Cost-effectiveness of 4 neonatal screening strategies for cystic fibrosis
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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 examined several neonatal screening strategies for cystic fibrosis (CF). In each strategy, the first test consisted of measuring serum concentrations of immunoreactive trypsin (IRT). The second step was either a second IRT test (IRT+IRT) or a single or multiple mutation analysis (IRT+DNA). A third step could be added to strategy 2. This was either a second IRT test (IRT+DNA+IRT) or an extended mutation analysis of the CF gene (i.e. denaturing gradient gas electrophoresis, DGGE, analysis) (IRT+DNA+DGGE).

In all strategies, infants with a positive screening test were referred to sweat testing to confirm or to exclude the CF diagnosis. Parents were informed about the carrier status of their child when a second IRT was necessary and were also offered genetic counselling.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of newborns.

Setting
The setting was a hospital. The economic study was carried out in the Netherlands.

Dates to which data relate
The effectiveness data were derived from studies published between 1977 and 2005. Some resource use data were obtained from a study published in 2001. The price year was 2004.

Source of effectiveness data
The clinical and epidemiological data used in the decision model were:

- the birth prevalence of CF,
- the proportion of newborns with meconium ileus,
- the life expectancy for newborns with CF,
- the mortality rate during childhood,
- the percentage of children covered by existing neonatal screening programmes, and
the sensitivity and specificity of all the screening tests.

**Modelling**
A decision analytic model was constructed to follow a hypothetical cohort of newborns for a lifetime horizon. No information on the decision model was provided. However, it was stated that probabilistic distributions were assigned to each model parameter.

**Sources searched to identify primary studies**
The majority of the clinical data were derived from published studies, but details of the primary sources of data were not reported. The design and other characteristics of the clinical studies were generally not described. The exception was a randomised clinical trial that was used to estimate the reduction in mortality for non meconium ileus-screened patients. Some assumptions were also made.

**Methods used to judge relevance and validity, and for extracting data**
The authors did not state whether the primary studies were identified selectively or through a systematic review of the literature. The authors used estimates from studies of diagnostic accuracy in which it was possible to derive the sensitivity and specificity of the individual tests.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of life-years (LYs). The LYs were derived using the decision model and were discounted at an annual rate of 3%. The number of CF patients without meconium ileus identified was also reported as a model output.

**Direct costs**
The analysis of the costs appears to have included only the direct medical costs. Such costs were those associated with screening tests, genetic counselling, testing patients for carrier status, inclusion of CF screening to existing neonatal screening programmes, sweat test, lifetime care for a CF patient, prenatal diagnosis and pregnancy termination. The cost items were broken down for most cost categories. The unit costs and the quantities of resources used were not presented separately. Most of the costs were derived from written communications, National Health Tariffs and the Dutch Handbook for Costing. Resource use data were based on assumptions and some published data. Discounting was relevant, as the long-term costs were evaluated, and an annual discount rate of 3% was used. The price year was 2004.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
It was unclear whether productivity costs were considered. The authors stated that costs for the parents, such as time and travel costs, were included. However, no details were provided.

**Currency**
Euros (EUR).

**Sensitivity analysis**
Univariate and multivariate sensitivity analyses were carried out to assess the robustness of the cost-effectiveness ratios to variations in clinical and economic inputs. Such inputs included the incidence of CF, percentage of newborns with meconium ileus, participation in neonatal screening, test accuracy, CF mortality in childhood, reduction in childhood
CF, LYs gained per prevented death, costs of tests, cost of clinical diagnosis of CF, and the cost of adding CF screening to neonatal screening programmes. Best- and worst-case scenarios were considered. In addition, a probabilistic multivariate sensitivity analysis was carried out by assigning stochastic distributions to model parameters. Consequently, cost-effectiveness acceptability curves were generated to show the probability that a screening strategy was cost-effective as a function of a determined willingness-to-pay (WTP).

**Estimated benefits used in the economic analysis**

The number of LYs gained in comparison with no screening for a cohort of 200,000 children was 12.7 with the IRT+IRT strategy, 13.9 with the IRT+DNA strategy, 13.6 with the IRT+DNA+IRT strategy and 13.8 with the IRT+DNA+DGGE strategy.

The number of CF patients without meconium ileus identified was 41 with the IRT+IRT strategy, 45 with the IRT+DNA strategy, 44 with the IRT+DNA+IRT strategy and 45 with the IRT+DNA+DGGE strategy.

**Cost results**

The total costs for a cohort of 200,000 children would be EUR 19.66 million with no screening, EUR 19.97 million with the IRT+IRT strategy, EUR 20.19 million with the IRT+DNA strategy, EUR 20.20 million with the IRT+DNA+IRT strategy and EUR 20.11 million with the IRT+DNA+DGGE strategy.

**Synthesis of costs and benefits**

An incremental cost-effectiveness ratio was calculated in order to combine the costs and benefits of the alternative strategies.

In comparison with no screening, the incremental cost per LY gained was EUR 24,800 with the IRT+IRT strategy, EUR 38,300 with the IRT+DNA strategy, EUR 39,800 with the IRT+DNA+IRT strategy and EUR 33,000 with the IRT+DNA+DGGE strategy.

When the screening strategies were compared with each other, the IRT+DNA+IRT strategy was dominated (more expensive and less effective than at least one other strategy), and the incremental cost per LY gained was EUR 2,154,300 with IRT+DNA over IRT+DNA+DGGE and EUR 130,700 with IRT+DNA+DGGE over IRT+IRT. Therefore, the IRT+IRT strategy appears to have been the most cost-effective screening option.

The sensitivity analysis revealed that CF incidence, CF mortality in childhood, and savings in lifelong savings in cost of treatment had the greatest impact on the cost-effectiveness ratios. Further, the cost-effectiveness ratios (compared with no screening) ranged from EUR 220,000 for the IRT+IRT strategy and EUR 306,900 for the IRT+DNA+DGGE strategy in the least favourable situation, to financial savings (range: EUR 1.8 to EUR 1.9 million) and LYs gained (range: 52 to 54) for all strategies in the most favourable scenario.

The probabilistic sensitivity analysis suggested that, for a WTP less than EUR 25,000, IRT+IRT was the preferred strategy. For WTP values between EUR 25,000 and EUR 800,000, the optimal strategy was IRT+DNA+DGGE. Only for values above EUR 800,000 was IRT+DNA the preferred strategy. Finally, it was noted that neonatal screening would also lead to changes in reproductive decisions (parents might opt for abortion in the case of CF findings). This would lead to additional costs for diagnosis and abortion, but also savings of up to EUR 2.3 million per year as a result of a fall in the birth rate of CF patients.

**Authors’ conclusions**

Neonatal screening for cystic fibrosis (CF) in the Netherlands was cost-effective. Specifically, a first and second test for immunoreactive trypsin (IRT+IRT strategy) was the preferred option, with a cost per life-year (LY) gained of EUR 24,800.
CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparators was not explicitly stated, but all possible screening strategies appear to have been considered. In addition, the strategy of no screening was also taken into account to reflect existing patterns of care. You should decide whether they are valid comparators in your own setting.

Validity of estimate of measure of effectiveness
It was difficult to assess the validity of the clinical data given that there was no information on the primary studies; the authors stated only that one study was a randomised clinical trial. The authors did not state whether a systematic review of the literature was undertaken to identify these studies.

Validity of estimate of measure of benefit
The estimation of health benefits (LYs) was modelled using a decision tree model. The choice of LYs was appropriate, not only because they capture the most important aspect of health (i.e. survival) but also because they can be compared with the benefits of other health care interventions. The authors stated that the impact of quality of life on health was not considered, owing to the lack of reliable published evidence on utility weights. Discounting was appropriately carried out.

Validity of estimate of costs
The authors stated that a societal perspective was adopted in the study, but the role played by productivity costs was unclear. The authors reported the main categories of costs included in the analysis and a breakdown of individual items was provided for some categories. Nevertheless, the cost of lifetime care for a CF patient was not broken down, thus it was unclear which costs were actually considered. The sources of the costs were reported for some items. Resource use appears to have been based on some published evidence but also on authors' opinions. The price year was reported, which will simplify reflation exercises in other time periods. Statistical analyses were performed in the sensitivity analysis, where the effect of changing assumptions on key costs was investigated.

Other issues
The authors stated that their findings were less favourable than those observed in a previous study, presumably due to differences in the cost estimates. The issue of the generalisability of the study results to other settings was implicitly addressed in the sensitivity analysis, in which alternative clinical and economic inputs were considered. The authors noted some limitations of the analysis due to the exploratory nature of the study. Another issue was the fact that the costs and effects of changes in reproductive decisions were not included in the cost-effectiveness analysis but were evaluated separately.

Implications of the study
The study results suggest that CF neonatal screening may be a cost-effective strategy. Decision-makers should discuss whether it should be introduced for CF, and which type of screening should be used.

Source of funding
Supported by the Nederlandse Cystic Fibrosis Stichting.

Bibliographic details

PubMedID
16950979

DOI
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Indexing Status
Subject indexing assigned by NLM

MeSH
Cost-Benefit Analysis; Cystic Fibrosis /blood /diagnosis /genetics; DNA Mutational Analysis; Electrophoresis, Gel, Two-Dimensional; Humans; Immunoassay; Infant, Newborn; Neonatal Screening /economics /methods; Trypsin /blood

AccessionNumber
22007000333

Date bibliographic record published
31/07/2007

Date abstract record published
31/07/2007