A cost-effectiveness evaluation of new-born hemoglobinopathy screening from the perspective of state health care systems
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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Four hemoglobinopathy screening strategies for new-borns to prevent adverse outcomes of sickle cell disease (SCD) from the perspective of state health care systems. The four strategies were as follows: targeted screening with complete follow-up (TCSF), universal screening with complete follow-up (USCF), targeted screening with selective follow-up (TSSF), and universal screening with selective follow-up (USSF). Universal screening would involve testing all new-borns while targeted screening would involve testing new-borns racially identified as black. Selective follow-up would require the follow-up only of infants who were homozygous or compound heterozygous for an abnormal haemoglobin variant while complete follow-up would require the follow-up of all infants with abnormal test results, including follow-up of infants with clinically insignificant traits. Follow-up was defined as tracking and contacting the families of affected infants and providing counselling, education, further hemoglobinopathy testing and, if appropriate, medical intervention.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
Hypothetical new-borns.

Setting
The economic analysis was carried out in the USA.

Dates to which data relate
Clinical probabilities and assumptions were based on literature published between 1972 and 1994. No dates were given for the resource use data. The price year was 1993.

Source of effectiveness data
The effectiveness outcomes were based on a review of the literature.

Modelling
A decision analytic model (decision tree) was constructed to estimate costs and effects associated with each screening strategy. The time frame for the health outcomes was 1.75 years, the average age at which a child with homozygous haemoglobin (HbSS) was diagnosed if he or she did not have a screen as a new-born. The time frame for costs was 45 years 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). The only adverse outcomes of hemoglobinopathies considered preventable by new-born screening were pneumococcal sepsis, splenic sequestration and their complications.

Outcomes assessed in the review
The following outcomes were assessed:

- Prevalence of SCD (per 100,000 persons);
- Prevalence of homo- or compound heterozygous hemoglobinopathy other than SCD (per 100,000 persons);
- Prevalence of hemoglobin-S beta-thalassemia (HbAS) (per 100,000 persons);
- Prevalence of haemoglobin trait other than HbAS (per 100,000 persons);
- Sepsis rate (per 100 person years);
- Proportion of sepsis cases that progress to death;
- Proportion of sepsis cases that progress to meningitis;
- Proportion of sepsis deaths with concurrent meningitis;
- Proportion of long-term sequelae among survivors of pneumococcal meningitis: deafness, hearing loss other than deafness, mental retardation, and seizures;
- Proportion of pneumococcal episodes preventable with antibiotic prophylaxis;
- Rate of splenic sequestration (per 100 person years);
- Proportion of splenic sequestration cases that progress to death;
- Proportion of splenic sequestration death preventable by new-born screening;
- Proportion of all instances of SCD and HbAS detected by targeting only black infants;
- Average age at which a child with SCD is diagnosed in the absence of new-born screening;
- Life expectancy of a person with SCD;
- Life expectancy of a person with SCD and either mental retardation or seizures;
- Number of relatives of an infant with an abnormal new-born screen who will request testing for themselves.

Based on the literature, some clinical assumptions were made regarding the early diagnosis of SCD, the sensitivity and specificity of the monoclonal immunoassay for identification of haemoglobin variants, clinical benefits from decreased child bearing among people who know they carry a hemoglobinopathy trait, antibiotic prophylaxis for all children identified by a screening programme with SCD, compliance to prophylactic penicillin therapy, risk of long-term neurologic sequelae from pneumococcal meningitis, and hospitalisation rates for children with SCD who were diagnosed through new-born screening.

Study designs and other criteria for inclusion in the review
Manuscripts published after 1980 (with two exceptions) and relying only on studies from developed countries where sufficient data existed were identified.
Sources searched to identify primary studies
The authors refer to the "National Library of Medicine database" by which they may mean MEDLINE.

Criteria used to ensure the validity of primary studies
The criteria used to ensure the validity of primary sources was not reported.

Methods used to judge relevance and validity, and for extracting data
These were not reported.

Number of primary studies included
A total of 40 primary studies were included.

Methods of combining primary studies
The method of combination of primary studies was not reported.

Investigation of differences between primary studies
Investigation of differences between primary studies was not reported.

Results of the review
The prevalence of SCD (per 100 000 persons), 14 (sensitivity analysis range: 1.8 - 282);

prevalence of homo- or compound heterozygous hemoglobinopathy other than SCD (per 100 000 persons), 15;

prevalence of HbAS (per 100 000 persons), 530;

prevalence of haemoglobin trait other than HbAS (per 100 000 persons), 240;

sepsis rate (per 100 person years), 8.2 (range: 5 - 15);

proportion of sepsis cases that progress to death, 0.15 (range: 0.05 - 0.25);

proportion of sepsis cases that progress to meningitis, 0.18 (range: 0.1 - 0.3);

proportion of sepsis deaths with concurrent meningitis, 0.31 (range: 0.2 - 0.4);

proportion of long-term sequelae among survivors of pneumococcal meningitis: deafness, 0.06 (range: 0.0 - 0.2),

hearing loss other than deafness, 0.15 (range: 0.05 - 0.25), mental retardation, 0.05 (range: 0.01 - 0.15), and seizures, 0.08 (range: 0.01 - 0.2);

proportion of pneumococcal episodes preventable with antibiotic prophylaxis, 0.81 (range: 0.5 - 1.0);

rate of splenic sequestration (per 100 person years), 5 (range: 1 - 10);

proportion of splenic sequestration cases that progress to death, 0.14 (range: 0.05 - 0.25);

proportion of splenic sequestration death preventable by new-born screening, 0.5 (range: 0 - 1.0);

proportion of all instances of SCD and HbAS detected by targeting only black infants, 0.75 (range: 0.5 - 1.0);

average age at which a child with SCD is diagnosed in the absence of new-born screening, 1.75 (range: 1 - 4) years;
life expectancy of a person with SCD, 45 (range 5 - 75) years;

life expectancy of a person with SCD and either mental retardation or seizures, 30 (range: 5 - 75);

number of relatives of an infant with an abnormal new-born screen who will request testing for themselves, 0.5 (range: 0.1 - 2.0).

It was assumed that clinical benefits resulted only from the early diagnosis of SCD among different hemoglobinopathies which neonatal screening might detect;

sensitivity and specificity of the monoclonal immunoassay for identification of haemoglobin variants were both 100%;

no clinical benefits resulted from decreased child bearing among people who know they carry a hemoglobinopathy trait;

appropriate antibiotic prophylaxis is given for all children identified by a screening programme with SCD at 2 months of age;

compliance to prophylactic penicillin therapy was supposed to be similar to that achieved by Gaston et al. (a conservative assumption favouring screening strategies);

risk of long-term neurologic sequelae from pneumococcal meningitis for children with SCD was supposed not to be greater than other children with pneumococcal meningitis;

and hospitalisation rates for children with SCD who were diagnosed through new-born screening were supposed to be similar to children diagnosed later.

**Measure of benefits used in the economic analysis**
The main benefit measures were the number of deaths averted and the number of cases of mental retardation (MR) averted. The number of detected cases with homozygous or compound heterozygous hemoglobinopathy were also reported. Benefits were not discounted due to the short time frame (1.75 years) considered for the clinical outcomes.

**Direct costs**
Costs were discounted. A few quantities were reported separately from the costs. Cost components were reported separately. Cost analysis covered the costs of adverse outcomes of pneumococcal sepsis and splenic sequestration, and costs resulting from administering a hemoglobinopathy screening programme, including test, programme and medicine costs. The perspective adopted in the cost analysis was that of a state health system. The sources of cost data were relevant literature, information from ADHSS and hospitals in Anchorage, and interviews with personnel from the new-born screening laboratory. For estimating the programme costs, a telephone questionnaire was administered to the hemoglobinopathy programme directors of three states with similar infant race distribution and reported distribution of abnormal haemoglobin results to that expected to occur in Alaska in order to determine the approximate number of personnel (including medical director, programme director and secretarial staff) and money for supplies (including telephone, paper, mailing and copying) dedicated to patient tracking and notification and genetic counselling. To determine the anticipated resources required to operate a screening programme in Alaska, the authors averaged the number of personnel required and the cost of supplies. The price year was 1993. The cost analysis did not cover the long-term costs associated with the treatment of SCD itself, since they would be equal for all strategies involved (because new-born screening does not prevent a hemoglobinopathy from occurring).

**Indirect Costs**
Indirect costs were not considered.

**Currency**
US dollars ($).
Sensitivity analysis
A set of one-way and two-way sensitivity analyses was performed on almost all parameters of the model.

Estimated benefits used in the economic analysis
It was predicted that 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 with an abnormal haemoglobin 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 haemoglobin trait. With universal screening and selective follow-up, the public health laboratory 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 number of deaths averted for the four screening strategies versus no screening were: 0.026 (TCSF), 0.039 (USCF), 0.026 (TSSF), and 0.039 (USSF). The corresponding values in terms of number of MR averted were 0.0010, 0.0015, 0.0010, and 0.0015.

Cost results
The discount rate was 5% (1 - 9% in sensitivity analysis). The net total cost (total costs-total savings) for the screening strategies over a 1-year screening period in Alaska were as follows: $17,011 (TCSF), $69,453 (USCF), $5,361 (TSSF), and $31,863 (USSF).

Synthesis of costs and benefits
Incremental cost-effectiveness analysis was conducted by calculating the cost per death averted and cost per MR averted for the four new-born hemoglobinopathy screening strategies versus no screening. The cost per death averted for the strategies were: $654,000 for TCSF, $1,780,000 for USCF, $206,000 for TSSF, and $817,000 for USSF. Incremental cost-effectiveness ratios of universal versus targeted strategies were also calculated, resulting in values of $4,034,000 for complete follow-up and $2,040,000 for selective follow-up. Other than four sensitive parameters (SCD prevalence, costs of race ascertainment, test cost, and age at diagnosis of SCD in the absence of new-born screening), the results were relatively robust over wide ranges of values for other parameters of the model. 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.

Authors' conclusions
The authors have shown that the optimal screening strategy depends on the values of variables likely to differ between states. Therefore, each state health department, rather than national medical organisations, should determine its own optimal screening strategy.

CRD COMMENTARY - Selection of comparators
The strategy of no screening was regarded as the comparator. It allowed the active added value of each screening strategy to be evaluated.

Validity of estimate of measure of effectiveness
The internal validity of the effectiveness results can not be objectively assessed as insufficient information was provided regarding the quality of the primary studies included in the review, the method of combination of primary studies, and the investigation of differences between primary studies. However, the authors argued that the fact that there had been no need to use expert opinion for the probability estimates, and that manuscripts published primarily after 1980 were used, would enhance the validity of the results. The authors speculated that the screening strategies with complete follow-up might result in the unsolicited knowledge of carrier status by parents and infants, possibly leading to
loss of insurance or employment, marriage restrictions, or the vulnerable child syndrome. States may lack legal safeguards to protect persons against these adverse outcomes. The authors suggested that it was possible that all screening options may lead to lawsuits resulting from death or wrongful birth.

Validity of estimate of measure of benefit
The estimate of benefits was modelled. The instrument used to derive a measure of health benefit (decision tree) was appropriate.

Validity of estimate of costs
A few quantities were reported separately from the costs and adequate details of the methods of cost estimation were given. It appears that all categories of costs relevant to the perspective adopted were included in the analysis. The effects of different screening strategies on productivity costs were not included in the cost analysis since it was reported that measurement of productivity in infants varies substantially according to the assumptions used. Sensitivity analyses were performed on all parameters of cost data. Costs were discounted and the price year was reported.

Other issues
The authors’ conclusions appear to be justified given the extensive sensitivity analysis performed. The study results were deemed to be generalisable to other US states and districts due to the broad range of values considered during sensitivity analysis. Some comparisons were made with other studies. The study limitations acknowledged by the authors were as follows: using probabilities that may not reflect the most current state of knowledge of practice; the possibility of changes in medical technology (for example, an effective universal administered pneumococcal vaccine which may lead to reduction in expected benefits for the screening strategies or test improvements could result in a less expensive screen); and the inclusion of productivity costs would increase the cost-effectiveness of all screening strategies relative to no screening.

Implications of the study
The authors have not determined whether Alaska or other states should implement new-born hemoglobinopathy screening. Even among populations of high-risk children, 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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