THE NEWBORN BLOOD SPOT SCREENING IN THE NETHERLANDS

MONITOR 2020

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 several 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.
During the COVID-19 pandemic, which affected the Netherlands from March 2020, the heel prick screening continued, because most target diseases must be detected as soon as possible after birth to prevent serious health damage. The RIVM-DVP monitored weekly whether there were any particularities related to COVID-19. Also, appointments with care givers were more often online or by telephone.

The national monitor with main results of the NBS is carried out annually by TNO at 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).

This monitor concerns the heel prick screening of children born in 2020.

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

- In the year 2020, the COVID-19 pandemic started in the Netherlands. The heel prick screening was not postponed, because most target diseases must be detected as soon as possible after birth.
- Despite the COVID-19 pandemic, the results of most of the indicators are still within 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 99.4% in 2020 (n=168,683) and is above the target value of 99.0%. Despite the pandemic, the participation rate has increased slightly compared to 2019 (99.3%).
- 450 children were referred from the neonatal heel prick screening (0.27%). At least 175 of them had one of the target diseases.
- In 2020 the total screening programme has a **detection rate** of 1.037 per 1000 screened children, a **positive predictive value** of 42%, a **sensitivity** of 99% and a **specificity** of 99.854%. The positive predictive value is lower than in 2019 (47%), but comparable to the average in 2016-2019 (40%).
- The target values set for the **specificity** of each screening are met for all conditions. This is almost true for the **positive predictive value,** only for CF the target value of >65% has not been achieved (59% excl. meconium ileus (MI), 64% incl. MI). Two children born in 2020 were reported as false negative (1 for CH, 1 for CF). Thus, the target values for sensitivity of CH and CF were not reached.
  Five children born before 2020 were also reported as cases that were not detected by the screening: TYR-1, CAH (2x), SCD and CF (respectively from 2010, 2014/2018, 2019 and 2014).
- The **timeliness target value** of the 1st heel prick (99.0%) was **not reached:** 98.5% was carried out within 168 hours after birth. 40% of the heel pricks was performed in the recommended period of 72-96 hours after birth. The pandemic does not seem to have had a negative impact on the timeliness.

- Of all heel pricks administered in 2020, 94.9% of the **heel prick cards** were **received** by the laboratory **on time** (≤3 days after collection).
- In 2020, the target value for the percentage of children who had to have a **repeated first heel prick** (≤0.50%) was achieved for all conditions.
- **CH:** it is notable that the **detection rate** in 2020 (0.037%) and 2018 (0.036%) is lower compared to 2019 (0.042%) and the period 2010-2017 (average: 0.044%).
- The target values for **timeliness of diagnostics (≥90%)** were achieved in 2020 for CAH (90%), but not for CH (88%), CF incl. MI (77%), HbP (81%) and MD (89%).
- In 2020 **screening costs** per child (diagnostic costs excluded) were €113. This is higher than in 2019 (€100), which is not only because of the indexation of the rates for blood sampling and laboratory analyses. Due to the preparation for the expansion of the heel prick screening with MPS1 and SCID, laboratory personnel increased in numbers and material costs rose. In addition, regular staff were deployed in 2020 for COVID-19 diagnostics, and relatively more expensive temporary workers were deployed for the heel prick screening.
- The number of parents who **object** to the **storage of blood remnants** for anonymous scientific research in 2020 is 7.1%. In 2015 this was 5.1%.

RECOMMENDATIONS

Existing recommendations that are still valid:
- Maintain or intensify actions to improve **timeliness of the first heel prick.**
- Improve the **timeliness of diagnostics** for CH, MD, HbP and CF.
- Continued attention is necessary for **timely and clear registration** of diagnostic data.

New recommendation:
- Of the seven children not detected through screening reported in the past year, the cause is still unknown for four children (1 with CH from 2020, 1 with CAH from 2018, 1 with CF from 2014 and 1 with TYR-1 from 2010). It is desirable to investigate why these children were missed by screening and to discuss whether this can be prevented.

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 diagnostic CH data were 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 2020** (Praeventis reference data: 11-3-2021, NEORAH: 2-7-2021 or later[3]).

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 hours before the heel

[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 (see draaiboek hielprikscreening (in Dutch)– Kinderarts). The NSCK signalling system (which was used until 1-1-2020) has been discontinued.
[3] The reference date was 3-8-2021 for CH, 9-8-2021 for HbP, 19-8-2021 for CF and 8-10-2021 for missed children.

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.

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.

DIFFERENCES IN CUT-OFF VALUES COMPARED TO PREVIOUS MONITORS AND THE ADDITION OF GALK-SCREENING

- As of January 27, 2020, the cut-off limits for the BIO screening have changed; the result is 'abnormal' if biot is ≤ 10% compared to the daily average (was ≤ 20%). At biot >10% en ≤ 20%, the result is unclassifiable and a repeated first heel prick (RFH) should be carried out. A RFH with a biot ≤ 20% is abnormal.
- Per May 1, 2020, the cut-off limits have been changed for the PA-screening: MCA≥2.0 µmol/l is abnormal (MCA was ≥1.0 µmol/l).
- As of June 1, 2020, there was a renewal in analysis equipment and kit for the GALT-screening. The cut-off limit has therefore been changed: TGAL≥1350 µmol/l is abnormal (this was ≥1600 µmol/l).
- The screening for GALK has been introduced per October 1st, 2020. The result is abnormal when TGAL≥2100 µmol/l and GALT>2.0 U/dl blood.

WHICH CONDITIONS ARE INCLUDED IN THE SCREENING?

- Congenital adrenal hyperplasia **(CAH)**
- Cystic fibrosis **(CF)**
- Congenital hypothyroidism **(CH)**
- Hemoglobinopathies **(HbP)**:
  - Sickle cell disease (**SZ**)
  - 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 deficiency type 1 **(CPT1)**
  - Galactokinase deficiency **(GALK)**[2]
  - Galactosemia **(GALT)**, formerly called 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 **(MCADD)**
  - Methylmalonic acidemia **(MMA)**
  - Multiple CoA carboxylase deficiency **(MCD)**[1]
  - Phenylketonuria **(PKU)**
  - Propionic Acidemia **(PA)**
  - 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] This condition was added to the screening programme on 1-10-2020.
[3] OCTN2-deficiency is not part of the NBS: it is considered an incidental finding.

PARTICIPATION

In 2020 169,734 children were eligible to participate in the NBS. A heel prick was performed on 168,683 children. This means that the participation rate in 2020 is 99.4%, which is higher than the target percentage of 99.0% and is also higher than it was in the period 2015 to 2019 (Figure 2). The increase compared to the years 2015-2018 is partly (estimated: 0.1%) due to an optimization of the calculation.[1]

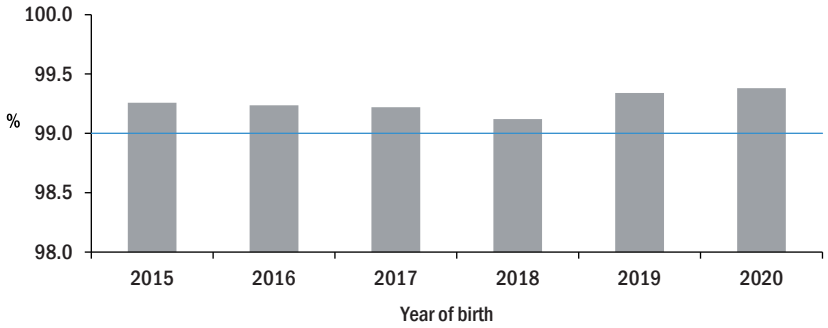

Figure 2
Participation rate of the neonatal screening programme by year of birth (2015-2020); to support readability the y-axis starts at 98%; the blue line indicates the target value.

Figure 3 shows that parents object more often (0.42% in 2020 versus 0.38% in 2019), but that the percentage of children who did not participate for an unknown reason decreased (0.01% in 2020, 0.03% in 2019, 0.11% in 2018). This decrease is partly caused by an optimisation of the calculation.[1] The number of heel pricks performed abroad has also decreased.

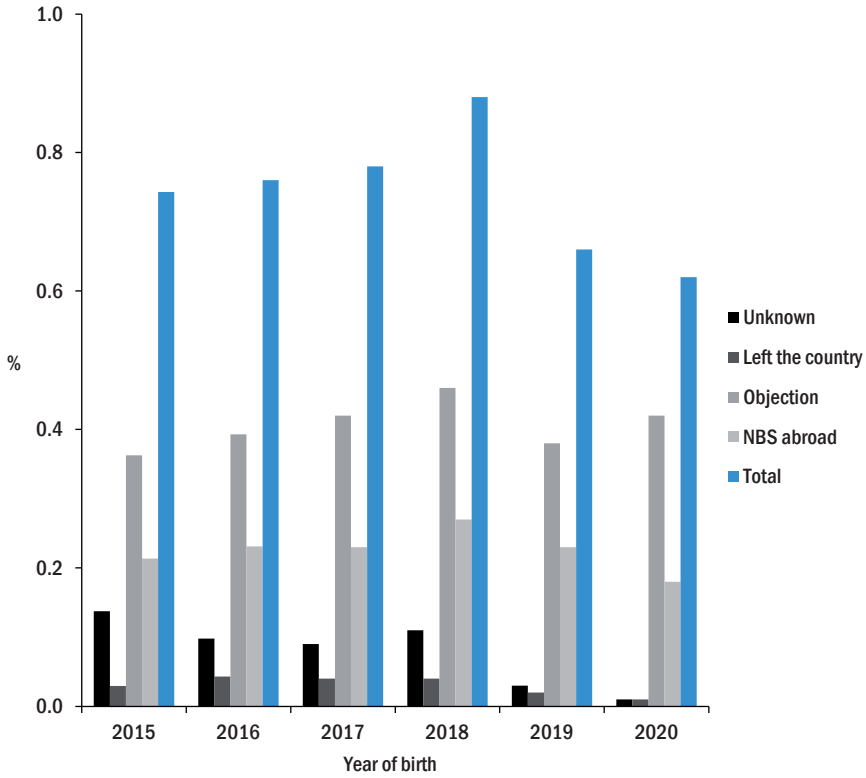

Figure 3
Reasons for non-participation in the neonatal screening programme by year of birth (2015-2020)

[1] Children who received a first heel prick twice were sometimes incorrectly classified as non-participants. From 2019 onwards extra checks have been build in to prevent this. See the report 'Evaluation of neonatal heel prick screening in children born in 2020 (in Dutch)' for details.

TIMELINESS OF BLOOD COLLECTION

The heel prick should be carried out within 168 hours (7 days) after birth, but ideally between 72 and 96 hours after birth. In 2020 the percentage of first heel pricks carried out within 168 hours after birth is 98.5% (excluding children born abroad). This is higher than in 2019 (98.4%), but lower than in 2018 (98.6%) and 2017 (98.8%). The target value of at least 99.0% still has not been achieved (figure 4). In 40% of children, newborn blood spots were collected in the recommended period between 72 and 96 hours after birth. Late birth registration and weekend days can make timely screening difficult.

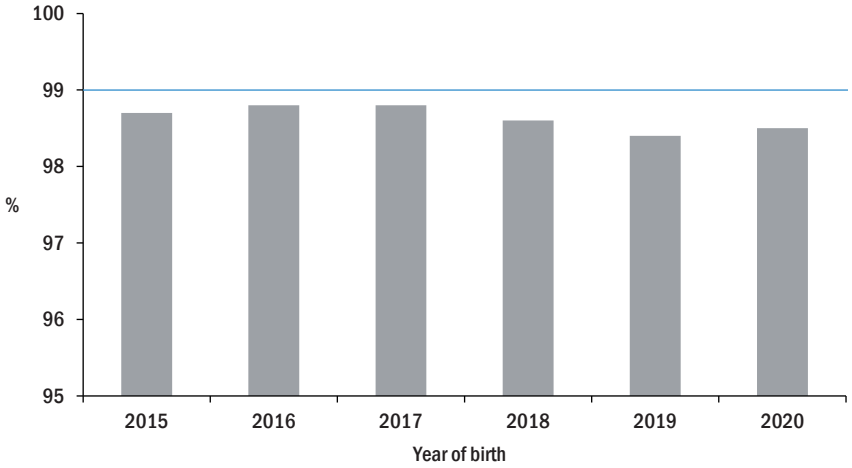

Figure 4
Timeliness of the blood spot collection by year of birth (2015-2020). Children born outside the Netherlands are excluded (the blue line indicates the target value; to support readability the y-axis starts at 95%)

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 2020, 94.9% were received by the laboratory on time (≤3 days after collection). This is equal to the percentage in 2019.

OBJECTIONS AGAINST STORAGE OF NEWBORN BLOOD

In 2020 7.1% of parents objected against the storage of the NBS blood remnants for the purpose of (non-deductible) scientific research. This percentage shows a steady upward trend from 5.1% in 2015 to 7.1% in 2020 (figure 5). The provision of information to parents about the storage of the blood remnants will be improved.

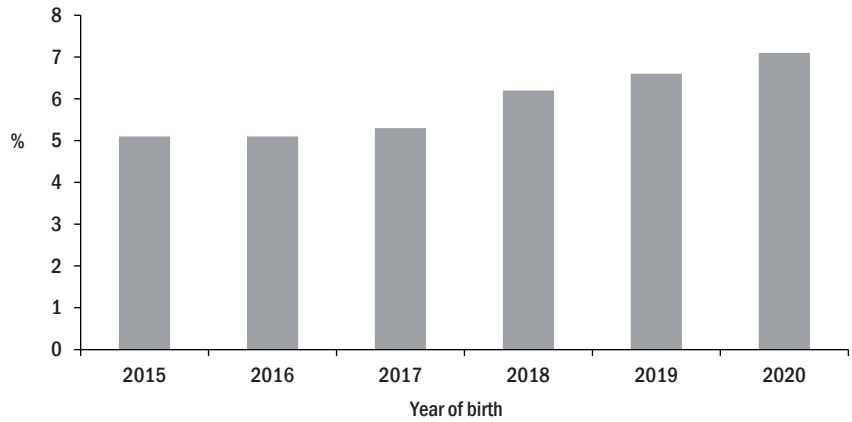

Figure 5
Objection of parents against the storage of NBS remnants for anonymous scientific research, by year of birth (2015-2020)

REPEAT FIRST HEEL PRICK

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 (table 1). In 2020, the target values were again achieved for all conditions.

Table 1
Repeat first heel pricks* according to birth year (2015-2020)

% of repeat first heel pricks		2015	2016	2017	2018	2019	2020	Number in 2020	Target value
CAH		0.09	0.10	0.09	0.08	0.06	0.04	62	≤0.50
CH		0.56	0.55	0.503	0.42	0.27	0.22	371	≤0.50
CF		0.58	0.61	0.52	0.42	0.30	0.24	406	≤0.50
HbP		0.82	0.82	0.70	0.59	0.47	0.43	724	≤0.80
MD	3-MHM	0.20	0.22	0.20	0.18	0.18	0.12	206	≤0.50
	BIO	0.51	0.54	0.46	0.37	0.29	0.26	432	≤0.50
	CPT1					0.15	0.12	206	≤0.50
	GALK						0.10	45	≤0.50
	GALT	0.31	0.27	0.23	0.18	0.15	0.11	189	≤0.50
	GA-1	0.20	0.22	0.20	0.18	0.18	0.12	207	≤0.50
	IVA	0.20	0.22	0.20	0.18	0.18	0.12	207	≤0.50
	MSUD	0.18	0.18	0.17	0.14	0.12	0.09	158	≤0.50
	MCADD	0.20	0.22	0.20	0.18	0.18	0.12	208	≤0.50
	MMA					0.15	0.12	208	≤0.50
	PA					0.15	0.12	208	≤0.50
	PKU	0.14	0.18	0.17	0.14	0.12	0.09	158	≤0.50
	TFP/LCHAD	0.20	0.22	0.20	0.18	0.18	0.12	207	≤0.50
	TYR-1	0.18	0.18	0.17	0.14	0.12	0.09	158	≤0.50
	VLCAD	0.20	0.22	0.20	0.18	0.18	0.12	207	≤0.50
	OCTN2	0.18	0.18	0.17	0.14	0.12	0.10	163	≤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=25 in 2020) are not included.

SECOND HEEL PRICK

In 2020 0.049% of the CAH-results of the first heel prick indicated the need for a second heel prick. For CH and OCTN2, this was 0.28% and 0.027% respectively. The target values for this indicator (≤0.09% for CAH, ≤0.50% for CH and ≤0.04% for OCTN2) were reached for all three conditions (table 2).

Table 2
Second heel prick according to birth year (2015-2020)

% of second heel pricks	2015	2016	2017	2018	2019	2020	Number in 2020	Target value
CAH	0.079	0.078	0.065	0.072	0.042	0.049	(83)	≤0.09
CH	0.82	0.53	0.21	0.36	0.36	0.28	(472)	≤0.50
OCTN2[1]		0.034	0.032	0.045	0.054	0.027	(45)	≤0.04

[1] OCTN2 is an incidental finding. In the event of an inconclusive result for OCTN2, a second heel prick is performed. If both results are inconclusive, the child will be referred. In that case, other metabolic disorders with a screening based on acylcarnitines are unclassifiable and are further examined in the hospital. No target value was used in the years 2015-2018.

REFERRALS

In 2020, a total of 450 referrals were made as a result of the heel prick (table 3). This includes 13 referrals for the incidental finding OCTN2. This gives a total referral rate of 0.27% of the number of screened children in 2020. This is slightly lower than in previous years.

The referral rate for TYR-1 is slightly higher (0.005%) in 2020 than in previous years (0.001-0.002% in 2014-2019). The referral rate for BIO is low (0.005%) in comparison to previous years. This may be due to a change in the cut-off limits for TYR-1 (per 1-4-2019) and BIO (per 27-1-2020).

Table 3
Referrals according to birth year (2015-2020)

% referrals		2015	2016	2017	2018	2019	2020	Number in 2020	Trend
CAH		0.015	0.015	0.016	0.016	0.012	0.012[1]	21	stable
CH		0.31	0.21	0.13	0.15	0.15	0.14[2]	228	stable since 2017
CF		0.020	0.026	0.016	0.021	0.022	0.016	27	fluctuates
HbP[3]	*subtotal*	*0.027*	*0.035*	*0.023*	*0.032*	*0.032*	*0.022*	*37*	
	SCD[3]	0.016	0.017	0.014	0.018	0.024	0.014	24	fluctuates
	HbH[3]			0.005	0.007	0.006	0.004	6	stable
	bTM[3]			0.004	0.007	0.002	0.004	7	stable
MD	*subtotal*	*0.105*	*0.091*	*0.098*	*0.095*	*0.079*	*0.081*	*137*	
	3-MHM	0.004	0.003	0.005	0.009	0.006	0.007	11	stable
	BIO	0.011	0.010	0.018	0.013	0.010	0.005[4]	8	2020: decrease
	CPT1					0.002[5]	0.001	2	-
	GALK						0.001[6]	1	-
	GALT	0.041	0.019[7]	0.021	0.025	0.004[7]	0.006	10	2019 and 2020: decrease
	GA-1	0.001	0.001	0.001	0	0.002	0.001	2	stable
	IVA	0.001	0.004	0.002	0.002	0.002	0.004	6	stable
	MSUD	0.007	0.012	0.010	0.002	0.003	0.002	4	fluctuates
	MCADD	0.011	0.012	0.011	0.012	0.013	0.013[1]	22	stable
	MMA					0.013[5]	0.014	23	-
	PA					0.009[5]	0.001	2	-
	PKU	0.012	0.012	0.008	0.010	0.008	0.007	11	stable
	TFP/LCHAD	0.001	0	0.001	0.001	0.002	0.001	2	stable
	TYR-1	0.002	0.002	0.002	0.001	0.002[8]	0.005[8]	8	2020: increase
	VLCAD	0.011	0.005	0.011	0.008	0.007	0.007	12	fluctuates
	OCTN2[9]	0.005	0.012	0.009	0.011	0.014	0.008	13	fluctuates
Total referral rate		0.48	0.37	0.29	0.31	0.29	0.27	450	

[1] CAH and MCADD: excluding a child who died before a referral could take place.
[2] CH: excluding four children with an abnormal result who died before referral.
[3] HbP: From 1-1-2017 HbH-disease and beta-thalassemia major also belong to the target group diseases of screening in addition to sickle cell disease.
[4] BIO: possibly as a result of adapted reference values for BIO per 27-1-2020.
[5] 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.
[6] The metabolic disease GALK was added to the screening per 1-10-2020. The denominator in the calculation of the referral figure is therefore 3 months.
[7] GALT: possibly as a result of adapted reference values for GALT per 1-7-2015 and 1-1-2019.
[8] TYR-1: possibly as a result of adapted reference values per 1-4-2019.
[9] OCTN2: is not a target disease of the screening programme but is included in the calculation of the total referral rate.

[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 2020, 437 children (excluding OCTN2) were referred for a target disease of the screening programme. In 175 (40%) cases one of the conditions was confirmed (table 4). This is lower than in 2019 (44%). Children with a referral for OCTN2 deficiency (n=13, 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.

Of the children born in 2020, one child was reported with a false-negative result for CH. Also, a false-negative result for CF was reported in a child who had the heel prick taken at 12 weeks of age (table 4, see also footnote 9).

Table 4
Diagnostic results of referred children born in 2020[1]

2020		Referred	Diagnosis confirmed	No target disease	Diagnosis (still) unknown	False-negative (test wrongly indicates no need for referral)[10]	Missed/ Other[10]
CAH		21	11[2]	8[3]	2	0	0
CH		228	63	155	10	1	0
CF		27	16[4]	9	2	1[9]	0
HbP	SCD	24	22	1	1	0	0
	HbH	6	3	3[5]	0	0	0
	bTM	7	3	4[6]	0	0	0
MD	3-MHM	11	7	4	0	0	0
	BIO	8	3	5	0	0	0
	CPT1[7]	2	0	2	0	0	0
	GALK[9]	1	0	1			
	GALT	10	4	6	0	0	0
	GA-1	2	0	2	0	0	0
	IVA	6	2	4	0	0	0
	MSUD	4	0	4	0	0	0
	MCADD	22	19	3	0	0	0
	MMA[7]	23	4	18	1	0	0
	PA[7]	2	1	1	0	0	0
	PKU	11	10	1	0	0	0
	TFP/LCHAD	2	0	2	0	0	0
	TYR-1	8	2	6	0	0	0
	VLCAD	12	5	7	0	0	0
Total		437	175	246	16	2	0

[1] This table does not include referrals for OCTN2-deficiency (n=13, of which two confirmed with OCTN2).
[2] CAH: Since 2018 both classic salt-wasting CAH as well as classic non-salt-wasting CAH are considered as a target condition. In 2020 9 children had classic salt-wasting CAH and two children had classic non-salt-wasting CAH.
[3] Of which 1 child with non-classical CAH.
[4] CF: including 3 children with meconium ileus.
[5] HbH: all with mild alpha-thalassemia.
[6] bTM: of which four with a mild form of beta-thalassemia.
[7] Per 1-10-2019 the conditions CPT1, MMA and PA have been added to the heel prick screening. The definition of the target disease is still under review for MMA: the diagnostic results may change.
[8] The metabolic disease GALK has been added to the heel prick screening per 1-10-2020.
[9] This child was already familiar with CF through screening abroad and was already in treatment. After arriving in the Netherlands, he/she received a heel prick at the age of 12 weeks, resulting in a false negative result for CF. The pediatrician stated that this was not due to the treatment, but that IRT values can decrease with age. The limited sensitivity of the IRT determination was already known in children older than 3 months, but this child is less than 3 months old and is therefore considered false negative.
[10] False-negative (when a test wrongly indicates no need for referral) refers specifically to children who have not been detected by the screening test. Missed patients for other reasons (e.g. administrative) fall under the indicator missed/other.

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.

Table 5
Detection rate, positive predictive value (PPV), sensitivity (Sens) and specificity (Spec) in children born in 2020 and the period 2016-20201.2

		2020				2016-2020[3]				Trend detection rate 2016-2020
		Detection rate (per 1000)	PPV (%)	Sens (%)	Spec (%)	Detection rate (per 1000)	PPV (%)	Sens (%)	Spec (%)	
CAH		0.065	58	100	99.995	0.061	46	98.113	99.993	stable
CH		0.373	29	98.438	99.908	0.400	28	98.266	99.895	low in 2018 and 2020
CF excl. MI		0.078	59	92.857	99.995	0.120	69	91.892	99.995	2020: decrease
incl. MI		0.095	64	94.118	99.995	0.146	73	93.233	99.995	2020: decrease
HbP	SCD	0.130	96	100	99.999	0.172	99	99.320	100	2020: decrease
	HbH[3,6]	0.018		100	99.998	0.017	33	100	99.997	stable[3]
	bTM[3,6]	0.018		100	99.998	0.019	36	100	99.997	stable[3]
MD	3-MHM[6]	0.041		100	99.998	0.026	45	100	99.997	stable
	BIO[6]	0.018		100	99.997	0.024	21	100	99.991	stable
	CPT1[4,5]	0		-	99.999	-	-	-	-	-
	GALK[5]	0		-	99.998	-	-	-	-	-
	GALT[6]	0.024		100	99.996	0.014	10	100	99.987	stable
	GA-1[6]	0		-	99.999	0.001	11	100	99.999	stable
	IVA[6]	0.012		100	99.998	0.014	57	100	99.999	stable
	MSUD[6]	0		-	99.998	0.004	6	100	99.995	stable
	MCADD	0.113	86	100	99.998	0.113	92	100	99.999	stable
	MMA[4]	0.024	18	100	99.989	-	-	-	-	-
	PA[4]	0.006		100	99.999	-	-	-	-	-
	PKU	0.059	91	100	99.999	0.080	92	100	99.999	stable
	TFP/LCHAD[6]	0		-	99.999	0.001	11	100	99.999	stable
	TYR-1	0.012		100	99.996	0.006	23	100	99.998	stable
	VLCAD	0.030	42	100	99.996	0.024	32	95.238	99.995	stable
Total		1.037	42	98.870	99.854	1.110	40	98.246	99.835	

[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 2017-2020. These conditions were added to the screening programme in 2017.
[4] Per 1-10-2019 the conditions CPT1, MMA and PA have been 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] The condition GALK has been added to the heel prick screening per 1-10-2020. It has not yet been included in the 5-year average.
[6] Only a few children per year are referred for HbH, bTM and for many of the metabolic diseases. Therefore no target values for the PPV have been esthablished. Due to the small numbers, the PPV is omitted.

The detection rates are comparable to those of previous years for most conditions (stable since 2016). However, the detection rate of CF in 2020 is low compared to the years 2016-2019 .

The target values of the positive predictive value (PPV) have been reached for CAH (>15%), CH (>15%), SCD (>90%), PKU (>60%) and MCADD (>70%) in 2020. The target value for CF (>65%) was not reached. The total PPV (42%) in 2020 is comparable to the average in the period 2016-2019 (40%), but is decreased compared to 2019 (47%). The detection rate for CF is lower in 2020 (-MI 0.08%; +MI 0.10%) than in the period 2016-2019 (-MI 0.13%; +MI 0.16%).

The target values for sensitivity were not achieved in 2020 due to a false-negative result for CH and CF. The child with CF was screened at 12 weeks of age and had an IRT value that was too low to indicate referral, however, the child was already under treatment because of a positive screening abroad at a younger age. The target values for specificity have been achieved for all conditions.

Five new patients born in previous years were also reported as being missed by the screening program: one child with classical non-salt-wasting CAH from 2014 (no target group at the time), one child with classical CAH (presumably salt-wasting) from 2018 (false-negative), one child with TYR-1 from 2010 (false-negative), one child with SCD from 2019 (born and screened abroad), and one child with CF from 2014 (false-negative). The false-negatives born before 2016 have no influence on the 5-year average of the sensitivity, but it is useful that they are reported because it is important to have an overview of all patients.

TIMELINESS OF DIAGNOSTICS

The timeliness of diagnosis is calculated based on data from all referred children. For almost all disorders the target values were not reached in 2020 (table 6). Only the target value for CAH was reached, for the first time since 2017. The decrease for HbP (from 100% in 2019 to 81% in 2020) can be explained by a change in the target value at the beginning of 2020. The diagnostic examination should now take place at an age of 6 weeks or younger; previously this was 12 weeks.

Table 6
Timeliness of diagnostic results in children born in 2017-2020.

Screening	2017	2018	2019	2020	Target value
CAH	81	77	86	90	≥90%<15 days
CH	85	84	86	88	≥90%<15 days
CF all referrals	85	77	58	77	≥90%<30 days
excl. MI[1]	86	74	53	74	≥90%<30 days
HbP[2]	97	91	100	81	≥90%≤6.0 weeks[4]
MD[3]	74	76	91	89	≥90%<10 days (most MD) or <14 d (PA/MMA)

[1] Calculated for 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-deficiency excluded.
[4] The target value has been changed to ≥90% ≤6.0 weeks since 1-1-2020 (this was ≥90% ≤12.0 weeks).

COSTS

The costs of the screening programme (excluding diagnostics) were about 19.0 million euro in 2020 (source: Final bill NBS, RIVM-CvB, excluding the costs for Caribbean Netherlands). Screening costs per child are approximately 113 euro. Compared to last year, there is a cost increase of approximately 12%, compared to 3-4% per year in previous years. This is not only due to indexation of the costs for blood collection and laboratory analyses, which were higher in 2020 than in previous years. Due to the preparation for the extension of the heel prick screening with MPS1 and SCID, the number of laboratory staff and the material costs increased. In addition, permanent staff was deployed in 2020 for COVID-19 diagnostics, and relatively more expensive temporary workers were deployed for the heel prick screening.

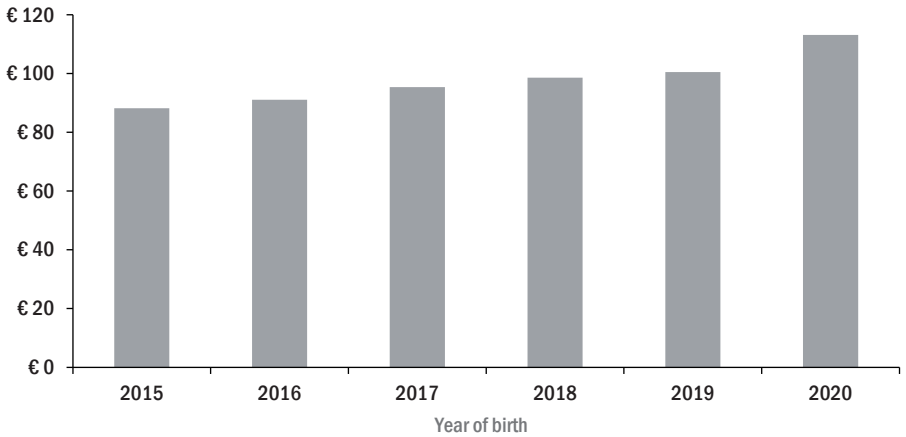

Figure 6
Costs of the screening programme per screened child according to year of birth (2015-2020)

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