Potential costs and benefits of newborn screening for severe combined immunodeficiency
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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
The study compared two screening strategies for severe combined immunodeficiency (SCID) in infants. Specifically, universal newborn screening was compared with a targeted screening programme where only infants with a family history of the disease and infants diagnosed with the infection were screened. All infants who screened positive received a follow-up screening test. All infants who were confirmed positive received subsequent treatment with bone marrow transplantation (BMT) and lifelong intravenous immune globulin (IVIG) therapy in monthly doses.

Type of intervention
Screening and treatment.

Economic study type
Cost-utility analysis.

Study population
As this was a modelling study, the target population comprised all newborn infants and infants with a family history of SCID. No inclusion or exclusion criteria for the study population were reported.

Setting
As this was a modelling study, the setting was explicitly stated. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness data were derived from studies published between 1982 and 2004. The cost data were derived from official sources published between 1997 and 2004. All costs were reported for the price year 2000.

Source of effectiveness data
The effectiveness data were derived from a review and synthesis of completed studies. Where data were not available in the literature, the model inputs were augmented by authors' assumptions.

Modelling
A decision tree was constructed to estimate survival outcomes for treated and untreated infants that suffered from SCID during the first 5 years of life. In the base-case scenario, the time horizon of the model was, on average, 45 years for infants needing IVIG and 55 years for infants who did not need IVIG therapy. The model was based on two assumptions. Specifically, all infants were assumed to have a donor in one of their parents, and all false-positive cases would be spotted with the follow-up test excluding improper transplantations.

Outcomes assessed in the review
The following input parameters were used in the model:

- False-negative and false-positive rate of the screening test,
- Incidence of the disease,
- Average incidence of a family of a sibling with SCID,
- Life expectancy in SCID infants after BMT and in patients treated with IVIG,
- The probability that BMT fails in late and early transplant,
- The probability that a patient needs IVIG, and
- The likelihood of missing a case of SCID.

**Study designs and other criteria for inclusion in the review**
Not reported.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
Not reported.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Approximately, 11 studies provided the effectiveness data.

**Methods of combining primary studies**
It would appear that the results from individual primary studies were not combined.

**Investigation of differences between primary studies**
The authors do not seem to have investigated differences between the primary studies.

**Results of the review**
The false-negative rate of the screening test was 1% (range: 0 - 10) and the false-positive rate was 0.4% (range: 0 - 10).

The incidence of SCID was 1:50,000 (range: 1:30,000 - 1:1,000,000).

The SCID life expectancy after BMT was 55 years (range: 10 - 77) in patients not needing IVIG therapy and 45 years (range: 10 - 77) in patients needing IVIG therapy.

The failure probability of BMT was 28% (range: 0 - 60) in late transplant and 5% (range: 0 - 28) in early transplant.

The probability that a patient would require IVIG therapy was 65% (range: 50 - 100), while the probability that a case
of SCIG would be missed was 50% (range: 0 - 80).

Methods used to derive estimates of effectiveness
Some estimates of effectiveness were based on authors’ assumptions.

Estimates of effectiveness and key assumptions
Due to controversy and a lack of adequate data in relation to the best screening test, the authors referred to no specific screening test. Therefore, the false-negative and false-positive rates were tested against thresholds at which SCID would become cost-effective.

Data on the probability of missing a case of SCID did not exist in the literature and was assumed to be 0.5 (range: 0 - 0.8).

The authors assumed that 50% of SCID cases would be autosomal recessive and 50% of cases to be X-linked. This assumption was based on data in the literature.

The estimates of life expectancy were also based on authors’ assumptions.

Measure of benefits used in the economic analysis
The authors used health utility (quality-adjusted life-years, QALYs) as the measure of benefit in the economic analysis. The values used were derived from the literature. Although details of the basic method used to value the health states were not reported, it seems that the authors have used health preference scores evaluated by investigators and not by patients. No further details were reported. The authors also used years of life saved because of screening.

Direct costs
The direct costs considered were the cost of the screening test, treatment cost (cost of an average admission for a patient with SCID used as the cost of the initial transplant), infection treatment cost (cost of an additional admission used as the cost of treating infections occurring after a failed transplant), follow-up cost and lifelong cost of IVIG therapy. The follow-up cost of patients who were positively screened covered the cost of an office visit, flow cytometry to estimate T-cell counts and the cost of T-cell proliferation studies. Lifelong IVIG costs were estimated using a model account of infusion costs and cost of IVIG for monthly doses, taking into account a median weight, discounted over the mean lifetime of an individual receiving therapy.

The costs were derived from official published sources. However, the authors reported only summary costs; unit costs were only reported in terms of the follow-up costs of positively screened patients. The costs, which were incurred during more than 2 years, were appropriately discounted. All the costs were appropriately adjusted for inflation and were reported for the price year 2000.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
US dollars ($).
Sensitivity analysis
Although not explicitly stated, it would appear that the authors carried out a threshold analysis for each of the variables, to estimate the values at which SCID would be cost-effective. The willingness-to-pay values used were $50,000 per QALY, $75,000 per QALY and $100,000 per QALY. The method used to select the ranges was not reported.

Estimated benefits used in the economic analysis
The estimated benefits were not reported separately for each of the screening options. The authors only reported that the implementation of a universal screening programme in the USA, assuming an annual birth cohort of 4 million, would result in 760 years of life saved for each year of screening.

Cost results
The authors reported that the total cost for the implementation of a universal screening programme in the USA, assuming an annual birth cohort of 4 million, would be $23,920,000.

Synthesis of costs and benefits
The threshold analysis demonstrated that with a willingness-to-pay of $100,000 per QALY, there was an 86% likelihood that universal screening for SCID would be cost-effective.

From the incremental analysis, the cost of screening and treating an additional case of SCID was estimated to be $485,000.

The authors also conducted a Monte Carlo analysis to estimate the acceptability curve of the likelihood of SCID universal screening being cost-effective at different thresholds of willingness-to-pay at varying values of the parameters used in the model.

The threshold sensitivity analysis demonstrated that the most sensitive parameters were the false-positive rate and the cost of the test. In particular, it was reported that for a willingness-to-pay of $100,000 per QALY, the cost of the test should not exceed $15.

Authors’ conclusions
Universal screening for severe combined immunodeficiency (SCID), although more expensive than other universal screening procedures addressed at newborns, can become cost-effective at different threshold values of willingness-to-pay for an additional quality-adjusted life-year (QALY).

CRD COMMENTARY - Selection of comparators
The authors compared universal screening for SCID against targeted screening of only infants with a family history of SCID. Targeted screening seemed to represent current practice in the authors’ setting. Details of the screening method (screening test) were not reported.

Validity of estimate of measure of effectiveness
No systematic review was undertaken; the studies appear to have been selected from the literature according to convenience. As such, the effectiveness estimates used in the model might not be the best available. The effectiveness estimates from the available studies were not combined and appear to have been used selectively. In addition, the impact of differences between the available studies was not taken into consideration. It is necessary to mention that the study did not refer to any particular test but rather a general universal screening process. This was because an adequate screening test is not yet available. Therefore, many of the estimates used were based on the authors' assumptions and not on data derived from the literature.
Validity of estimate of measure of benefit
The measure of benefit was health utility (QALYs), reflecting values of health professionals rather than patients. Details of the method used to evaluate the health states were not reported, making it difficult to judge the quality of the benefit measure used.

Validity of estimate of costs
The analysis of the costs was performed from the perspective of a health care system. It appears that all the relevant categories of costs have been included in the analysis. With the exception of follow-up costs for positively screened patients, the authors used summary costs. This makes it difficult to comment on aspects of costs used in each category. In addition, some cost estimates were based on authors’ assumptions due to a lack of accurate data. However, the authors did not conduct any statistical analysis on the costs or quantities, which may limit the validity of the estimates used and introduce uncertainty into the results. The costs came from various sources and all were appropriately adjusted for inflation. Discounting was appropriately carried out and the price year was reported.

Other issues
The authors compared their results with those of universal screening processes for other diseases in infants. They reported that universal screening for SCID is more expensive than other universal screening strategies addressed at newborns. The issue of generalisability of the results was not directly addressed. The authors do not appear to have presented their results selectively. The authors acknowledged that a main limitation to their study was the uncertainty in the results due to a lack of robust effectiveness and cost data.

Implications of the study
The authors did not make any recommendations for changes in policy or practice. They recommended that future research should focus on the development of an accurate screening test for evaluation in a prospective trial on SCID screening. In addition, cost data should be prospectively collected during this future trial to allow for robust cost estimates.

Source of funding
Supported by the human and molecular development training grant NIH/NICHD T32 HD07612, and by the Culpepper Biomedical Pilot Initiative of the John D Rockefeller Foundation.

Bibliographic details

PubMedID
16291349

DOI
10.1016/j.jpeds.2005.06.001

Indexing Status
Subject indexing assigned by NLM

MeSH
Bone Marrow Transplantation /economics; Cost-Benefit Analysis; Decision Trees; Health Care Costs; Humans; Immunoglobulins, Intravenous /economics; Infant, Newborn; Models, Econometric; Neonatal Screening /economics; Quality-Adjusted Life Years; Sensitivity and Specificity; Severe Combined Immunodeficiency /prevention & control; United States