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Fact Sheet on Neonatal Heel Prick Screening

What does the neonatal heel prick screening programme involve?

A heel prick is offered for all newborns within a few days of birth. Since 1 March 2021, the blood samples obtained have been screened for 25 serious, rare and often genetic disorders. Early detection and treatment of these conditions can prevent or limit serious damage to the child's physical and mental development. Screening for sickle cell disease can also reveal carrier status. Parents can choose not to receive information about carrier status.

1 Disease profile

Most of the disorders covered by the neonatal heel prick screening programme are genetic and treatment is often drug-based or diet-based.

The screening programme currently covers the following conditions:

Thyroid disease:

- Congenital hypothyroidism **(CH)**: a group of diseases with the common feature that the thyroid does not produce enough thyroid hormone (thyroxine, T4). CH is usually permanent and not usually genetic. T4 plays an important role in regulating metabolism, as well as being essential for growth and development. T4 deficiency at a young age has a negative impact on brain development, with a risk of permanent intellectual and motor disability. Early treatment with T4 can mean that this risk is negligible. Treatment: life-long daily thyroxine tablets. Prevalence: 80 children per year on average.

Adrenal disease:

- Adrenogenital syndrome **(AGS)**: a congenital, life-threatening, genetic disorder of the hormone production in the adrenal glands. The abnormality results in a cortisol deficiency, often accompanied by aldosterone deficiency and overproduction of androgens. In newborns there is a risk of excessive loss of salts, resulting in water loss and dehydration. Girls have varying degrees of masculinization of the external genitalia at birth. Early treatment can prevent serious dysregulation of the salt and water balance. Treatment: life-long use of cortisol preparations and other additional medication. Prevalence: 10 to 15 children per year on average.

Metabolic disease (MD):

- Biotinidase deficiency **(BIO)**: a genetic metabolic disease in which too little biotin (vitamin H) is produced. Left untreated, the disease results in skin problems, epileptic seizures, in some cases full or partial baldness, delayed development and muscle problems. When treated early, all symptoms are avoided. Treatment: life-long use of biotin. Prevalence: 2 to 4 children per year on average.

- Carnitine palmitoyltransferase deficiency type 1 **(CPT1)**: a genetic metabolic disease in which fatty acids are not broken down properly. Insufficient breakdown of fatty acids can lead to a lack of energy, causing the level of sugar in the blood to drop too low. This is known as hypoglycaemia. The child can become drowsy and weak and fall into a coma. These symptoms are most likely to occur in the event of illness or fasting. CPT1 is an easily treatable disease. Prevalence in the Netherlands: very rare, 1 child per 5 years on average.
- Galactokinase deficiency **(GALK)** Galactokinase deficiency is a form of galactosaemia. It is a genetic metabolic disease in which galactose is not broken down properly. If the disease is not treated, the patient can develop the eye disease cataracts in both eyes as soon as a few months after birth. This can be prevented through a diet. Prevalence: 1 child per year on average.
- Classical galactosaemia **(GALT)**: a genetic metabolic disease in which galactose (part of milk sugar, lactose) is not broken down sufficiently in the liver. Lactose is found in breast milk and in many food products for infants. Left untreated, galactosaemia results in jaundice, infections, the eye disease cataracts and death. Despite effective treatments, galactosaemia can lead to developmental delay and to reduced fertility in females. Treatment: life-long strict galactose-restricted diet. Prevalence: 3 to 4 children per year on average.
- Glutaric aciduria type I **(GA-I)**: a genetic metabolic disease in which the amino acids lysine and tryptophan are not broken down properly. Left untreated, it can result in very severe brain damage. Brain damage can be largely or entirely prevented with diet-based and drug-based treatment. Treatment: life-long protein-restricted diet with 'amino acid preparation' and medication. Prevalence: 1 child per year on average.
- HMG CoA lyase deficiency **(HMG)**: a genetic metabolic disease in which the amino acid leucine is not broken down properly and fatty acid oxidation is disrupted. This results in a lack of energy. Problems occur with low or no food intake over longer periods, for example in the event of fever, sleeping through the night without eating, vomiting and diarrhoea or in the event of surgery. Low blood sugar levels mean that this can result in vomiting, weakness and drowsiness, loss of consciousness, neurological problems and impaired development. Treatment: in some cases medication (carnitine) and diet. Prevalence: very rare, 1 child per ten years on average.
- Isovaleriac acidaemia **(IVA)**: a genetic metabolic disease in which the amino acid leucine is not broken down properly. This can result in vomiting, dehydration, weakness and drowsiness, loss of consciousness, neurological problems and impaired development. Treatment: life-long protein-restricted diet, 'amino acid preparation' and medication. Prevalence: 2 children per year on average.
- 3-methylcrotonyl-CoA carboxylase deficiency **(3-MCC)**: a genetic metabolic disease in which certain proteins containing the amino acid leucine are not sufficiently broken down. This can result in convulsions, developmental delay and loss of consciousness. However, most children only have symptoms in the event of

illness. Treatment: most children only require dietary advice in the event of illness. In very rare cases, a protein-restricted diet and medication are necessary. Prevalence: 1 to 2 children per year on average.

- Medium-chain acyl-CoA dehydrogenase deficiency **(MCADD)**: a genetic metabolic disease in which medium-chain fatty acids cannot be used as an energy source. Problems occur with low or no food intake over longer periods, for example in the event of fever, sleeping through the night without eating, or in the event of vomiting and diarrhoea. This can result in low blood sugar levels, leading to tiredness, drowsiness, loss of consciousness and ultimately death. Treatment: avoid longer periods of no food intake. Additional food and medication are required in some cases. Prevalence: 15 to 20 children per year on average.
- Multiple CoA carboxylase deficiency **(MCD)**: a genetic metabolic disease in which proteins from food cannot be properly converted into usable substances. This can result in dehydration, loss of consciousness, skin defects, baldness, neurological problems, epilepsy and immune system disorders. Treatment: life-long administration of biotin (vitamin H), in some cases supplemented with a protein-restricted diet. Prevalence: extremely rare.
- Methylmalonic acidaemia **(MMA)**: metabolic disease in which two amino acids are not broken down properly. In one form of MMA this is due to dysfunction of the enzyme methylmalonyl-CoA mutase (MCM). A child with MMA usually develops symptoms in the first days or weeks after birth. The child can be drowsy and weak and vomit. These symptoms are usually triggered by fasting or an infection or fever. The disease can also present later and with less obvious symptoms. MMA mainly leads to problems in the brain and kidneys. Treatment of the disease reduces the risk of these problems. Without treatment, patients will ultimately die. Prevalence: 1 to 2 children per year on average. Please note: there is ongoing debate regarding the target disease definition of MMA for the neonatal heel prick screening programme.
- Mucopolysaccharidosis type 1 **(MPS I)**: MPS I is a genetic metabolic disease caused by a deficiency of the enzyme alpha-L-iduronidase (IDUA). This enzyme deficiency leads to lysosomal accumulation of the glycosaminoglycans (GAGs) heparan sulphate and dermatan sulphate. MPS I has a number of variants. Patients with the severe form develop increasingly severe physical symptoms in the first year of life and progressive brain disease from the age of around two. Without treatment, they do not survive past the age of 20. Treatment: enzyme therapy and stem cell transplantation. Prevalence: 1 to 4 children per year on average.

- Maple syrup urine disease **(MSUD)**: a genetic metabolic disease in which the breakdown of the amino acids leucine, isoleucine and valine is disrupted. Left untreated, both the child's urine and the child himself or herself can develop a somewhat sweet smell. A lack of timely treatment results in vomiting, loss of consciousness, severe developmental delay and death. Treatment: life-long low-protein diet and an 'amino acid preparation'. Prevalence: 1 child per two years on average.
- Long-chain hydroxyacyl-CoA dehydrogenase deficiency **(LCHADD)**: a genetic metabolic disease in which long-chain fatty acids cannot be used as an energy source. Problems occur with low or no food intake, for example in the event of fever, sleeping through the night without eating, or in the event of vomiting and diarrhoea. This can result in low blood sugar levels, which can lead to tiredness, drowsiness and loss of consciousness. Muscle and cardiac muscle disorders can also occur. Treatment: avoid longer periods of no food intake, diet including extra carbohydrates and special fats. Prevalence: 1 child per year on average.
- Propionic acidaemie **(PA)**: a genetic metabolic disease in which two amino acids are not broken down properly. This is due to dysfunction of the enzyme propionyl-CoA carboxylase (PCC). A child with PA usually develops symptoms in the first days or weeks after birth. The child can be drowsy and weak and vomit. These symptoms are usually triggered by fasting or an infection or fever. PA can lead to problems affecting the brain in particular and cardiac dysfunction. Treatment of the disease reduces the risk of problems. Without treatment, patients will ultimately die. Prevalence in the Netherlands: 1 child per year on average.
- Phenylketonuria **(PKU)**: a genetic metabolic disease in which the amino acid phenylalanine is not sufficiently broken down. This can result in severe developmental delay, epilepsy, spasticity and behavioural problems. Treatment: life-long strict protein-restricted diet with 'amino acid preparation' and in some cases medication. Prevalence: 12 to 15 children per year on average.
- Tyrosinaemia type 1 (**(TYR- I)**: a genetic metabolic disease in which the amino acid tyrosine is not sufficiently broken down. This can lead to liver function disorders, kidney problems, nerve disorders, liver cancer and death. Treatment: life-long medication and protein-restricted diet and amino acid preparation. A liver transplant is required in rare cases. Prevalence: 1 child per year on average.
- Very long-chain acyl-CoA dehydrogenase deficiency **(VLCADD)**: a genetic metabolic disease in which very long-chain fatty acids cannot be used for energy. Problems occur with low or no food intake, for example in the event of fever, sleeping through the night without eating, or in the event of vomiting and diarrhoea. This can result in low blood sugar levels, which can lead to tiredness, drowsiness and loss of consciousness. Muscle and cardiac muscle disorders can also occur. Treatment: avoid longer periods of no food intake, diet including extra carbohydrates and special fats. Prevalence: 2 to 4 children per year on average.

Blood diseases (Haemoglobinopathies; HbP):

- Alpha-thalassaemia **(HbH disease)**: a genetic disorder in which not enough alpha-globin chains are produced. Children have moderate anaemia immediately after birth. Treatment: folic acid, blood transfusion. If the patient is blood transfusion dependent, stem cell transplantation is considered. Prevalence: 5 children per two years on average.
- **Beta thalassaemia major**: a genetic disorder in which no or insufficient beta-globin chains are produced. Progressively severe anaemia develops from around the age of three months and can be life threatening. Treatment: chronic blood transfusion schedule and iron removal, daily folic acid. If the patient is blood transfusion dependent, stem cell transplantation is considered. Prevalence: 2 to 5 children per year on average.
- Sickle cell disease **(SCD)**: a genetic haemoglobin defect; in the event of low oxygen tension this leads to abnormally shaped red blood cells, which can block small blood vessels. This results in severe bone pain and organ infarction (cerebral and pulmonary infarction), as well as an increased risk of serious infection due to dysfunction of the spleen. The accelerated breakdown of blood cells leads to anaemia. Treatment: analgesics, extra fluid and antibiotics. Blood transfusions are required in some cases. Prevalence: around 35 children per year. Screening for sickle cell disease can also detect carrier status. Parents can be informed of these results if they wish. (On average, more than 800 children per year are found to be carriers).

Lung disease:
Cystic fibrosis **(CF)**: a genetic disease in which mucus is produced in various parts of the body that is thicker and stickier than normal. This thick and sticky mucus creates problems in the respiratory tracts and the gastrointestinal tract. Early treatment can help to prevent or reduce these problems. Treatment: medication, a high-calorie diet and physiotherapy. Prevalence: 25 children per year on average.

Immune disease
Severe combined immunodeficiency **(SCID)** is a serious, rare disease of the immune system. SCID prevents immune cells from developing properly, leading to infections in areas such as the lungs, the gastrointestinal tract and the skin. Infections usually start in the first few months of life. Infections that are not usually dangerous can be life threatening for children with SCID. Without treatment, children with SCID can die in the first year of life. Treatment: stem cell transplantation, and avoiding infections until this time. Prevalence: 2 to 4 children per year on average.

From mid-2022:
- Spinal muscular atrophy **(SMA)** is a serious muscle disease that can lead to paralysis and death. It is caused by a deletion in the survival motor neuron 1 (*SMN1*) gene. As a result, no SMN1 protein is produced, motorneuron function is lost and there is a progressive loss of muscle strength. The lack of function of the *SMN1* gene means that patients are dependent on the *SMN2* gene for the production of SMN proteins. This gene produces SMN2 protein, which is less functional than SMN1 protein.

Generally speaking, the more copies of the *SMN2* gene (varies from zero to four, in very rare cases more than four) an SMA patient has, the more SMN2 protein is produced and the milder the disease.
Several treatments have become available for the disease SMA in recent years.

2 Target group

The neonatal heel prick screening programme is aimed at all newborns up to the age of six months. Approximately 170,000 heel pricks are carried out every year. The heel prick should be carried out at the earliest opportunity between 72 hours and 168 hours after birth. Where combined with neonatal hearing screening, heel prick screening is carried out from 96 hours after birth. If it is not possible to carry out the heel prick between 72 and 168 hours after birth, for example because the child was born abroad, the heel prick is carried out at a later time. Heel prick screening is offered up to the age of six months. Results of heel pricks collected more than 168 hours after birth can be less reliable.

3 Figures

Approximately 170,000 heel pricks are carried out every year, of which around 10% at a hospital. Participation in the heel prick screening programme has exceeded 99% for a number of years now and was 99.4% in 2020.

NHS (Screening in 2020)	Figure
Burden of disease (incidence)	Around 175 children per year
Size of target group (2020 evaluation)	169,734
Number of children who underwent heel prick screening (2020 evaluation)	168,683
Participation rate (2020 evaluation)	99.4%
Number and percentage of referrals (2020 evaluation)	Total 437 (0.26%)* 21 (0.012%) AGS 228 (0.14%) CH 124 (0.074%) MD*, 37 (0.022%) HbP 27 (0,016%) CF
Detection figure per disease (per 1000 screened) (2020 evaluation)	Total 1.037 0.065 AGS 0.373 CH 0.339 MD 0.166 HbP 0.095 CF
Positive predictive value of an abnormal result (2020 evaluation)	Total 42% 58% AGS 29% CH 46% MD 96% HbP

NHS (Screening in 2020)	Figure
	64% CF
False positives (per 1000 screened) (2020 evaluation)	1.46 (n=246)
False negatives (per 1000 screened) (2020 evaluation)**	0.012 (n=2)
Missed patients (per 1000 screened) (2020 evaluation)***	0 (n=0)
Timeliness of 1st heel prick (% of live births where the 1st heel prick was collected <168 hours after birth)	98.5%
Timeliness of diagnostic testing (2020 evaluation)****	90% AGS 88% CH 98% MD 81% HbP 77% CF

* Excluding 13 referrals for OCTN2
** Number of children with a disease included in the NHS programme that was not detected via screening despite participation in the programme.
*** Number of children with a disease included in the NHS programme that was not detected via screening, whereby there was a problem in the process that was not attributable to the test.
**** The percentage of children given an immediate referral due to suspected presence of a specific disease included in the NHS programme and whereby the first diagnostic test was carried out within the agreed period after birth.

Explanatory notes to the table:

- Burden of disease (incidence): number of new cases diagnosed each year.
- Participation rate: the percentage of people invited to participate who actually undergo a screening test.
- Percentage of referrals: the percentage of people screened who are referred to hospital for follow-up tests.
- Detection figure: the number of diseases detected, expressed per number of people screened. This is a measure of the probability that a disease for which screening is carried out will be detected.
- Positive predictive value of referral: the probability that a disease will actually be found following a hospital referral.
- False positives: the number of people referred to hospital (expressed per number of people screened) whereby the disease for which screening is carried out is not detected.
- False negatives: the probability that a relevant abnormality will be detected after normal screening results (following clinical diagnosis).

The table below provides an overview of all children detected through the heel prick screening programme in the period 2007–2020.

	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
AGS	7	8	7	5	5	8	8	6	3	8	12	9	12	11
CH	57	90	65	95	80	69	72	76	79	72	70	57	72	63
MD	70	97	87	61	70	51	47	59	49	49	52	58	48	57
SCD	41	30	29	41	39	34	35	34	25	29	24	31	40	22
Thalassaemia											7	6	8	6
CF					18	20	21	18	21	29	23	25	31	16
Total	**175**	**224**	**188**	**202**	**212**	**182**	**183**	**193**	**177**	**187**	**188**	**186**	**211**	**175**

4 Implementation

Process

Selection

- The National Institute for Public Health and the Environment Department for Vaccine Supply and Prevention Programmes (RIVM-DVP) regional offices receive the child's details after the parents have registered the birth via the Key Register of Persons (BRP), or following an administrative birth notification submitted by a midwife. The DVP also receives data via the Central Agency for the Reception of Asylum Seekers (COA).

Invitation

- The RIVM regional offices instruct the relevant Youth Health Care Services (JGZ) organisation to carry out the heel prick.
- Obstetric care providers (midwives, GPs who provide obstetric care and gynaecologists) provide information about the neonatal heel prick screening in the third trimester of pregnancy. The prospective parent(s) are given a copy of the information leaflet. The choice of whether or not to be informed about the child's carrier status for sickle cell disease is specifically discussed, as is the option to object to the use of residual heel prick blood for anonymous scientific research.

The screening test

- The heel prick is preferably carried out between 72 and 168 hours after birth, usually at the same time as neonatal hearing screening. The heel prick is carried out wherever the child is. Most children undergo the heel prick at home.
- During the heel prick, a few drops of blood are removed from the child's heel using a special instrument (lancet) and collected on a heel prick card.
- The heel prick card is then sent to one of the five screening laboratories. The laboratory carries out the tests and reports the results to the regional RIVM office.

Results

- Since April 2020, parents are informed of normal results in writing.

- If a result is abnormal, the RIVM regional office's medical adviser will first contact a paediatrician or specialist paediatrician and then the general practitioner. The GP refers the child to a university medical centre (for CH, children are also referred to the general hospitals).
- Further tests (diagnostic testing) are carried out at the hospital. Following a diagnosis, treatment is started where necessary.

Who is involved in the screening programme?

- At national level, the screening programme is organised on behalf of the Ministry of Health, Welfare and Sport by the National Institute for Public Health and the Environment (RIVM) Centre for Population Screening (CvB). The Policy Framework for Prenatal and Neonatal Screening provides an overview of the legal and policy frameworks and describes the collaboration between the parties involved in preparing, leading and implementing the prenatal and neonatal screening programmes. Further information can be found on the website.
- Regional implementation is carried out by the Department for Vaccine Supply and Prevention Programmes (DVP).
- RIVM-DVP purchases and distributes the necessary materials, manages the Praeventis information system and engages the screening organisations and screening laboratories.
- The obstetric care provider (midwife, gynaecologist or GP providing obstetric care) provides the prospective parent(s) with information about the heel prick and hands out the leaflet.
- The official from the municipal Department of Civil Affairs gives them the same leaflet when the birth is registered with the municipality.
- The blood is collected by screeners from JGZ organisations. In two regions (Gelderland and Zuid-Holland) the heel prick is also carried out by midwives, under the responsibility of the JGZ. In Twente, the heel prick is also carried out by maternity assistants, under the responsibility of the JGZ.
- If a child is hospitalised during the sampling period, the heel prick is performed by an employee of the hospital.
- The blood test is carried out by five contracted screening laboratories. One of these laboratories is the RIVM Centre for Health Protection (GZB), which also acts as a reference laboratory.
- In the case of cystic fibrosis screening, additional DNA analysis of the CFTR gene takes place around 100 times a year at the Department of Clinical Genetics at Amsterdam UMC, VUmc site.
- The annual monitor of the screening programme is carried out by TNO-Child Health on behalf of RIVM-CvB.
- The Programme Committee for Neonatal Heel Prick Screening, appointed by RIVM-CvB, advises RIVM on the national coordination of the programme. The Programme Committee is made up of experts from relevant professional groups and organisations that have authority within their profession or network and that have contacts in the field.
- The Board of the Dutch Paediatric Association (NVK) has appointed the following advisory committees for the neonatal

screening programme: the Advisory Committee for AGS-CH (ANS-AGS-CH), the Advisory Committee for Metabolic Diseases (ANS-MD), the Advisory Committee for Haemoglobinopathies (ANS-HbP), the Advisory Committee for Cystic Fibrosis (ANS-CF) and the Advisory Committee for Severe Combined Immune Deficiency (ANS-SCID). The Advisory Committee for Spinal Muscular Atrophy (ANS-SMA) is to be set up at the start of 2022. These committees also advise the Programme Committee and are responsible for drawing up guidelines for diagnosis and treatment.

Subsequent care

In principle, all children referred through the screening programme who have a confirmed diagnosis are treated at the university medical centres (or in the case of CH, also the general hospitals).
If the result for the AGS test is abnormal, the child is seen by a paediatric endocrinologist as soon as possible and by 12.00 p.m. the next day.
If the result for the CH test is abnormal, the child is seen by a paediatrician or paediatric endocrinologist the same day or by 12.00 p.m. the next day following a consultation between colleagues.
If the result for the CF test is abnormal, the child is seen by a paediatric lung specialist from a CF centre within one week, depending on the scheduled date of the sweat test.
If the result for a metabolic disorder is abnormal, the child is seen as soon as possible on the same day by a paediatric specialist in metabolic disorders at a university medical centre.
If the result for the MPS I test is abnormal, the child is referred as soon as possible on the day after the heel prick result, unless this falls on a weekend or public holiday, in which case on the next working day. Due to the nature of the disease, referrals are less urgent than for other metabolic diseases included in the screening. Such children will be referred to one of the three UMCs that are centres for expertise for MPS I. The medical adviser contacts the paediatrician as soon as the abnormal result is known and discusses the best time to see the child. The medical adviser then contacts the GP to discuss the referral.
If the result for the SCID test is abnormal, the child is referred on the same day or by 12.00 p.m. the next day following a consultation between colleagues. This referral can be to a paediatric endocrinologist at a university hospital or to a paediatric endocrinologist or paediatrician at a general hospital.
If the result for sickle cell disease, alpha thalassaemia (HbH disease) and beta thalassaemia major is abnormal, the child is seen by a paediatric haematologist at a university medical centre within four weeks after the heel prick result.

Advantages and disadvantages of taking part in the programme

Advantages
The neonatal heel prick screening programme detects serious, rare, often genetic disorders. Interventions are available for these conditions, provided they are detected in good time. This prevents or limits damage to the child's health and provides many health benefits. Another

advantage is the avoidance of a lengthy, burdensome diagnostic process.

Disadvantages
If a result is abnormal, parents are confronted with information about a potentially serious condition in their child very soon after the birth. Moreover, an abnormal result usually means that the child needs to be seen quickly by a paediatrician. This leads to anxiety for the family involved. The child may ultimately be found not to have the disease for which he or she was referred (false positive result).

Secondary findings
Carnitine transporter (OCTN2) deficiency is a secondary finding in neonatal heel prick screening. A study is being carried out via the Netherlands Organisation for Health Research and Development (ZonMw), known as the ODIN study, to determine whether OCTN2 should be included as a target disease in the heel prick test. Screening for sickle cell disease also identifies carriers. From the perspective of the child, information about sickle cell disease carrier status can be seen as a disadvantage. From the perspective of the parents and other family, this information can be advantageous with a view to any future pregnancies.

5 History

Screening for phenylketonuria (PKU) using heel prick blood has been carried out in the Netherlands since 1974. Since 1981, the blood has also been checked for congenital hypothyroidism (CH) markers and since 2002 for adrenogenital syndrome (AGS).
In November 2005, the State Secretary for Health announced that the screening would cover more diseases. Based on an advisory report issued by the Health Council of the Netherlands in August 2005, 14 additional disorders, mainly metabolic diseases, were included in the screening with effect from 1 January 2007. In 2010, the Health Council of the Netherlands recommended that cystic fibrosis (CF) be added to the heel prick screening programme. CF was added to the screening with effect from 1 May 2011. Screening for homocystinuria (HCY) ceased as of 1 April 2016 on the Health Council of the Netherlands' advice. This test had already been suspended since October 2010 due to the large number of false negative results obtained with the screening method used. Alpha thalassaemia (HbH disease) and beta thalassaemia major were added to the heel prick screening programme on 1 January 2017. CPT1, PA and MMA were added to the heel prick screening programme on 1 October 2019. This was followed by the addition of GALK deficiency (Oct. 2021), SCID (Jan. 2021) and MPS I (March 2021) to the heel prick screening programme. The screening now includes a total of 25 diseases.

6 Developments

Lower rate of false positives
In recent years, optimisation of the screening methods has led to a reduction in the number of children referred for diagnostic tests based

on an abnormal heel prick result who are subsequently found not to have the disease.

Heel prick screening in the Caribbean Netherlands
In October 2013, the Minister of Health, Welfare and Sport decided to introduce the heel prick screening programme in the Caribbean Netherlands. On the instructions of the Ministry of Health, Welfare and Sport, RIVM-CvB has prepared for the implementation of heel prick screening in the Caribbean Netherlands. The heel prick screening programme was launched in Bonaire on 1 January 2015, followed by Sint Eustatius and Saba in October 2015.

Policy on the further use of remaining heel prick blood
In anticipation of general legal regulations on the use and further use of bodily material (proposed bill for a Use of Bodily Materials [Consultation] Act), a clear policy has to be determined for population screening programmes regarding storage and use of bodily material taken in the context of population screening for purposes that are covered by the screening (primary diagnostic testing and follow-up diagnostic testing, internal quality control and quality improvement, education and training) and other purposes (further use). The current procedures for the further use of remaining heel prick blood can be found at https://www.pns.nl/hielprik/professionals. The current legal conditions for the further use of remaining heel prick blood can be found at https://www.pns.nl/hielprik/juridische-informatie-en-privacy. Policies are being updated in light of the GDPR.

Advisory Report of the Health Council of the Netherlands 'Neonatale screening: nieuwe aanbevelingen' (New recommendations for neonatal screening).
On 8 April 2015, the Health Council of the Netherlands issued a broad advisory report on the heel prick screening programme. The Council recommended that the heel prick screening programme be expanded to include 14 new diseases, that screening for homocystinuria be terminated, that no untreatable diseases be included in the screening programme and that reporting of sickle cell disease carrier status be stopped.
On 9 July 2015, the then Minister of Health, Welfare and Sport published the 'Neonatal Heel Prick Screening Programme' policy viewpoint. The then Minister planned to expand the heel prick screening through the addition of 14 diseases. RIVM-CvB was commissioned to analyse the feasibility of this proposal by carrying out an implementation test. In support of the rapid addition of alpha and beta thalassaemia, RIVM-CvB delivered the first part of the implementation test – in the form of the memorandum on 'Expansion of the neonatal heel prick screening programme to include alpha and beta thalassaemia' – in November 2016. These diseases were added to the heel prick screening programme with effect from 1 January 2017. The second part of the implementation test was drawn up in close collaboration with the relevant parties and presented to the Ministry of Health, Welfare and Sport on 6 July 2017. On 21 December 2017, the State Secretary for Health, Welfare and Sport informed the House of Representatives of his decision to expand the heel prick screening programme with the remaining 12 diseases from the Health Council of the Netherlands' 2015

advisory report. The expansion is being implemented in phases over the period 2018–2022. Additional research is required for each disease.

In its policy viewpoint on 9 July 2015, the Ministry of Health, Welfare and Sport announced that it was looking at the possibility of neonatal heel prick screening for untreatable diseases, for which parents can opt in. The State Secretary for Health, Welfare and Sport stated in a Letter to Parliament on 21 December 2017 that it is still too early for research into the feasibility of screening for untreatable diseases. On 14 March 2019, he asked the Health Council of the Netherlands for advice on the conditions and preconditions under which such screening could be offered. The Council published its advisory report in September 2020. The Council does not recommend screening for untreatable diseases with the heel prick test: the associated advantages do not outweigh the disadvantages. One of the Council's recommendations was to use alternative measures to ensure that parents can get rapid access to diagnostic testing as soon as a child starts to fall behind in their development.

The Health Council of the Netherlands also issued an advisory report on screening for spinal muscular atrophy (SMA) in 2019. The Council recommended that SMA be included in the heel prick screening programme. Screening offers the possibility of treating children before they develop symptoms. The Council recommended that this screening should be evaluated after both five and ten years, however, since knowledge of the importance of presymptomatic treatment and of the long-term effects of treatment is currently still limited. In 2020, RIVM carried out an implementation test for SMA and SMA is expected to be added to the heel prick screening programme in October 2022.
The State Secretary has decided to make no changes to policy on the reporting of sickle cell disease carrier status for the time being. Carrier status will continue to be reported within the programme where parents have not expressed any objections.

Expansion of the heel prick screening programme: current situation
The expansion of the heel prick screening programme to include 12 additional diseases:

- October 2019: CPT1, PA and MMA added
- October 2020: GALK added
- January 2021: SCID added (postponed from October 2020 to January 2021 due to COVID-19)
- March 2021: MPS I added (postponed from October 2020 to March 2021 due to COVID-19)

SMA will be added to the NHS programme by 1 October 2022. The current expectation is that it will be possible to introduce SMA screening early from 1 June 2022, subject to unforeseen events.
In 2020, the ANS-MD recommended that the addition of BKT, CACT and CPT2 should be postponed. The studies being carried out via ZonMw on screening for ALD, OCTN2 and GAMT have also been delayed, leading to a suspension and revision of the original schedule.

On 1 October 2019, the provinces of Noord-Holland, Flevoland, Gelderland and Utrecht launched an implementation pilot study (SCAN

study) on screening for the treatable form of ALD, X-linked adrenoleukodystrophy. ALD is a rare, genetic metabolic disorder. The treatable form only occurs in boys. On 15 November 2020, the decision was taken to place this pilot on hold due to inconsistencies in the test results. The regional ALD screening pilot was relaunched on 1 January 2021. The pilot will last for one year, ending in December 2021. A plan of action is being drawn up for further research into the implementation of ALD.

Psychosocial aspects of the heel prick screening programme and its expansion
In June 2019, a study was launched via ZonMw on the psychosocial aspects of the neonatal heel prick screening programme and its expansion (the PANDA study). The expansion of the heel prick screening programme raises new ethical and other questions. Recent information about how parents experience the current heel prick screening and how parents deal with false positive results is also lacking. The aim of this project is to gain insight through questionnaire surveys and interviews into the psychosocial consequences of the neonatal heel prick screening programme and its expansion. The study provides insight into the value that parents attach to the heel prick screening programme and its expansion, and the perception and meaning of the results. The initial findings were published in 2021. The study will be completed in 2022. Based on the findings, recommendations will be made with regard to the screening programme and its expansion.

Flexible decision-making and further expansion of the heel prick screening programme
In her policy viewpoint on 9 July 2015, the former Minister of Health, Welfare and Sport expressed a desire to be able to respond faster to innovations to achieve more rapid health benefits in the context of the neonatal heel prick screening programme. With this in mind, she wanted to seek the advice of the Health Council of the Netherlands more often when developments so required. A permanent Neonatal Screening Committee was set up in January 2019 to this end. This Committee was the first to consider the request for a recommendation on 21 December 2018, in which the State Secretary for Health, Welfare and Sport requested advice on neonatal screening for spinal muscular atrophy (SMA). In the advisory report issued by the Health Council of the Netherlands in 2015 (the ongoing expansion), this disease did not qualify for inclusion in the heel prick programme, as a usable screening test was not yet available for SMA at that time. Information on treatment options was also still lacking. Both conditions for inclusion in the heel prick screening programme have now been met and the State Secretary has agreed to the Council’s July 2019 recommendation to include this disease in heel prick screening. In late December 2019, the State Secretary for Health, Welfare and Sport asked RIVM-CvB to carry out an Implementation Test for SMA screening and to deliver the results in September 2020. The decision to add SMA to the heel prick screening programme by October 2022 and to therefore include this disease in the ongoing expansion of the programme means that priority has been given to the rapid introduction of SMA screening.

Evaluation of the current screening programme

The Health Council of the Netherlands issues recommendations on the addition of diseases to the neonatal heel prick screening programme. These recommendations are often, by necessity, based on limited information. As a result, the screening sometimes falls short of prior expectations either because the test does not perform as well as anticipated, or because the treatment of children detected delivers fewer health benefits than anticipated. It is important that the screening package only includes diseases for which real health benefits can be achieved. It was for this reason that the State Secretary for Health, Welfare and Sport asked the Health Council of the Netherlands in 2020 to evaluate the scientific data on the gains achieved through screening and, based on this evaluation, to advise on the content of the existing screening package. This advisory report is expected to be published at the end of 2021.

NHS Foresight Study
An NHS Foresight Study will be commenced in early 2022, commissioned by the Ministry of Health, Welfare and Sport in close cooperation with RIVM-CvB. The study will address the key question of how additional health benefits can be achieved and what changes are needed within the heel prick screening programme in order to do this. The underlying principle is the existence of a national heel prick screening programme under the direction of RIVM over the next 10–15 years. The Ministry of Health, Welfare and Sport and RIVM are looking for out-of-the-box recommendations for improvements to the NHS programme.

7 Financial

The implementation of the heel prick screening programme has been funded by central government since 1 January 2015. The price of a heel prick set in 2021 was €2.37. An annual total of 176,127 heel pricks is assumed, based on the number of live births. Implementation costs consist of the performance of the heel prick test and the laboratory analyses. For the performance of the heel prick test, the JGZ organisation receives €22.78 per heel prick carried out. The laboratory analysis costs €74.51 per heel prick card, which is exempt from VAT. RIVM-DVP's organisational costs are approximately €4.94 million per year, and RIVM's directive task costs around €1.9 million per year. Around €25.2 million was spent on the programme in 2021. This will rise to around €26.3 million in 2022. Referrals for diagnostic testing and any treatment fall under regular healthcare and healthcare financing.

8 International

The content of neonatal screening programmes differs widely from country to country and, in some cases, from region to region. In North America, most of Europe, parts of Latin America, Japan, Australia and New Zeeland, neonatal screening is part of regular healthcare services, with the number of diseases included in the screening ranging from just a few to more than 40.
In the rest of Europe, Latin America, the Middle East/North Africa and some Asian countries efforts are under way to bring this provision up to standard, however it is likely to be some time before this is achieved.

In most of Africa neonatal screening is still largely non-existent, and no significant changes are expected in this area in the short term.
With its current package of 25 diseases supplemented by hearing screening, the Netherlands' screening programme is one of the most extensive in Europe.
The countries with the largest screening programmes in terms of the number of diseases covered include Italy with 40, Spain with 33 and Iceland with 28.
Source ISNS: An ISNS perspective on the current state and developments since 2010

9 Websites

https://www.pns.nl/prenatal-and-newborn-screening/heel-prick (public)
https://www.pns.nl/hielprik/professionals (professional - in Dutch)

10 Contact

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