Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program

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
Newborn babies were screened for congenital hypothyroidism (CH) using the following protocol. Blood samples were taken and the thyroxine (T4) measured; the T4 concentration was measured as the standard deviation (SD) relative to the daily mean. If the T4 concentration was among the lowest 20%, then the thyroid-stimulating hormone (TSH) (in microunits per millilitre of serum, microUI/mL) was measured. If the T4 concentration was in the lowest 5%, then the T4-binding globulin (TBG) levels were measured (in nanomoles per litre, nmol/L). The initial screening results were used to determine whether a second blood sample should be taken or whether the baby should be referred to a paediatrician. Immediate referral took place if the T4 level was ≤ -3.0 SD and/or the TSH level was ≥ 50 microIU/mL serum. Borderline T4 and a low T4-to-TBG ratio and/or borderline TSH resulted in a second blood sample being taken. If the T4 level was then ≤ -1.6 SD with either a low T4-to-TBG ratio or a TSH level of ≥ 20 microIU/mL, then the baby was referred to a general paediatrician. Babies weighing ≤ 2,500 g and having a gestational age of ≤ 36 weeks were referred on the basis of TSH concentrations alone.

Two comparator protocols were studied. One involved not reporting T4 levels, which are used to determine whether or not TSH measurements are indicated. Referral was indicated for all infants with TSH concentrations of ≥ 50 microIU/mL and for infants with TSH between 20 and 50 microIU/mL if these findings were confirmed with a repeat blood sample. The second comparator protocol involved reporting both T4 and TSH readings, which were then used to determine referral. Referral took place when the T4 level was ≤ -3.0 SD and/or the TSH level was ≥ 50 microIU/mL if a second blood sample confirmed these findings.

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised babies aged less than a week old in the Netherlands.

Setting
The setting for the taking of the blood sample was not described. The economic study was carried out in the Netherlands.

Dates to which data relate
The effectiveness and resource use evidence was from the period 1995 to 2000. No price year was given.
Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The same patients provided both the cost and the effectiveness data. The costs were based on the theoretical costs of the different components of the screening procedures. The costing was conducted retrospectively.

Study sample
No power calculations were reported. There was no sample selection and nearly all (99.6%) of the babies in the Netherlands, 1,181,079 in all, were screened. All the babies were screened according to the Netherlands protocol. The effect of the two comparator protocols was estimated using the results of the actual screening that took place.

Study design
This was a diagnostic yield study of a screening protocol that took place in multiple centres. The effect of alternative comparator protocols was estimated using the results of the screening protocol that took place. No loss to follow-up was reported.

Analysis of effectiveness
The primary health outcomes used to evaluate the screening protocols were the numbers and percentages of patients with CH of central origin and of thyroid origin who were detected. The number of false-positive results for every actual case of CH detected was also calculated. The number of patients who were given a final diagnosis of CH was made after a paediatric examination at 4 years.

Effectiveness results
A total of 393 (100%) patients with CH of thyroid origin and 66 (91.6%) patients with CH of central origin were detected under the Netherlands screening programme. The programme resulted in 4.7 false-positive results for every actual case of CH detected.

Under the T4+TSH screening programme, 378 (96.2%) of the CH-thyroid origin patients and 22 (30.6%) of the CH-central origin patients would have been detected. This would have resulted in 3.3 false-positive cases per case of CH detected.

Under the (T4)+TSH screening programme, 371 (94.4%) of the CH-thyroid origin cases and none of the CH-central origin cases would have been detected. This would have resulted in 0.5 false-positive cases per case of CH detected.

Clinical conclusions
The Netherlands screening programme is superior to the (T4)+TSH and T4+TSH screening programmes as it results in higher detection rates of CH of thyroid and central origins. However, it has the disadvantage of a high false-positive rate.

Measure of benefits used in the economic analysis
The summary measure of benefit was the number of cases detected.

Direct costs
No discounting was carried out for the costs that were measured. Some of the quantities and the costs were analysed separately. The costs included were the laboratory costs for T4, TSH and TBG measurements, the cost of a second heel puncture, and the cost of an initial diagnostic evaluation for infants with abnormal screening results. Wages and salaries
of laboratory personnel, housing, and laboratory equipment were assumed to be constant for all three screening protocols and, therefore, were not calculated. No price year was given.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were estimated.

**Currency**
US dollars ($). A conversion rate of 1 Euro to 1 dollar was used.

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
The numbers of cases detected were 371 for the (T4)+TSH strategy, 400 for the T4+TSH strategy, and 459 for the T4+TSH+TBG strategy.

**Cost results**
The cost of the Netherlands screening procedure was $3,144,787. The cost of the T4+TSH screening procedure would have been $2,483,614, while the cost of the (T4)+TSH procedure would have been $2,357,054.

**Synthesis of costs and benefits**
The incremental costs per case detected were:

- $6,353 when comparing (T4)+TSH with no screening,
- $4,363 when comparing T4+TSH with (T4)+TSH, and
- $11,206 when comparing the Netherlands screening procedure with T4+TSH.

**Authors' conclusions**
The Netherlands screening programme resulted in more cases of congenital hypothyroidism (CH) being detected than would have happened with the other two screening programmes considered. The authors considered that the extra cost of the Netherlands screening programme is worth the benefit of a baby correctly diagnosed. This benefit, which the authors did not calculate, is the prevention of morbidity, death and a lifetime of severe disability.

**CRD COMMENTARY - Selection of comparators**
The comparators were chosen because they represented two alternative methods of taking T4 measurement for detecting CH into consideration.

**Validity of estimate of measure of effectiveness**
The source of the effectiveness data was a single study. The study design seemed appropriate for the hypothesis; as it was not possible to subject a large population to the alternative screening methods, the effects were assessed using data
from the existing screening method. As all babies were included in the study, they were representative of the study population. There was no need to test for comparability of the patient groups. There were no other sources of effectiveness data.

Validity of estimate of measure of benefit
The number of cases of CH detected was used as a benefit measure. If the benefit of screening had been assessed as the prevention of death, morbidity and disability, then the screening programme which detected the most CH cases (i.e. the one in operation in the Netherlands) would have produced a much larger benefit.

Validity of estimate of costs
The costs measured appear to have included those relevant to the cost perspective adopted in the analysis (i.e. that of the health system). The costs and the quantities were reported separately in the text, but were not presented clearly in tabular form. The resource use quantities were taken from a single study, while the prices were taken from the authors' setting. No statistical, sensitivity, or any other kind of analysis of the quantities or prices was undertaken. No price date was given.

Other issues
The authors made appropriate comparisons of their results with the findings from other studies. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. The authors' conclusions reflected the scope of the analysis, but they could have made their conclusions stronger if they had estimated the savings in future medical expenditure resulting from an early diagnosis of CH. The authors reported some limitations of their study. For example, they did not take the number of cases of transient CH into account in their analysis. Also, they relied on the paediatrician's diagnosis as the final diagnosis since it is not always clear whether mild permanent or transient CH is present. Whenever possible, the final diagnosis was made at 4 years of age. It is not clear that these drawbacks would affect the overall conclusions.

Implications of the study
The main implication of this study is that the screening method used in the Netherlands (i.e. T4+TSH+TBG) is the one that will detect most cases of CH and, therefore, is to be recommended as the cost of the screening programme is worth the benefit (i.e. the avoidance of death and disability). Apart from the cost of screening, the only undesirable consequence of the Netherlands method is the high number of false positives which cause unnecessary anxiety.

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