Evaluating newborn blood spot screening: a framework and initial assessment

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Executive summary

Health Council of the Netherlands

Each year around 170,000 infants are tested in the Netherlands for serious, treatable conditions through newborn blood spot screening (NBS). Within a week after birth, a few drops of blood are collected on a heel prick card and tested in a laboratory. Early detection and treatment can prevent or ameliorate serious harm to the physical and mental development of children with a serious but treatable health condition. In 2020, 180 infants in the Netherlands were detected with such conditions through newborn screening.

The NBS programme was launched in 1974 to test for a single condition (the metabolic condition phenylketonuria). Since then, it has been expanded in the Netherlands to cover 25 conditions. The Health Council assesses whether a condition meets the criteria for inclusion in the programme. Based on current scientific knowledge, the Council assesses whether the anticipated health benefits outweigh the potential harms of screening, such as the risk of incorrect screening results. For this assessment the Council uses a framework that is derived from the internationally accepted principles for population screening. Whether the health benefits do indeed outweigh the harms can only be determined once screening is effectuated. As testing techniques and treatments improve over time, more and even rarer conditions – about which much less is known at the time of the initial assessment – will become eligible for NBS in the near future. Accordingly, in 2019 the Council recommended that all conditions included in the NBS programme should be periodically evaluated, and adjustments made if necessary.

At the request of the State Secretary for Health, Welfare and Sport (VWS), the Health Council has provided advice on the aspects relevant to this evaluation. Based on these aspects, the permanent Committee on Preconception, Prenatal and Neonatal Screening conducted an initial evaluation of 11 conditions included in the NBS programme. The National Institute for Public Health and the Environment (RIVM) selected these 11 conditions to be given priority for evaluation, following consultation with clinical experts.

Evaluation framework: two guiding questions

The committee stated that the assessment framework it uses to give advice on whether a condition should be included in the NBS programme contains principles that are relevant to an evaluation of the health benefits achieved, and the harms.

The committee used the following two questions to guide the evaluation:

1. Does screening for the condition lead to significant health benefits for screened infants with the condition?
2. Are the negative consequences of false positive and false negative test results, milder disease variants and incidental findings, as observed in practice, comparatively minor?

In terms of the health benefit achieved, it is important to know how many children with the condition have been detected through screening and what the short and long-term effects of screening have been. Those effects should be determined primarily based on scientific research into the long-term differences in mortality rates, disease burden and quality of life between infants with the condition detected through NBS versus those diagnosed based on clinical symptoms.

One disadvantage of screening is that results do not provide complete certainty or clarity. Infants who receive an abnormal screen result may in fact not have the condition tested for (false positives), or infants with the condition may incorrectly receive a normal result (false negatives). Milder variants of the disease may also be detected, which would only lead to health problems much later in life, if at all. Screening may also reveal conditions that are not sought after, known as 'incidental findings'. For evaluation, it is important to establish how often these findings occur (based on data from the RIVM database) and what their consequences are for screened individuals and their families. Negative consequences of NBS include both physical and psychological harms.

For most of the conditions evaluated, the health benefits outweigh the harms

For the majority of conditions prioritised for evaluation, there is evidence that the benefits of screening outweigh the harms. For these conditions – which the committee labelled 'Category A' – there is no immediate need to make adjustments to the screening programme, although ongoing monitoring remains important. For some conditions, the balance between benefits and harms of screening could not be assessed due to lack of evidence, either because there are no scientific studies available, or there is not yet enough data because the condition was only recently added to the NBS programme. In the committee's view, these conditions ('Category B') should be evaluated in the near future – in other words, as soon as there has been an opportunity to collect the necessary data.

For one condition, 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD), there are indications that the health benefits achieved may not outweigh the harms of screening ('Category C'). International research suggests that the symptoms caused by 3-MCCD may be less serious than initially thought, which may indicate that the health benefits of screening are limited. On the other hand, there is the disadvantage that screening can also detect 3-MCCD

in mothers, who may not be displaying any symptoms. To obtain greater clarity on whether the health benefits outweigh the harms, in-depth research is required as soon as possible. At present, no clinical research data is kept on the children who test positive for 3-MCCD in the Dutch NBS programme.

Systematic data collection and more research required

Overall, the committee's assessment of the Dutch NBS programme is positive. From the initial evaluation, it appears that in most cases significant health benefits are achieved, without disproportionate harms. The committee believes it is important to evaluate whether the benefits continue to outweigh the harms over the long term. To this end, systematic data collection is required.

In the database maintained by RIVM, data is recorded on referrals and diagnoses, including true positives and false positives. Data is also recorded on patients missed by the screening, i.e. false negative results.

Table 1 Results of the initial assessment for the 11 prioritised conditions.

Category A Sufficient evidence that the health benefits outweigh the harms	Category B Insufficient evidence to determine benefit-harm ratio	Category C Sufficient evidence that the health benefits may not outweigh the harms
• Biotinidase deficiency (BIO) • Classic galactosaemia (GAL) • Medium-chain acyl-CoA dehydrogenase deficiency (MCADD) • Very-long-chain acyl-CoA dehydrogenase deficiency (VLCADD) • Congenital adrenal hyperplasia (CAH) • Congenital hypothyroidism (CH) • Phenylketonuria (PKU)	• Propionic acidaemia (PA) • Methylmalonic acidaemia (MMA) • Long-chain hydroxyacyl-CoA dehydrogenase deficiency/Mitochondrial trifunctional protein deficiency (LCHADD/MTPD)	• 3-methylcrotonyl-CoA carboxylase deficiency (3-MCCD)

The committee recommends that results for mild variants and incidental findings also be recorded. This data is relevant, but is not systematically recorded at present. This is partly to do with an issue of disease definition. For example, mild variants are sometimes recorded as false positives, as is the case with variants that are known to never or rarely cause health problems.

Although the numbers of referrals and types of results are recorded, there is no centralised repository of research data on the long-term effects of screening on the burden of disease, mortality rates and quality of life, or for studies on the negative physical and psychological impact of screening. Establishing such a repository would be necessary for a proper assessment of the long-term benefits and harms of NBS in practice.

The committee recommends working with a core outcome set for each condition: a set of outcome measures that are most relevant to determining long-term health benefits and harms of screening. This will limit the amount of data to be collected for each condition. It will also make it easier in the future to compare the findings of different studies.

Expert committees would be best placed to decide – in consultation with parents and patient groups – on what the core outcomes are for each condition in the NBS panel. Likewise, the design and execution of effectiveness studies should be left to the relevant scientific and clinical experts. The committee recommends involving clinical experts who treat patients with an NBS-detected condition as adults. For very rare conditions, the committee recommends exploring whether it may be possible to collaborate with international clinical registries.

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