with mental retardation. All costs and savings were converted to 1993 U.S. dollars. The discount rate was 5% with a range during sensitivity analysis of 1 to 9%.

2.4.1. Data sources for costs

To estimate most costs, we reviewed relevant literature and collected information from ADHSS and hospitals in Anchorage. Test cost and costs related to racial targeting were estimated from price quotes from the Oregon Public Health Laboratory (OPHL), the newborn screening reference laboratory used by Alaska. Racial targeting costs were corroborated during an interview with personnel from the newborn screening laboratory in one other state.

To determine program costs, we identified three states which had a percentage of

Table 2
Costs and ranges for sensitivity analysis for a cost-effectiveness analysis of newborn hemoglobinopathy screening, Alaska, 1995

Factor	Cost (\$)	Sensitivity analysis range	Reference
Hemoglobin monoclonal immunoassay	3	1.0-5.0	OPHL*
Oral penicillin (per person per year)	9.26	5-50	[3]
Hemoglobin electrophoresis for relatives requesting testing	84.75	10-150	Providence Hospital, Anchorage, AK
Race ascertainment costs	0.5	0-3	[34,35],OPHL*
Overall yearly programmatic costs for running a hemoglobinopathy screening program (per 100 abnormal tests)	47 803 ^a	5000-100 000	ADHSS ^b , three state hemoglobinopathy screening program directors
Hospitalization for sepsis	1764	500-5000	[3]
Hospitalization for meningitis	11 000	5000-15 000	Providence Hospital
Yearly medical treatment:			
Seizures	2050	1000-10 000	ADHSS ^b
Deafness/hearing loss	760	100-1500	ADHSS ^b
Additional yearly education costs			
Mental retardation	14 540	5000-25 000	[26]
Deafness	19 256	5000-50 000	[26]
Hearing loss	1287	500-5000	[67]
Yearly home care costs:			
Deafness	1926	500-5000	ADHSS ^b
Hearing loss	129	50-500	ADHSS ^b
Yearly institutional, home and medical care for severe mental retardation	104 046	25 000-300 000	[33,68]

* Oregon Public Health Laboratory.

^aAlaska Department of Health and Social Services.

^bFor every 100 abnormal screening tests, 0.55 project coordinators (salary \$67,300), 0.17 secretaries (salary, \$33,200), 0.034 medical directors (salary, \$95 600) and \$1894 worth of supplies were required.

infants racially identified as black at birth and a reported distribution of abnormal hemoglobin results [28] similar to that expected to occur in Alaska. We then administered by telephone a questionnaire to the hemoglobinopathy program directors in each of these three states. At the time of the interview, all three states attempted to notify and offer counseling to all persons with abnormal hemoglobin detected by screening, including those with clinically insignificant traits, a practice consistent with other program descriptions [29–32].

For each state, we determined the approximate number of personnel (including medical director, program director and secretarial staff) and money for supplies (including telephone, paper, mailing and copying) dedicated to patient tracking and notification and genetic counseling. To determine the anticipated resources required to operate a screening program in Alaska, we averaged the number of personnel required and the cost of supplies. Personnel costs, including salaries and benefits, were obtained from ADHSS.

2.4.2. Assumptions for costs

1. Each case of meningitis, whether the patient lived or died, resulted in a hospital stay of 10 days, including 1 day in the intensive care unit.
2. Children who developed one or more adverse neurologic sequelae following meningitis were permanently affected. These children received schooling for 15 years and incurred additional medical and institutional costs their entire lives. All education costs were calculated as a proportion of the standard \$5614 for 1 year of public education [33].
3. Children who developed mental retardation as a result of meningitis were assumed to have severe mental retardation; half of those affected would receive institutional care and half would be cared for at home [26,27].
4. Because newborn screening does not prevent a hemoglobinopathy from occurring, the long term costs associated with the treatment of SCD itself would be equal for any of the strategies evaluated and thus these costs were not included.

3. Results

3.1. Base-case analysis

For Alaska, based upon the given assumptions, we predicted the following outcomes. During a 1-year testing period, 1.6 children with SCD would be born, 1.8 with a homozygous or compound heterozygous hemoglobinopathy other than SCD, 61.9 with sickle cell trait, and 28.0 with an abnormal hemoglobin trait other than sickle cell. Both universal screening options would detect all persons with a homozygous or compound heterozygous hemoglobinopathy. Both targeted screening options would detect 1.1 persons with SCD, 0.2 with another homozygous or compound heterozygous hemoglobinopathy, 26.4 with HbAS, and 1.8 with another

abnormal hemoglobin trait. With universal screening and selective follow-up, OPHL would report only the 3.4 infants with SCD or another homozygous or compound heterozygous hemoglobinopathy compared to 1.3 infants with targeting screening and selective follow-up.

The expected costs and savings varied for different screening strategies (Table 3). Because all savings accrued from identifying those persons with SCD, both universal screening strategies would lead to identical savings as would be true of both targeted strategies. The costs for administering programs with complete follow-up would be higher than the corresponding programs with selective follow-up.

Compared to no screening, targeted screening with selective follow-up would be the most cost-effective strategy, in terms of cost per death or case of mental retardation averted (Table 4). The incremental cost-effectiveness of universal compared to targeted screening would be greater than \$2 000 000 per death averted and \$50 000 000 per case of mental retardation averted for both follow-up options.

3.2. Sensitivity analysis

Space does not permit a presentation of the sensitivity analysis of all variables. Four variables merit discussion because they are likely to vary between states and because either changes in their estimates altered the cost-effectiveness ordering of the four screening strategies or the screening strategies were sensitive to changes in the

Table 3
Projected costs and savings, in dollars, for various newborn hemoglobinopathy screening strategies over a 1-year screening period, Alaska, 1995

	TSCF*	USCF*	TSSF*	USSF*
<i>Costs</i>				
Program	10 846	34 307	400	601
Test	1554	35 028	1554	35 028
Relative testing	1250	3953	46	69
Penicillin prophylaxis	18	26	18	26
Race ascertainment	5838	—	5838	—
<i>Savings through prevention^a</i>				
Hospitalization for sepsis without meningitis	179	268	179	268
Hospitalization for sepsis with meningitis	202	417	202	417
Sequelae of meningitis				
Mental retardation	1693	2544	1693	2544
Seizures	49	73	49	73
Deafness	287	432	287	432
Hearing loss	85	127	85	127
Total costs-total savings	17 011	69 453	5361	31 863

* TSCF, targeted screening with complete follow-up; USCF, universal screening with complete follow-up; TSSF, targeted screening with selective follow-up; USSF, universal screening with selective follow-up. Targeted implies testing all infants where the race indicated on the birth certificate is black.^aAll savings were discounted at a rate of 5% per year.

Table 4
Cost-effectiveness ratios for four newborn hemoglobinopathy screening strategies, Alaska, 1995

	No. deaths averted	Cost per death averted (\$)	No. MR* averted	Cost per MR* averted (\$)
Complete follow-up				
Targeted ^a	0.026	654 000	0.0010	17 000 000
Universal	0.039	1 780 000	0.0015	46 300 000
Incremental CER ^b of universal vs. targeted	0.013	4 034 000	0.0005	104 900 000
Selective follow-up				
Targeted ^a	0.026	206 000	0.0010	5 360 000
Universal	0.039	817 000	0.0015	21 200 000
Incremental CER ^b of universal vs. targeted	0.013	2 040 000	0.0005	53 000 000

*MR, Mental retardation.

^aTargeted implies testing all infants where the race indicated on the birth certificate is black.

^bCER, cost-effectiveness ratio.

variable's value. Other than these four, no other variables over the range of values analyzed changed the conclusions of the analysis.

3.2.1. SCD prevalence

Only the universal screening options would be sensitive to the SCD prevalence since the targeted screening options would always be directed towards all persons racially identified as black. As the SCD prevalence varies from 1.8/100 000 persons (e.g. Wyoming or Montana) to 210/100 000 persons (e.g. in Washington D.C.), the cost per death averted, compared with no screening, would vary from \$659 000 to \$10 100 000 with universal screening and complete follow-up and from a savings of \$21 500 to a cost of \$6 992 000 with universal screening and selective follow-up.

For the complete follow-up options, the incremental cost per death averted for universal compared to targeted screening would be at least \$600 000, even at the highest SCD prevalences (Fig. 1). By contrast, for the selective follow-up options, the incremental cost per death averted for universal compared to targeted screening would be less than \$100 000, once the SCD prevalence increased to greater than approximately 68/100 000 persons.

3.2.2. Race ascertainment

Only the targeted screening options would be sensitive to changes in the hospital and laboratory costs associated with screening based on race. As the cost of race ascertainment varies from \$0 to \$3, the cost per death averted, compared to no screening, would vary from \$436 000 to \$1 803 000 for targeted screening and complete follow-up and from a savings of \$18 600 to \$1 348 000 for targeted screening and selective follow-up.

For complete follow-up, the incremental cost per death averted for universal compared to targeted screening would be at least \$1 700 000, even if the cost of race ascertainment equals \$3. For selective follow-up, the incremental cost per death

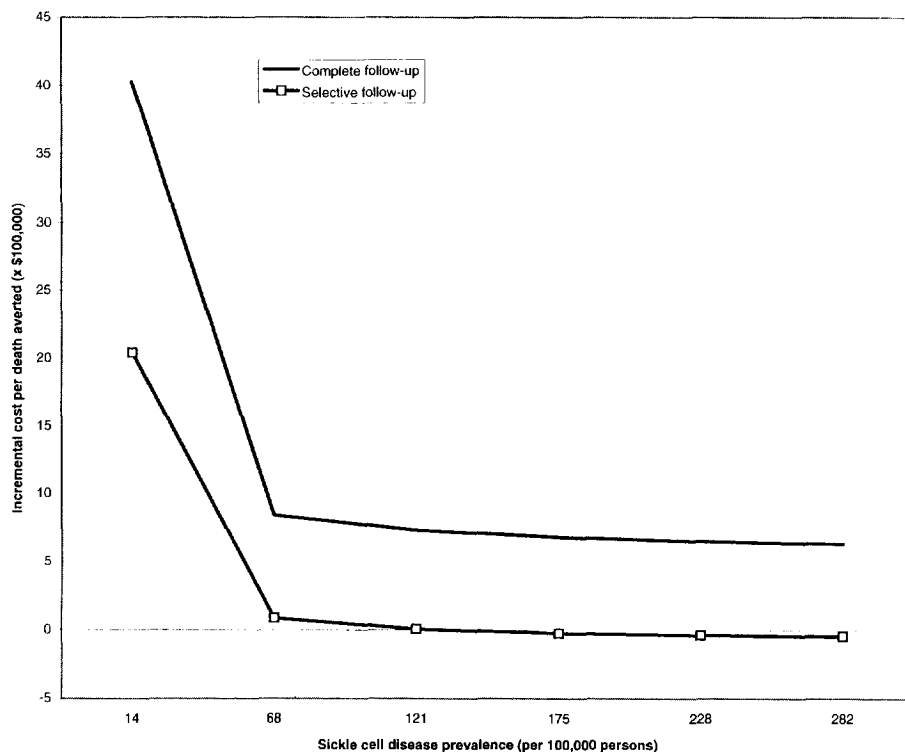


Fig. 1. Incremental cost per death averted of universal versus targeted newborn hemoglobinopathy screening at different sickle cell disease prevalences for complete and selective follow-up options; Alaska, 1995.

averted for universal compared to targeted screening would become less than \$0 at race ascertainment costs higher than approximately \$2.75, although it would still be greater than \$1 000 000 if race ascertainment costs are less than \$1.50.

3.2.3. Test cost

Both universal and targeted screening options would be affected by changes in test cost. For the complete follow-up options, as the test cost varies from \$1 to \$5, the cost per death averted for universal screening would vary from \$1 197 000 to \$2 410 000 compared to \$623 000 to \$704 000 for targeted screening. For the selective follow-up options, as the test cost varies from \$1 to \$5, the cost per death averted for universal screening would vary from \$221 000 to \$1 434 000 compared to \$169 000 to \$250 000 for targeted screening.

For the complete follow-up options, the incremental cost per death averted of universal versus targeted screening would equal at least \$600,000 regardless of the test cost or SCD prevalence (Fig. 2). For the selective follow-up options, the incremental cost per death averted of universal versus targeted screening would be greater than \$300 000 for all test cost levels, if the SCD prevalence equalled

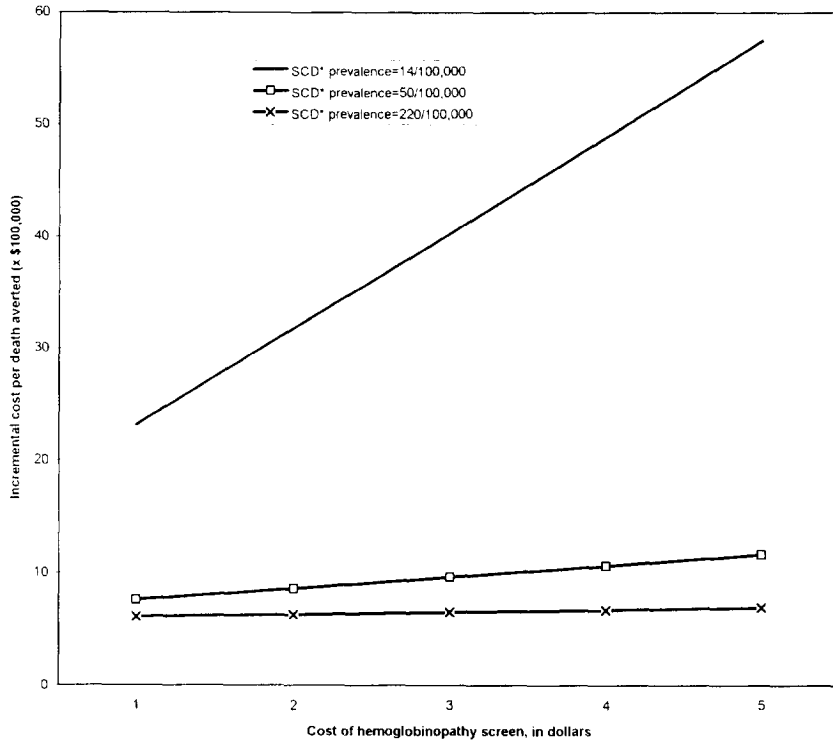


Fig. 2. Incremental cost per death averted of universal versus targeted newborn hemoglobinopathy screening at different hemoglobinopathy screening costs and different sickle cell disease prevalences for the complete follow-up option; Alaska, 1995. *Sickle cell disease.

14/100 000 persons, but would be less than \$0 for all but the highest test cost level, if the SCD prevalence equalled 220/100 000 persons (Fig. 3).

3.2.4. Age at diagnosis of SCD in the absence of newborn screening

All four screening strategies were sensitive to changes in this variable. For the complete follow-up options, as the age at diagnosis varies from 1 to 4 years, the cost per death averted for universal screening would vary from \$3 231 000 to \$733 000 compared to \$1 234 000 to \$236 000 for targeted screening. For the selective follow-up options, as the age at diagnosis varies from 1 to 4 years, the cost per death averted for universal screening would vary from \$1 523 000 to \$306 000 compared to \$439 000 to \$37 000 for targeted screening.

For the complete follow-up options, the incremental cost per death averted of universal versus targeted screening would vary from \$7 165 000 to \$1 724 000, as the age at diagnosis varies from 1 to 4 years. For the selective follow-up options, the incremental cost per death averted of universal versus targeted screening would vary from \$3 660 000 to \$824 000, as the age at diagnosis varies from 1 to 4 years.

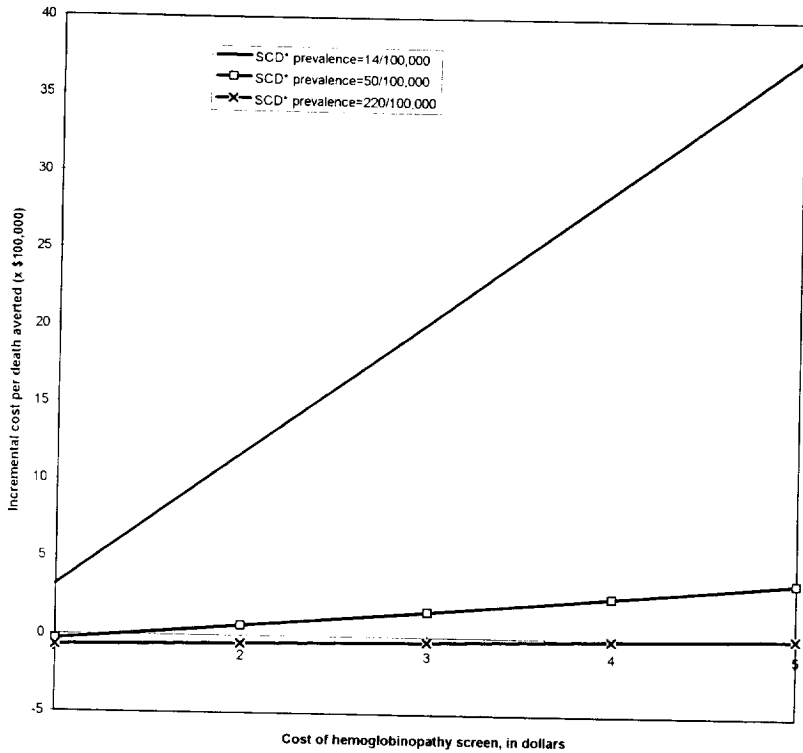


Fig. 3. Incremental cost per death averted of universal versus targeted newborn hemoglobinopathy screening at different hemoglobinopathy screening costs and different sickle cell disease prevalences for the selective follow-up option; Alaska, 1995. *Sickle cell disease.

4. Discussion

We have conducted a cost-effectiveness evaluation of four newborn hemoglobinopathy screening strategies from the perspective of a state health-care system and found that, for Alaska, a strategy of targeted screening with selective follow-up would be the most cost-effective. Compared with no screening, this strategy would cost \$206 000 per death averted; furthermore, the incremental cost of universal compared with targeted screening would be in excess of \$2 000 000. Because we evaluated variables over a broad range of values during sensitivity analysis, our results may be applicable to other states and districts.

Some states have chosen a strategy of universal screening with complete follow-up, the strategy recommended by the National Institutes of Health [1,2,11]. States wishing to use a strategy of complete follow-up must be prepared to invest considerable resources, even more so if they choose to conduct universal screening. For the complete follow-up options, we found that, compared to no screening, neither targeted nor universal screening would cost less than \$200 000 per death averted over the range of variable values evaluated during sensitivity analysis. Furthermore, the

incremental cost per death averted of universal versus targeted screening would be at least \$600 000 regardless of the SCD prevalence, cost of race ascertainment, test cost, or age at diagnosis of SCD in the absence of newborn screening. The high minimum cost of the complete follow-up options, particularly universal screening, would result primarily from the effect of program costs. Thus, although more adverse outcomes could be prevented as the prevalence of SCD increased, greater program costs would be incurred because of the increased detection and subsequent identification and follow-up of persons with clinically insignificant traits.

Selective follow-up is an approach that may allow state health departments to pursue newborn hemoglobinopathy screening in a cost-effective manner without compromising the public health. With selective follow-up, all infants would receive testing but only the families of infants with a homozygous or compound heterozygous hemoglobin variant would receive notification, counseling, education and testing of family members. By using this strategy, no persons with traits would be identified and, since persons with traits comprise the majority of those persons with positive screens, programmatic costs would be minimal. Furthermore, selective reporting and follow-up would prevent the same number of adverse outcomes as universal follow-up.

Even with the selective follow-up option, the cost of screening compared to no screening may be prohibitively expensive at some extreme variable values (e.g. if the test cost is high and the SCD prevalence low). For the range of most variable values used during sensitivity analysis, however, either targeted or universal screening would become reasonably cost-effective. For example, compared to no screening, the cost per death averted would decrease to less than \$200 000 (and in some cases to less than \$0) for universal screening at high SCD prevalences and low test costs and for targeted screening at low race ascertainment costs, low test costs and low age at diagnosis in the absence of newborn screening. Having established that screening may be cost-effective, the incremental cost of universal versus targeted screening provides the information necessary to select between these strategies. For many of the variable values evaluated during sensitivity analysis, the incremental cost of universal versus targeted screening would be less than \$200 000. Under other circumstances, however, the incremental cost of universal screening may exceed \$3 000 000.

These results suggest that states should evaluate the cost-effectiveness of universal versus targeted screening regardless of which follow-up strategy they select. This is particularly true since three of the variables evaluated during sensitivity analysis (SCD prevalence, test cost, and age at diagnosis in the absence of newborn screening) vary considerably between states. The SCD prevalence may vary almost 200-fold between states, which is the largest relative variation between high and low values of any variable examined during sensitivity analysis. Test costs depend on several factors: location of testing site within or outside the state, economies of scale when samples from several states are pooled at one laboratory, and the use of different laboratory procedures. For example, states which use a local newborn screening laboratory may only pay for labor and materials while states that use a reference laboratory may also pay a processing charge. Finally, the age at which an infant is diagnosed with SCD in the absence of newborn screening will vary depending on the

awareness and training of medical personnel and the use of prenatal hemoglobinopathy screening.

The fourth variable evaluated during sensitivity analysis, the costs related to targeting a screening program based on race, is not easy to evaluate even within a single state. The cost to Alaska charged by the reference laboratory is easily defined and would be approximately \$0.50, a value similar to that quoted from a second screening laboratory. The cost of ascertaining race in the hospital is less quantifiable. One author estimated this cost as \$2.73 based on a trained nurse being able to accurately determine race for six infants per hour [34]. We believe, as does another author [35], that in most instances the cost of racial ascertainment will be nominal. While the cost of race ascertainment would not change the ordering of the complete follow-up options, this cost is important to quantify because of its large impact on the ordering of the selective follow-up options.

As mentioned previously, legal and ethical issues may be the primary determinant of the decision to choose complete or selective follow-up, and a secondary determinant of the decision to choose universal or targeted screening. For example, although no evidence exists that people who know their carrier status alter their reproductive outcome [14–20], even if this were not true ethical considerations suggest that government agencies should not sponsor screening programs to promote eugenic ends [36–38]. The screening strategies with complete follow-up, in addition to possible prohibitive costs, would result in the unsolicited knowledge of carrier status by parents and infants. This may lead to loss of insurance [16] or employment [39–41], marriage restrictions [42], or the vulnerable child syndrome [43]. States may lack legal safeguards to protect persons against these adverse outcomes [44,45]. The screening strategies with selective follow-up involve testing persons without informing them of the test results. Finally, all screening options may lead to wrongful birth or death lawsuits [43,44].

The analysis we performed was relatively robust. The conclusions from our study did not change over a wide range for most variables tested. The absence of a need to use expert opinion for our probability estimates, and our use of manuscripts published primarily after 1980, enhanced the validity of these models. However, our study, as with all cost-effectiveness evaluations, has several limitations. We used probabilities that may not reflect the most current state of knowledge or practice. For example, recent studies suggest that many neurologic sequelae resolve with time [46] and that administration of dexamethasone can substantially reduce the occurrence of neurologic complications [47,48]. Additionally, expected benefits occur in the future, and it is not possible to predict changes in medical technology. For example, an effective, universally administered pneumococcal vaccine might decrease expected benefits from screening or test improvements could result in a less expensive screen. Finally, we did not include productivity costs in our model because we limited our analysis to direct costs and measurement of productivity in infants varies substantially by the assumptions used [49]. The inclusion of productivity costs would increase the cost-effectiveness of all screening strategies relative to no screening.

We have shown that since the optimal screening strategy depends on the value of variables likely to differ between states, each state health department, rather than

national medical organizations, should determine its own optimal screening strategy. We have not determined, however, whether Alaska or other states should implement newborn hemoglobinopathy screening. Even among high risk child populations, sickle cell disease may be relatively rare when compared with other conditions such as lack of prenatal care, premature birth, injuries, child abuse and malnutrition. For this reason, state health departments must compare the most cost-effective and ethically and legally sound hemoglobinopathy screening option with other competing health-care priorities.

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