THE NEWBORN BLOOD SPOT SCREENING IN THE NETHERLANDS

MONITOR 2019

TNO innovation for life

The Newborn Blood Spot screening programme (NBS) was introduced in the Netherlands in 1974. The programme is coordinated by the Centre for Population Screening (CvB) of the National Institute for Public Health and the Environment (RIVM). The aim of the NBS is the early detection of a number of serious congenital diseases in newborns. Children with these (rare) diseases benefit from early interventions such as medication or a diet, which can prevent or limit irreparable health damage.

The national monitor with main results of the NBS is carried out annually by TNO at the request of the RIVM-CvB. The monitor enables insight into the functioning of all aspects of the NBS as well as insight into a possible need for extra measures to allow for an improvement in functioning of the screening programme.
A separate monitor is made about the NBS in the Caribbean Netherlands (in Dutch).

Parties involved in the realization of the NBS are presented in figure 1. A blood sample from the newborns heel is taken by a youth health care worker, maternity nurse or midwife. When the baby is admitted to the hospital during the first week after birth, the newborn blot spot is collected by a hospital health care worker.

Figure 1
Parties involved in the execution of the NBS

SUMMARY

- The results of most of the indicators matched the defined target- or signal values and the results of most indicators are in line with the results of previous years.
- NBS **participation rate** was 99.3% in 2019 (n=170.065) and is above the target value of 99.0%. Participation had fallen from 99.4% to 99.1% in the period 2014-2018. The increase in 2019 is partly (estimated 0.1%) due to an optimisation of the calculation of the participation rate.
- 500 children were referred to a paediatrician (0.3%), of which 211 (42% of 500 referred children and 0.12% of the total number of participants) had one of the target group diseases.
- The **timeliness target value** of the 1st heel prick (99.0%) was **not reached:** 98.4% was carried out within 168 hours after birth. This is lower than in 2017 and 2018 (98.8% and 98.6% respectively). The percentage was also below 99% in the years 2011-2016 with the exception of 2013, 38% of the heel pricks was performed in the recommended period of 72-96 hours after birth.
- The laboratories received 94.9% of all heel prick cards up or before three days after blood was collected.
- The target values concerning the percentage of children who needed a **repeat 1st heel prick** were reached for all conditions in 2019.
- **CH:** Many indicators have been recalculated for 2018, because last year's diagnostic data were incomplete. It is notable that the detection rate is very low in 2018 (0.034%) compared to the past five years (average: 0.041%). In 2019, the detection rate is again around this average (0.042%).
- In 2019 the total screening programme has a **detection rate** of 1.241 per 1000 screened children, a **positive predictive value** of 48%, a **sensitivity** of 98% and a **specificity** of 99.865%. The positive predictive value is higher than in 2014-2018 (between 24% and 42%).

- All conditions reached the target values in terms of **specificity** and **positive predictive value.** Four children born in 2019 were reported as false negative (3x for CH, 1x for VLCAD). The target values for sensitivity of CH and VLCAD have therefore not been achieved.
- **GALT:** In 2019, the change in the cut-off limit for GALT resulted in a lower referral rate and higher specificity.
- The target values for **timeliness of diagnostics (≥90%)** were not achieved for CAH (86%), CH (86%) and CF (58%) in 2019.
- The number of parents who **object** to the **storage of blood remnants** for anonymous scientific research in 2019 is 6.6%. Over the years there has been a steady increase in this percentage (e.g. in 2014 this was 4.9%).
- In 2019 **screening costs** per child (diagnostic costs excluded) were €100. These costs show a rising trend mainly because of the indexation of the costs for blood collection and laboratory analysis, and the addition of new conditions to the screening programme.

RECOMMENDATIONS

New recommendations:

- Improvement of the **timeliness of diagnostics** in CAH, CH and CF, and of registration of the date at first consultation with the paediatrician.

Existing recommendations that are still valid:

- Continue or intensify measures to improve the **timeliness of the first heel prick.**
- Gain more insight into why parents **object** to the **storage of blood remnants** for scientific research.
- Continued attention for **timeliness and clarity of registration** of diagnostic data.

DATA SOURCES

The screening data in this monitor originate from the Praeventis registration system of the RIVM. Diagnostic data originate from the NEORAH registration system of the RIVM (http://www.neorah.nl).[1]
In previous years the diagnostic CH data was registered by TNO; from 2018, paediatricians register these diagnostic CH data in Neorah. The NEORAH data related to metabolic diseases have been retrieved from the Dutch Diagnosis Registration Metabolic Diseases (www.ddrmd.nl). Notifications of the Dutch Paediatric Surveillance System (NSCK) have been used to detect possible missed cases until 1st of January 2020.[2] This monitor concerns **children who were born in 2019** (Praeventis reference date: 19-3-2020 or later[3], NEORAH: 11-6-2020 or later[4]).

READING GUIDE

This monitor differentiates between the first heel prick, a repeat first heel prick, a second heel prick and a repeat second heel prick:

- First heel prick: the first heel prick that has been carried out;
- Repeat first heel prick: the newborn blood spot collection that is repeated because insufficient blood has been collected during the first heel prick in order to carry out the required laboratory analyses ('insufficient filling') or because the material is unreliable (contamination), or because the first heel prick was taken too early (within 48 hours after birth), or because a child received a blood transfusion within 24 hrs before the heel prick was carried out. If a blood transfusion with erythrocytes has been carried out, the heel prick needs to be repeated after 91 days to test for haemoglobinopathies (HbP);
- Second heel prick: carried out if the first heel prick gives an inconclusive laboratory result;
- Repeat second heel prick: as in repeat first heel prick.

[1] In the spring of 2019, NVK and RIVM signed a new cooperation statement in which RIVM is designated as responsible for Neorah.
[2] Missed patients discovered after January 1, 2020 should be reported to RIVM by the paediatricians, whether or not through the chairman of the ANS. The NSCK alert (which was used until 1-1-2020) has been cancelled.
[3] The reference date was 16-4-2020 for CPT1, HbP, OCTN2 and VLCAD.
[4] The reference date was 29-6-2020 for PA and MMA, 22-7-2019 for CPT1, 7-9-2020 for CH, 21-9-2020 for CAH and 13-11-2020 for MCADD.

In this monitor the colours green and red indicate whether the results meet the prior indicated signal- or target values.

- The values which fall within the indicated limits. are indicated in green.
- Values outside the formulated limits are indicated in red. If possible, actions can be taken to improve the results or to get the results to fall within the limits of the target value.
- Signal- or target values for trends do not exist. Trends which require vigilance, are indicated in orange. Stable trends are indicated in green.

DIFFERENCE COMPARED TO PREVIOUS MONITORS

As of January 1, 2019, the cut-off limits for the GALT screening have been changed; the result is 'abnormal' for GALT≤2.0 U/dL blood and TGAL≥1600 µmol/L blood (TGAL was ≥1100 µmol/L blood).

The cut-off limits for MSUD have been changed (Valine and Leucine from ≥ 400 µmol/L blood to ≥ 340 µmol/L blood) on April 1, 2019.

On April 1, 2019, the cut-off limits have changed for PKU (from Phe ≥ 200 µmol/L blood to Phe ≥ 180 µmol/L blood), TYR-1 (from SA ≥ 0.90 µmol/L blood to SA ≥ 0.60 µmol/L blood) and GA-1 (from C5DC ≥ 0.70 µmol/L blood to C5DC ≥ 0.35 µmol/L blood).

Per April 15, 2019, the cut-off limits have changed for MCADD (from C8 ≥ 0.50 µmol/L blood to C8 ≥ 0.43 µmol/L blood) and IVA (from C5 ≥ 1.0 µmol/L blood to C5 ≥ 0.8 µmol/L blood).

Screenings for CPT1, PA and MMA have been implemented on October 1, 2019.

WHICH CONDITIONS ARE INCLUDED IN THE SCREENING?

- Congenital adrenal hyperplasia **(CAH)**
- Cystic fibrosis **(CF)**
- Congenital hypothyroidism **(CH)**
- Hemoglobinopathies **(HbP):**
  - Sickle cell disease **(SCD)**
  - HbH-disease **(HbH),** a form of alpha-thalassemia
  - Beta-thalassemia major **(bTM)**
- Metabolic diseases **(MD):**
  - 3-Methylcrotonyl-CoA carboxylase deficiency **(3-MCC)**[1]
  - Biotinidase deficiency **(BIO)**
  - Carnitine palmitoyltransferase I deficiency **(CPT1)**[2]
  - Galactosemia **(GAL)**
  - Glutaric acidemia type 1 **(GA-1)**
  - HMG-CoA lyase deficiency **(HMG)**[1]
  - Isovaleric acidemia **(IVA)**
  - Maple syrup urine disease **(MSUD)**
  - Medium-chain acylCoA dehydrogenase deficiency **(MCAD)**
  - Methylmalonic acidemia **(MMA)**[2]
  - Multiple CoA carboxylase deficiency **(MCD)**[1]
  - Phenylketonuria **(PKU)**
  - Propionic Acidemia **(PA)**[2]
  - Trifunctional Protein deficiency/ Long-chain hydroxyacyl-CoA dehydrogenase deficiency **(TFP/LCHAD)**
  - Tyrosinemia type 1 **(TYR-1)**
  - Very-long-chain acyl-CoA dehydrogenase deficiency **(VLCAD)**
  - Carnitine transporter (OCTN2) deficiency **(OCTN2)**[3]

More information about these conditions can be found on the RIVM website:
https://www.pns.nl/hielprik

[1] These three conditions are reported altogether under one name, 3-MHM, since they have the same marker.
[2] These conditions were added to the screening programme on 1-10-2019.
[3] OCTN2-deficiency is not part of the NBS: it is considered an incidental finding.

PARTICIPATION

In 2019 171.195 children were eligible to participate in the NBS. A heel prick was performed on 170.065 children. This means that the participation rate in 2019 is 99.3%, which is higher than the target percentage of 99.0% and which is also higher than it was in the period 2014 to 2018 (figure 2). The increase is partly (estimated: 0.1%) due to an optimisation of the calculation.[1]

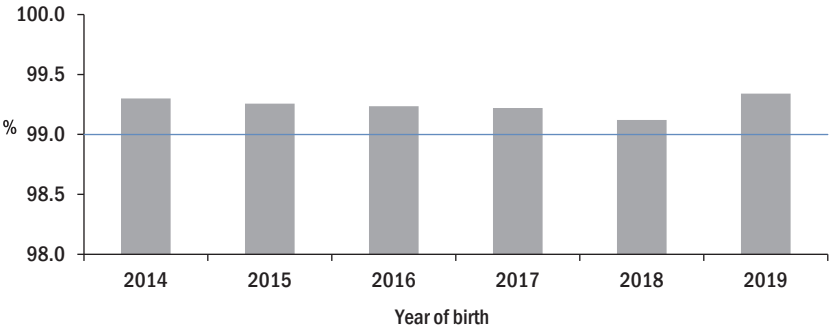

Figure 2
Participation rate of the neonatal screening programme by year of birth (2014-2019); to support readability the y-axis starts at 98%. The blue line indicates the target value

Figure 3 shows that parents object less often (0.38% in 2019 versus 0.46% in 2018) and that the percentage of children who did not participate for an unknown reason has decreased (2019: 0.03%, 2018: 0.11%). This decrease is partly caused by an optimisation of the calculation.[1]

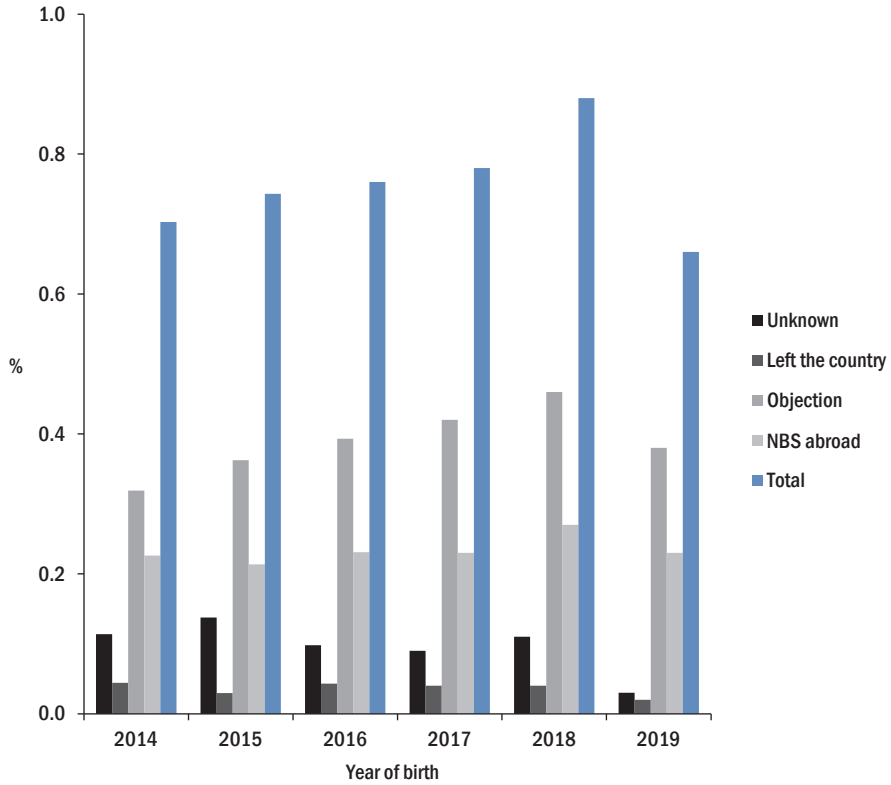

Figure 3
Reasons for non-participation in the neonatal screening programme by year of birth (2014-2019)

[1] Data from children with two first heel prick tests were checked more thoroughly in 2019. See the report 'Evaluatie van de neonatale hielprikscreening bij kinderen geboren in 2019' (Dutch only) for details.

TIMELINESS OF BLOOD COLLECTION

Timing of the NBS is crucial. The heel prick should be carried out within 168 hours (7 days) after birth, but ideally between 72 and 96 hours after birth. In 2019 the percentage of first heel pricks carried out within 168 hours after birth is 98.4%. This is lower than in 2017 (98.8%) and 2018 (98.6%). The target value of at least 99.0% has not been achieved, as in previous years (figure 4). In 38% of children, newborn blood spots were collected in the recommended period between 72 and 96 hours after birth.

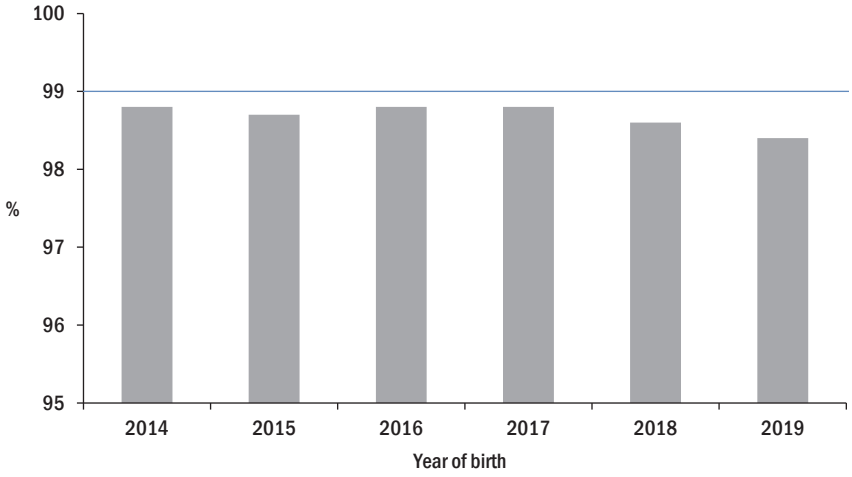

Figure 4
Timeliness of the blood spot collection by year of birth (2014-2019). Children born outside the Netherlands are excluded (the blue line indicates the target value; to support readability the y-axis starts at 95%)

TIMELINESS RECEIPT OF HEEL PRICK CARDS IN THE LABORATORY

From 2019 onwards, the percentage of timely received heel prick cards in the laboratory will also be reported, because timely receipt is an important precondition for a timely analysis and, if necessary. referral, diagnosis and treatment. The desired interval between carrying out the heel prick and its receival in the laboratory is three days or less.

Of all heel pricks cards collected in 2019, 94.9% were received by the laboratory on time (≤3 days after collection).

OBJECTIONS AGAINST STORAGE OF NEWBORN BLOOD

In 2019 6.6% of parents objected against the storage of the NBS blood remnants for the purpose of (anonymous) scientific research. This percentage shows a steady upward trend from 4.9% in 2014 to 6.6% in 2019 (figure 5).

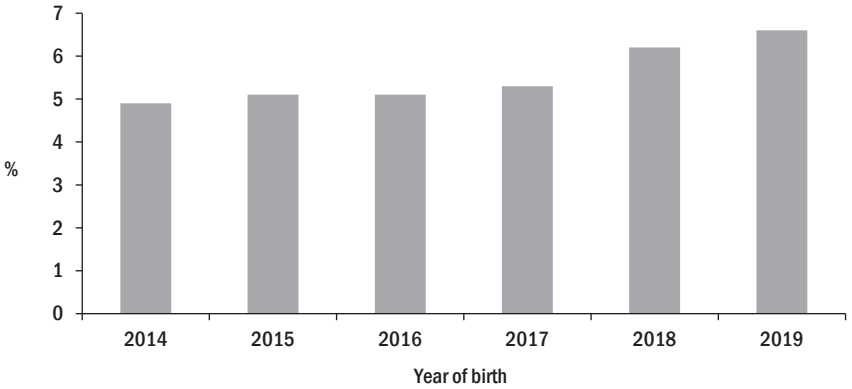

Figure 5
Objection of parents against the storage of NBS remnants for anonymous scientific research, by year of birth (2014-2019)

REPEAT FIRST HEELPRICK

Some of the blood spot collections need to be repeated, for example because insufficient blood was collected on the heel prick card. From 2016, there has been a decreasing trend in the percentage of repeated first heel pricks for most conditions. In 2019, the target values were again achieved for all conditions.

Table 1
Repeat first heelpricks* according to birth year (2014-2019)

% of repeat 1st heelpricks		2014	2015	2016	2017	2018	2019	Number in 2019	Target value
CAH		0.10	0.09	0.10	0.09	0.08	0.06	108	≤0.50
CH		0.38	0.56	0.55	0.503	0.42	0.27	465	≤0.50
CF		0.48	0.58	0.61	0.52	0.42	0.30	511	≤0.50
HbP		0.71	0.82	0.82	0.70	0.59	0.47	798	≤0.80
MD	3-MHM	0.17	0.20	0.22	0.20	0.18	0.18	299	≤0.50
	BIO	0.42	0.51	0.54	0.46	0.37	0.29	494	≤0.50
	CPT1						0.15	70	≤0.50
	GALT	0.31	0.31	0.27	0.23	0.18	0.15	249	≤0.50
	GA-1	0.17	0.20	0.22	0.20	0.18	0.18	299	≤0.50
	IVA	0.17	0.20	0.22	0.20	0.18	0.18	299	≤0.50
	MSUD	0.14	0.18	0.18	0.17	0.14	0.12	207	≤0.50
	MCADD	0.17	0.20	0.22	0.20	0.18	0.18	299	≤0.50
	MMA						0.15	69	≤0.50
	PA						0.15	68	≤0.50
	PKU	0.14	0.14	0.18	0.17	0.14	0.12	207	≤0.50
	TFP/LCHAD	0.17	0.20	0.22	0.20	0.18	0.18	299	≤0.50
	TYR-1	0.14	0.18	0.18	0.17	0.14	0.12	207	≤0.50
	VLCAD	0.17	0.20	0.22	0.20	0.18	0.18	299	≤0.50
	OCTN2	0.14	0.18	0.18	0.17	0.14	0.12	205	≤0.50

*Based on 'unclassifiable' result i.e. insufficient/unreliable blood or <24 hours after blood transfusion. Heel pricks that were carried out too early (n=22 in 2019) are not included.

SECOND HEELPRICK

In 2019 0.042% of the CAH results of the first heel prick indicated the need for a second heel prick. This means that the target value for this indicator (≤0.09%) was reached (table 2).

In 2019 0.36% of the CH results of the first heel prick indicated the need for a second heel prick. The target value for this indicator (≤0.50%) was also reached.

Table 2
Second heelprick according to birth year (2014-2019)

% of second heel pricks	2014	2015	2016	2017	2018	2019	Number in 2019	Target value
AGS	0.070	0.079	0.078	0.065	0.072	0.042	(72)	≤0.09
CH	0.74	0.82	0.53	0.21	0.36	0.36	(609)	≤0.50
OCTN2[1]			0.034	0.032	0.045	0.054	(92)	≤0.04

[1] OCNT2 is an incidental finding, but an abnormal C0 level can cause other metabolic diseases to be missed. Therefore, in case of an inconclusive result for OCTN2, a second heel prick is also performed. The table shows an increase in the percentage of second heel pricks in 2018 and 2019. The target value (≤0.04%) was not achieved in 2019. No target value was used in previous years.

REFERRALS

In 2019 the NBS resulted in 500 referrals (table 3). This includes 24 referrals for the incidental finding OCTN2.[1] This gives a referral rate of 0.29% of the total number of screened children in 2019. This is comparable to 2017 and 2018.

The referral rate for GALT is low in 2019 compared to previous years. This favourable decrease can possibly be explained by a change in the cut-off limits for GALT per 1-1-2019.

Table 3
Referrals according to birth year (2014-2019)

% referrals		2014	2015	2016	2017	2018	2019[6]	Number in 2019	Trend
CAH		0.013	0.015	0.015	0.016	0.016	0.012	(21)	stable
CH		0.22	0.31	0.21	0.13	0.15	0.15	(251)	fluctuates
CF		0.019	0.020	0.026[1]	0.016	0.021	0.022	(38)	fluctuates
HbP[2]		0.040	0.027	0.035	0.023	0.032	0.032	(54)	stable
	SCD[2]				0.014	0.018	0.024	(40)	
	HbH[2]				0.005	0.007	0.006	(11)	
	bTM[2]				0.004	0.007	0.002	(3)	
MD	3-MHM	0.004	0.004	0.003	0.005	0.009	0.006	(10)	stable
	BIO	0.007	0.011	0.010	0.018	0.013	0.010	(17)	fluctuates
	CPT1[4]						0.002	(1)	-
	GALT	0.035	0.041	0.019[3]	0.021	0.025	0.004[3]	(7)	2019 low[3]
	GA-1	0.001	0.001	0.001	0.001	0	0.002	(4)	stable
	IVA	0.002	0.001	0.004	0.002	0.002	0.002[7]	(3)	stable
	MSUD	0.005	0.007	0.012	0.010	0.002	0.003[7]	(5)	fluctuates
	MCADD	0.012	0.011	0.012	0.011	0.012	0.013	(22)	stable
	MMA[4]						0.013	(6)	
	PA[4]						0.009	(4)	
	PKU	0.011	0.012	0.012	0.008	0.010	0.008[7]	(14)	stable
	TFP/LCHAD	0.001	0.001	0	0.001	0.001	0.002	(3)	stable
	TYR-1	0.001	0.002	0.002	0.002	0.001	0.002	(4)	stable
	VLCAD	0.003	0.011	0.005	0.011	0.008	0.007	(12)	fluctuates
	OCTN2[5]	0.006	0.005	0.012	0.009	0.011	0.014	(24)	fluctuates
Total referral rate		0.38	0.48	0.37	0.29	0.31	0.29	(500)	

[1] CF: possibly due to change of reference values for CF per 1-7-2016.
[2] HbP: Until and including 2016: Concerns HPLC patterns appropriate to sickle cell disease, and incidental findings of alpha-thalassemia and beta-thalassemia. From 1-1-2017, HbH-disease and beta-thalassemia major also belong to the target group diseases of screening and are reported accordingly.
[3] GALT: Possibly as a result of adapted reference values for GALT per 1-7-2015 and 1-1-2019.
[4] These metabolic diseases were added to the screening per 1-10-2019. The denominator in the calculation of the referral figure therefore only concerns 3 months.
[5] OCTN2: is not part of the screening programme but is included in the calculation of the total referral rate.
[6] In 2019, not a single child with an abnormal result died before a referral could take place.
[7] From 1-1-2018 the screening laboratories are using new equipment and analysis kits. As a precautionary measure, until April 2019 (in order to ensure that no patients are missed), an area just below the cut-off limit was used to see whether referral was appropriate. This resulted in 3 additional referrals in 2019 (one each for PKU, MSUD and IVA). The numbers include these referrals.

[1] OCTN2 is not a target disease of the screening programme but is an incidental finding. Nevertheless, the C0 level is determined for each child, because a possible deficiency makes the acylcarnitine profile unreliable, which may cause that children with the metabolic diseases MCADD, VLCAD, TFP/LCHAD, IVA, GA-1 and 3-MHM remain undetected.

DIAGNOSTIC RESULTS

In 2019, a total of 476 children (excluding 24 referrals for OCTN2) were referred for a target condition that is part of the screening programme. In 211 (44%) cases one of the conditions was confirmed (table 4). This is higher than in 2018 (37%).[1]
Children with a referral for OCTN2 deficiency (n=24, of which two were diagnosed with OCTN2) are not included in these numbers, because this condition is not a target condition of the screening programme, but an incidental finding.

In 2019, three children were reported with a false negative result for CH and one with a false negative result for VLCAD (table 4). Possible false negative results have also been reported in five children born in the period 2013-2018 (1 with CH, 1 with classic CAH non-salt-wasting form, 1 with both CF and CH[2] and 2 with CF). The false negative results have been confirmed in all children except for the child with CAH. This result is not considered false negative, because in 2017 (when the child was born) only classic CAH with the salt-wasting form was considered a target disease.

Table 4
Diagnostic results of referred children born in 2019[1]

2019		Referred	Diagnosis confirmed	No target disease	Diagnosis (still) unknown	False-negative (test improperly indicates no need for referral)	Missed/ other
CAH		21	12[2]	6	3	0	0
CH		251	72	154	25[3]	3	0
CF		38	31[4]	7	0	0	0
HbP	SCD	40	40	0	0	0	0
	HbH	11	6	5[5]	0	0	0
	bTM	3	2	1[6]	0	0	0
MD	3-MHM	10	5	5	0	0	0
	BIO	17	4	12	1	0	0
	CPT1[7]	1	0	0	1	0	0
	GALT	7	4	3	0	0	0
	GA-1	4	0	4	0	0	0
	IVA	3	0	3	0	0	0
	MSUD	5	0	5	0	0	0
	MCADD	22	21	1	0	0	0
	MMA[7]	6	1	4	1	0	0
	PA[7]	4	1	2	1	0	0
	PKU	14	10	2	2	0	0
	TFP/LCHAD	3	0	3	0	0	0
	TYR-1	4	0	3	1	0	0
	VLCAD	12	2	9	1	1	0
Total		476	211	229	36	4	0

[1] This table does not include referrals for OCTN2-deficiency (n=24, two confirmed). Since 2018, both the classic salt-wasting form and the classic non-salt-wasting form of CAH are considered as a target condition.
[2] CAH: 11 children have the classic salt-wasting form and one child has the classic non-salt-wasting form.
[3] CH: from 16 children the diagnosis is (still) unknown, and from 9 children the diagnostic data are not registered in NEORAH.
[4] CF: including 4 children with meconium ileus.
[5] HbH: mild alpha-thalassemia.
[6] bTM: mild bèta-thalassemia (HBEE).
[7] Per 1-10-2019, the conditions CPT1, MMA and PA are added to the heel prick screening. The definition of the target disease is still under review for MMA: the diagnostic results may change.

[1] Last year, many diagnostic data on CH were missing (n=112, 45%). Therefore, the percentage of all referrals with a confirmed diagnosis (29%) was difficult to interpret. This year, the data on CH from 2018 has been largely supplemented (94%) and the percentage for 2018 has been recalculated.
[2] This child (with a false negative result for both CH and CF) from 2017 was already discovered in 2018 but was not registered in Neorah for (still) unknown reasons. For this reason, the child was reported only this year in the monitor.

DETECTION RATES AND VALIDITY

Table 5 shows the detection rates (per 1000 screened children), the positive predictive value (PPV), the sensitivity (Sens) and Specificity (Spec) of the programme.
The detection rates are comparable to that of previous years for most conditions (stable since 2015). In 2018, many diagnostic data for CH were missing, and therefore the validity could not be properly interpreted. A new calculation has been made since the data are now almost completed. It is noteworthy that the detection rate in 2018 is very low (0.338, not in table) compared to the past five years (average: 0.411). In 2019, the detection rate is again around the average (0.423).

The positive predictive value (PPV) target values have been reached for CAH (>15%), CH (>15%), CF (>65%), SCD (>90%), PKU (>60%) and MCADD (>70%) in 2019. The total PPV (48%) is higher than in the period 2015-2018 (between 24% and 42%). The difference is mainly because there were fewer referrals and false positive results for GALT in 2019. The PPV for GALT was between 1% and 7% in the period 2015-2018 and in 2019 it was 57%. Also, a higher PPV for CAH, CH, CF and SCD contributed to a higher total PPV.

In 2019, the sensitivity target values were not achieved for CH due to three false negative results and for VLCAD due to one false negative result. The target values for specificity have been achieved for all conditions. New false negative results have also been reported for children born in the period 2015-2018 for CH (1x) and CF (3x). Consequently, the sensitivity is lower than the target value of 100%.

Table 5
Detection rate, positive predictive value (PPV), sensitivity (Sens) and specificity (Spec) in children born in 2019 and the period 2015-2019[1,2]

		2019				2015-2019[3]				Trend detection rate 2015-2019
		Detection rate (per 1000)	PPV[3] (%)	Sens (%)	Spec (%)	Detection rate (per 1000)	PPV (%)	Sens (%)	Spec (%)	
CAH		0.070	67	100	99.996	0.052	38	100	99.992	stable
CH		0.423	32	96	99.909[4]	0.411	24	98.592	99.871	stable
CF	excl. MI	0.159	79	100	99.996	0.124	68	92.983	99.994	stable
	incl. MI	0.182	82	100	99.996	0.151	72	94.161	99.994	stable
HbP	SCD	0.235	100	100	100	0.175	98	100	100	stable
	HbH[3,6]	0.035		100	99.997	0.018	29	100	99.996	stable[3]
	bTM[3,6]	0.012		100	99.999	0.024	57	100	99.998	stable[3]
MD	3-MHM[6]	0.029		100	99.997	0.020	39	100	99.997	stable
	CPT1[4,5]	-		-	-	-	-	-	-	-
	BIO[6]	0.024		100	99.993	0.021	17	100	99.990	stable
	GALT[6]	0.024		100	99.998	0.011	5	100	99.979	stable
	GA-1[6]	0		-	99.998	0.001	11	100	99.999	stable
	IVA[6]	0		-	99.998	0.013	65	100	99.999	stable
	MSUD[6]	0		-	99.997	0.005	7	100	99.994	stable
	MCADD	0.123	95	100	99.999	0.110	94	100	99.999	stable
	MMA[4]	0.022	20	100	99.991	-	-	-	-	-
	PA[4]	0.022	33	100	99.996	-	-	-	-	-
	PKU	0.059	83	100	99.999	0.085	90	100	99.999	stable
	TFP/LCHAD[6]	0		-	99.998	0.002	22	100	99.999	stable
	TYR-1	0		-	99.998	0.005	25	100	99.999	stable
	VLCAD	0.012	18	67	99.995	0.026	33	95.652	99.995	stable
Total		1.241	48	98	99.865	1.104	36	98.543	99.803	

[1] Since 2018, the PPV, Sens and Spec of five years combined are calculated, because for some conditions only few children are found per year. For these conditions a calculation over several years gives a more stable outcome.
[2] The incidental finding OCTN2 is not included in this table.
[3] The data pertaining to HbH-disease and bTM are from the period 2017-2019. These conditions were added to the screening programme in 2017.
[4] Per 1-10-2019, the conditions CPT1, MMA and PA are added to the heel prick screening. These have not yet been included in the 5-year average. The definition of the target disease is still under review for MMA: the diagnostic results may change.
[5] In 2019 there was one referral for CPT1, but the diagnosis is (still) unknown.
[6] Only a few children per year are referred for HbH, bTM and for many of the metabolic diseases. There are therefore no target values for the PPV of these diseases.

TIMELINESS DIAGNOSTICS

The timeliness of diagnosis is calculated based on all referred children.

The target values for the conditions CAH, CH and CF were not achieved in 2019 (table 6). For CF there was a sharp decrease in 2019 in children who were seen in time. The target value for MD was achieved for the first time since 2017.

Table 6
Timeliness of diagnostic results in children born in 2019

Screening	2017	2018	2019	Target value
CAH	81	77	86	≥90%<15 days
CH	85	84	86	≥90%<15 days
CF all referrals	85	77	58	≥90%<30 days
excl. MI[1]	86	74	53	≥90%<30 days
HbP[2]	97	91	100	≥90%≤12.0 weeks
MD[3]	74	76	91	≥90%<10 days (most MD) or <14 d (PA/MMA)

[1] Calculated on all children referred for CF excluding children with meconium ileus (MI).
[2] All children referred for HPLC patterns matching with sickle cell disease, HbH-disease and beta-thalassemia.
[3] OCTN2 excluded.

COSTS

The costs of the screening programme (excluding diagnostics) were about 17.1 million euro in 2019 (source: Final bill NBS, RIVM-CvB, excluding the costs for Caribbean Netherlands). Screening costs per child are approximately 100 euro. Since 2015, the costs per screened child have increased by about 3.3% per year. This increase is mainly due to indexation of the costs for blood collection, the heel prick set and laboratory analysis, and by adding three new conditions (CPT1, MMA and PA) to the NBS.

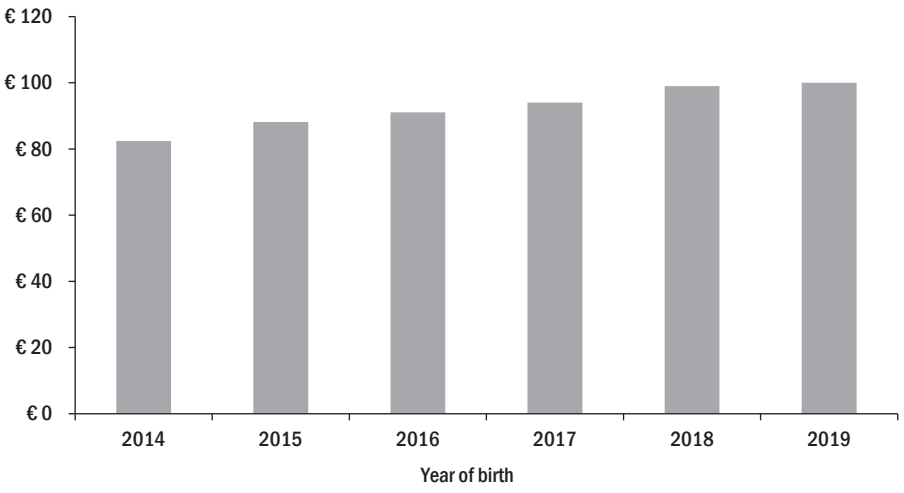

Figure 6
Costs of the screening programme per screened child according to year of birth (2014-2019)

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