

THE NEWBORN BLOOD SPOT SCREENING IN THE NETHERLANDS

MONITOR 2018



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 certain serious congenital disorders in newborns. Children with these (rare) disorders 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 program.

Parties involved in the realization of the NBS are presented in figure 1. The NBS is carried out 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 blood 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 99.1% in 2018 (n=168,565) and is just above the target value of 99.0%. Participation has fallen by 0.3% since 2013. This is mainly explained by an increase in the number of objections by parents to participate in the NBS and because the NBS has been performed abroad more often.
- 524 children were referred to a paediatrician (0.3%), of which at least 145 (28% of 524 referred children and 0.086% of the total number of participants) had one of the target group diseases.
- The **timeliness target value** of the **1st heelprick** was **not reached**: 98.6% was carried out within 168 hours after birth against a target value of 99.0%. The percentage was also below 99% in the years 2011-2017 with the exception of 2013. 37% of the heelpricks was performed in the recommended period of 72-96 hours after birth.
- The target values concerning the percentage of children who needed a **repeat 1st heelprick** were reached for all conditions in 2018.
- **CH**: The diagnostic data has not yet been delivered from 45% (n=112) of the 248 referred children. As a result, the CH and total detection rate, specificity and positive predictive value must be interpreted with caution.
- In previous years, the number of children detected with CH through screening has always been more than 70. Only 26 were discovered in 2018. This is a low number, even after accounting for the missing diagnostic data of 45% of children referred for CH.
- After exclusion for missing data, the total screening programme has a **detection rate** of 0.86 cases with the target group disease per 1000 screened children in 2018, a **positive predictive value** of 40%, a **sensitivity** of 100% and a **specificity** of 99.87%. The detection rate is presumably higher, because many CH patients may still be unknown due to missing diagnostic data.
- All conditions reached the target values in terms of **specificity, sensitivity and positive predictive value**.

- The target values for **timeliness of diagnostics** ($\geq 90\%$) were not achieved for CAH (77%), CH (85%), CF (77%) and metabolic diseases (76%) in 2018.
- The number of parents who **object** to the storage of blood remnants for scientific research purposes rose slightly in 2018 to 6.2%. In 2013 this was 4.6%.
- In 2018 **screening costs** per child (diagnostic costs excluded), were €99: they show a rising trend mainly because of the indexation of the costs for blood collection and laboratory analysis.

RECOMMENDATIONS

New recommendations:

- For CH it is important to find out why so many diagnostic data are (still) missing, and to complement these data.
- The participation rate of the screening programme has declined slowly in the last years to just above the target value. It is advisable to ascertain why this decline has occurred.

Existing recommendations that are still valid:

- Continue or intensify measures to improve the **timeliness of the 1st heelprick**.
- Gain more insight into the background of **objections against the heelprick** and objections against the **use of blood remnants** for scientific research.
- Continued attention for **timeliness and clarity of registration** of diagnostic data.
- Improvement of the timeliness of diagnostics in CAH, CH, CF and metabolic diseases.

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 NVK (the Dutch Society of Paediatrics) and the RIVM (<http://www.neorah.nl>).

In previous years the diagnostic CH data was registered by TNO; from 2018, pediatricians 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 Pediatric Surveillance System (NSCK) have been used to detect possible missed cases. This monitor concerns **children who have been born in 2018** (Praeventis reference date: 22-3-2019, NEORAH: 4-7-2019 or later¹).

READING GUIDE

This monitor differentiates between the 1st heelprick, a repeat 1st heelprick, a 2nd heelprick and a repeat 2nd heelprick.

- 1st heelprick: the first heelprick that has been carried out.
- Repeat 1st heelprick: the newborn blood spot collection that is repeated when insufficient blood has been collected during the 1st heelprick in order to carry out the required laboratory analyses or when a child received a blood transfusion within 24 hrs before the heelprick was carried out. If a blood transfusion with erythrocytes has been carried out, the heelprick needs to be repeated after 91 days to exclude haemoglobinopathies (HbP).
- 2nd heelprick: carried out if the 1st heelprick gives an inconclusive laboratory result.
- Repeat 2nd heelprick: as in repeat 1st heelprick.

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**.



¹ The reference date was 4-7-2019 for MZ, 17-7-2019 for CAH, 19-7-2019 for HbP, 1-8-2019 for CF and 26-8-2019 for CH.

DIFFERENCE COMPARED TO PREVIOUS MONITORS

As a result of a renewal in the analysis equipment and test kit, the cut-off limits for abnormal TYR-1 screening results have been changed from $SA \geq 1,20 \mu\text{mol/l}$ to $SA \geq 0,90 \mu\text{mol/l}$ per 1-1-2018.

From 2018 onwards, the aim of CAH screening is to detect all patients with a classic form of CAH, so both the classic salt-wasting form and the classic non-salt-wasting form (simple-virilising). Previously, only children with a classic salt-wasting form belonged to the target group.

An improved methodology for MSUD (XEvo MSMS and the Neobase 2-assay) was introduced on 1-1-2018, with immediate use of new cut-off limits of $340 \mu\text{mol/l}$ for valine en leucine (the official date of change of the cut-off limit is April 1st, 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**)
 - 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**)
 - Multiple CoA carboxylase deficiency (**MCD**)¹
 - Phenylketonuria (**PKU**)
 - 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**)²

More information about these conditions can be found on the RIVM website:

<https://www.rivm.nl/Onderwerpen/H/Hielprik>



¹ These three conditions are reported altogether under one name: 3-MHM, since they have the same marker.

² OCTN2-deficiency is not part of the NBS: it is considered an incidental finding.

PARTICIPATION

In 2018 170,057 children were eligible to participate in the NBS. Newborn blood was collected in 168,565 children. This means that the participation rate in 2018 is 99.1%, which is just higher than the target percentage of 99.0% (figure 2).

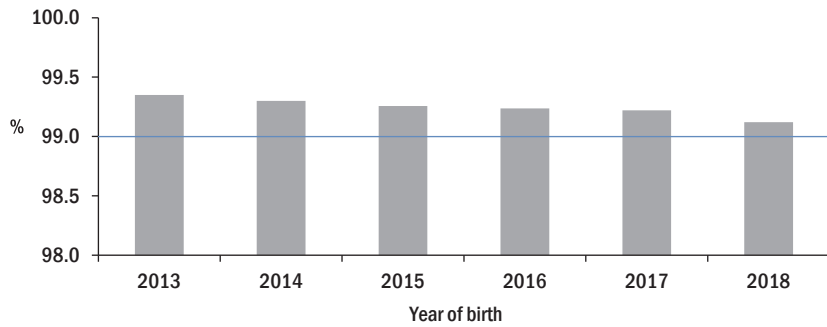


Figure 2
Participation rate of the neonatal screening programme by year of birth (2013-2018); to support readability the y-axis starts at 98%. The blue line indicates the target value

From 2013 to 2018 a slight decrease from 99.4% to 99.1% is visible. Figure 3 shows that this is mainly explained by an increase in the number of objections by parents to participate in the NBS (0.46% in 2018 versus 0.28% in 2013) and because the heelprick has been carried out more often abroad.

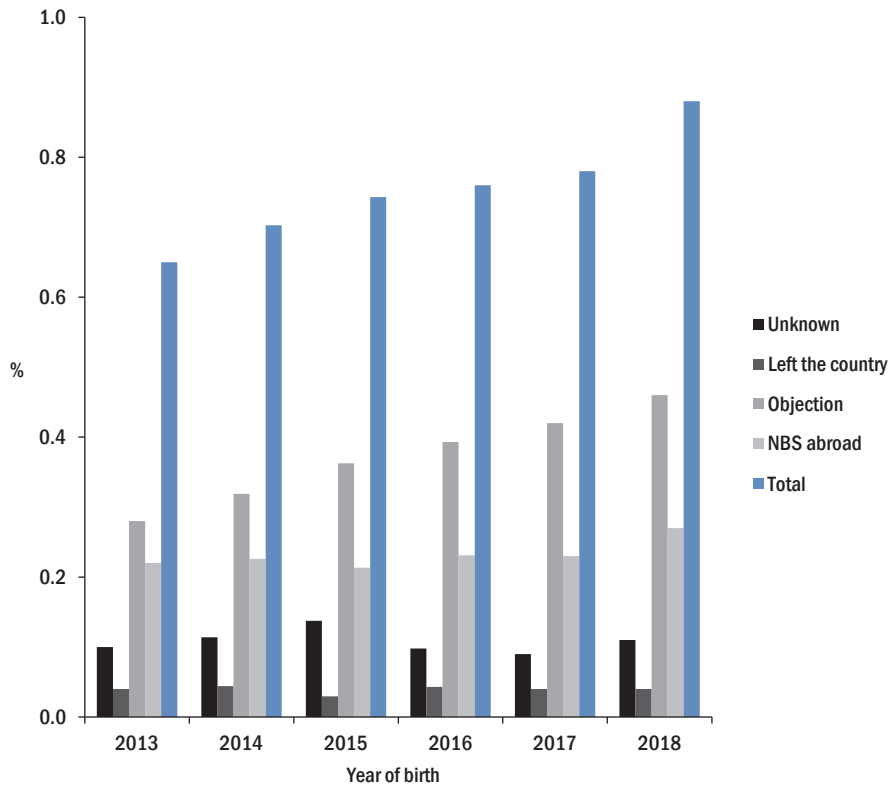


Figure 3
Reasons for non-participation in the neonatal screening programme by year of birth (2013-2018)

TIMELINESS OF BLOOD COLLECTION

Timing of the NBS is crucial. The heelprick should be carried out within 168 hours (7 days) after birth, but ideally between 72 and 96 hours. In 2018 the percentage of 1st heelpricks carried out within 168 hours (7 days) after birth is 98.6%. The target of at least 99.0% was therefore not reached. This was also the case in previous years with the exception of the year 2013 (figure 4). In 37% of children, newborn blood spots were collected in the recommended period between 72-96 hours after birth.

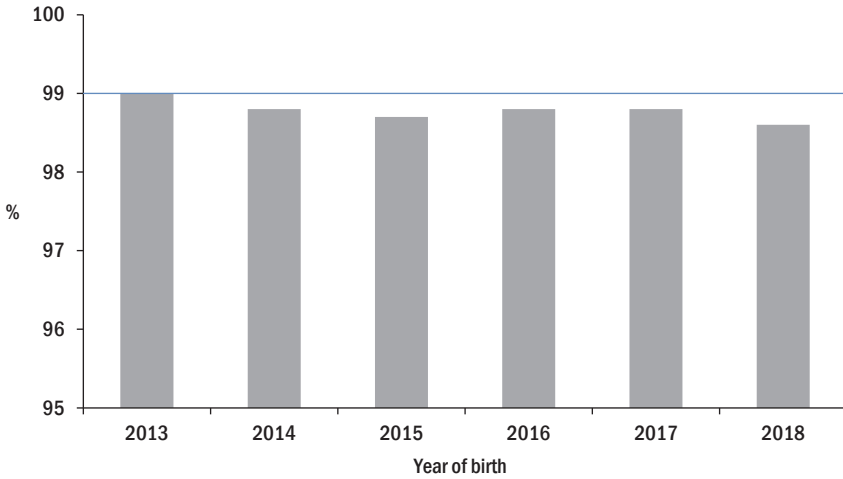
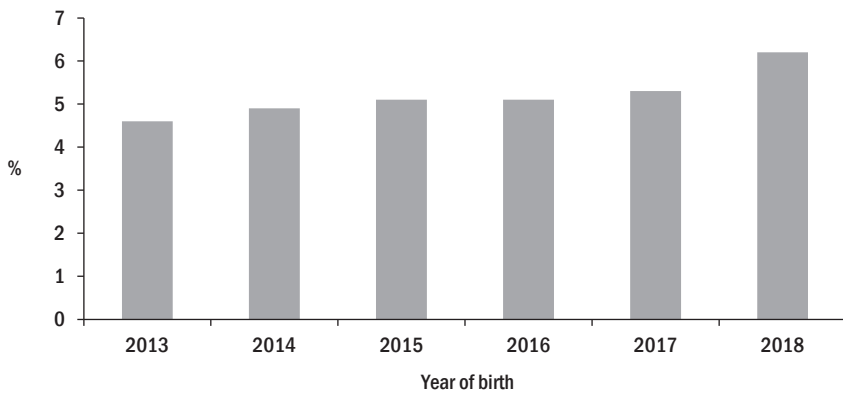


Figure 4
Timeliness of the blood spot collection by year of birth (2013-2018). Children born outside the Netherlands are excluded (the blue line indicates the target value; to support readability the y-axis starts at 95%)

OBJECTIONS AGAINST STORAGE OF NEWBORN BLOOD

In 2018 6.2% of parents objected against the storage of the NBS blood remnants for the purpose of (anonymous) scientific research. This percentage shows a rising trend from 4.6% in 2013 to 6.2% in 2018 (figure 5).



Figuur 5
Objection of parents against the storage of NBS remnants for anonymous scientific research, by year of birth (2013-2018)

REPEAT FIRST HEELPRICK

Some of the blood spot collections needed to be repeated, for example because insufficient blood was collected on the blood spot card. In 2018, the target values for all conditions were achieved for the first time since 2014 (table 2).

Table 1
Repeat first heelpricks according to year of birth (2013-2018)

% of repeat 1st heelpricks	2013	2014	2015	2016	2017	2018	Number in 2018	Target value	
CAH	0.09	0.10	0.09	0.10	0.09	0.08	(137)	≤0.50	
CH	0.29	0.38	0.56	0.55	0.503	0.42	(712)	≤0.50	
CF	0.33	0.48	0.58	0.61	0.52	0.42	(702)	≤0.50	
HbP	0.58	0.71	0.82	0.82	0.70	0.59	(992)	≤0.80	
MD	PKU	0.11	0.14	0.14	0.18	0.17	0.14	(229)	≤0.50
	3-MHM	0.16	0.17	0.20	0.22	0.20	0.18	(304)	≤0.50
	BIO	0.29	0.42	0.51	0.54	0.46	0.37	(623)	≤0.50
	GAL	0.23	0.31	0.31	0.27	0.23	0.18	(308)	≤0.50
	GA-1	0.16	0.17	0.20	0.22	0.20	0.18	(305)	≤0.50
	IVA	0.16	0.17	0.20	0.22	0.20	0.18	(305)	≤0.50
	MSUD	0.11	0.14	0.18	0.18	0.17	0.14	(229)	≤0.50
	MCAD	0.16	0.17	0.20	0.22	0.20	0.18	(305)	≤0.50
	TFP/LCHAD	0.16	0.17	0.20	0.22	0.20	0.18	(305)	≤0.50
	TYR-1	0.11	0.14	0.18	0.18	0.17	0.14	(229)	≤0.50
	VLCAD	0.14	0.17	0.20	0.22	0.20	0.18	(305)	≤0.50
	OCTN2	0.11	0.14	0.18	0.18	0.17	0.14	(229)	≤0.50

SECOND HEELPRICK

In 2018 0.072% of the CAH results indicated the need for a 2nd heelprick. This means that the target value for this indicator (≤0.090%) was reached (table 2).

In 2018 0.36% of the CH results indicated the need for a 2nd heelprick. The target value for this indicator (≤0.50%) was also reached, just like last year.

Table 2
Second heelprick according to birth year (2013-2018)

	2013	2014	2015	2016	2017	2018	Number in 2018	Target value
CAH % of 2nd heelpricks	0.096	0.070	0.079	0.078	0.065	0.072	(122)	≤0.09
CH % of 2nd heelpricks	0.55	0.74	0.82	0.53	0.21	0.36	(607)	≤0.50

REFERRALS

In 2018 the NBS resulted in 524 referrals (table 3). This includes 18 referrals for the incidental finding OCTN2¹. This gives a referral rate of 0.31% of the total number of screened children in 2018. This is, just like in 2017, a lower percentage when compared to previous years.

The referral rate for 3-MHM is high in 2018 compared to previous years. However, similar fluctuations have been seen in the last ten years, so this outlier is probably due to chance.

The number of referrals for MSUD are low in 2018: in 2013-2017 6 to 20 children per year were referred for MSUD, in 2018 only 3. This decrease might possibly be explained by the introduction of an improved testing methodology.

Table 3
Referrals according to birth year (2013-2018)

% referrals	2013	2014	2015	2016	2017	2018	Number in 2018	Trend	
CAH	0.024	0.014	0.015	0.015	0.016	0.016	(27)	stable	
CH	0.19	0.22	0.31	0.21	0.13	0.15	(248)	fluctuates	
CF	0.023	0.019	0.020	0.026 ¹	0.016	0.021	(35)	fluctuates	
HbP²	0.041	0.040	0.027	0.035	0.023 ⁶	0.032 ⁴	(54)	stable	
	SCD ²				0.014 ⁶	0.018	(31)		
	HbH ²				0.005	0.007	(12)		
	bTM ²				0.004	0.007	(11)		
MD	PKU	0.009	0.011	0.012	0.012	0.008	0.010 ⁵	(17)	stable
	3-MHM	0.003	0.004	0.004	0.003	0.005	0.009 ⁷	(16)	2018 high
	BIO	0.006	0.007	0.011	0.010	0.018	0.013 ⁷	(22)	2018 reduction
	GAL	0.032	0.035	0.041	0.019	0.021	0.025	(42)	reduction ³
	GA-1	0.002	0.001	0.001	0.001	0.001	0 ⁷	(0)	stable
	IVA	0.001	0.002	0.001	0.004	0.002	0.002 ⁷	(4)	stable
	MSUD	0.005	0.005	0.007	0.012	0.010	0.002 ⁵	(3)	2018 reduction
	MCAD	0.013	0.012	0.011	0.012	0.011	0.012 ⁷	(21)	stable
	TFP/LCHAD	0.001	0.001	0.001	0	0.001	0.001	(2)	stable
	TYR-1	0.001	0.001	0.002	0.002	0.002	0.001	(2)	stable
	VLCAD	0.009	0.003	0.011	0.005	0.011	0.008	(13)	fluctuates
	OCTN2 ⁸	0.008	0.006	0.005	0.012	0.009	0.011	(18)	fluctuates
Total referral rate	0.37	0.38	0.48	0.37	0.29	0.31	(524)		

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 GAL: Possibly as a result of adapted reference values for GAL per 01-07-2015.

⁴ HbP: Excluding a child with an abnormal heelprick result that died before referral could take place.

⁵ PKU, MSUD: Excluding two children who were not referred, because they died shortly after the heelprick.

⁶ An error was made in the number of referrals for SCD in the 2017 monitor. A child appeared to be from Aruba and was wrongly included in the report. The figures have been corrected in this monitor.

⁷ 3-MHM, BIO, GA-I, IVA, MCAD: Excluding a child who was not referred, because he/she died shortly after the heelprick was carried out.

⁸ OCTN2: Is not part of the screening program, 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. The level of C0 is nevertheless determined in each child, because a possible deficiency makes the acylcarnitine profile unreliable, which may cause that children with the metabolic conditions MCAD, VLCAD, TFP/LCHAD, IVA, GA-I and 3-MHM remain undetected.

DIAGNOSTIC RESULTS

In 2018, 506 children (excluding 18 referrals for OCTN2) were referred for a target condition that is part of the screening program. In 145 (29%) cases one of the condition was confirmed (table 4). This is lower than in 2017 (38%), which can largely explained by the fact that many diagnostic data (45%, n=112) from CH were not delivered. The diagnostic outcomes of CH and Total should therefore be interpreted with caution.

Children with a referral for OCTN2 deficiency (n=18, of which two are diagnosed with OCTN2) are not included in these numbers, because this condition is not a target condition of the screening program, but an incidental finding.

In 2018 one child with CAH was reported as missed. The result of the first heelprick of this child was inconclusive. A second heelprick was not performed, because the child was already in treatment for CAH before the first heelprick was carried out. The child is therefore not considered as false-negative or missed.

Table 4
Diagnostic results of referred children born in 2018¹

2018	Referred	Diagnosis confirmed	No target disease	Diagnosis (still) unknown	False-negative (test improperly indicates no need for referral)	Missed/ other
CAH	27	9 ²	16	2	0	1 ⁷
CH	248	26	102	120 ³	0	0
CF⁴	35	24 ⁴	9	2	0	0
HbP	SCD	31	26	1 ⁵	4	0
	HbH	12	0	9	3	0
	bTM	11	3	4 ⁶	4	0
MD	PKU	17	16	0	1	0
	3-MHM	16	5	11	0	0
	BIO	22	2	19	1	0
	GAL	42	3	37	2	0
	GA-1	0	0	0	0	0
	IVA	4	4	0	0	0
	MSUD	3	2	0	1	0
	MCAD	21	19	2	0	0
	TFP/LCHAD	2	0	2	0	0
	TYR-1	2	0	2	0	0
VLCAD	13	6	5	2	0	
Total	506	145	219	142⁸	0	1⁷

¹ This table does not include 18 referrals for OCTN2-deficiency (n=18, 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: All children have the classic salt-wasting form.

³ CH: For eight children the diagnosis is (still) unknown, and for 112 children (45%) the diagnostic data are not registered in NEORAH.

⁴ CF: Including four children with meconium ileus.

⁵ SZ: Carrier of mild alpha-thalassemia.

⁶ bTM: Two children have a mild form of beta-thalassemia (HBEE). One child has beta-thalassemie intermedia. One child is carrier of bTM. These four children do not belong to the target group of the screening.

⁷ Already under treatment for CAH (non-classical form) before the first heelprick was carried out.

⁸ Of which 112 children (referred for CH) have no reported diagnostic data. Among 30 children diagnostic data were delivered, but diagnosis is (still) unknown.



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 since 2013 (stable) in most cases. The detection rate for every 1000 children screened for CH (0.154) is much lower compared to 2014-2018 (0.388), which means that the total detection rate is also much lower (0.861 in 2018 and 1.04 in 2014-2018). This difference can largely be explained by the fact that many diagnostic data for CH are missing in 2018 (45%, 112 children). As a result, the total number of children with a abnormal blood spot for CH is unknown and the detection rate is presumably higher. Based on the detection rate for CH in previous years (± 0.42), 71 children with CH are expected in 2018. The number of 26 CH patients found is still low even when the 45% missing diagnoses are taking into account.

The PPV target values have been reached for CAH (>15%), CH (>15%), SCD (>90%), PKU (>60%) and MCAD (>70%) in 2018.

The PPV value for CH is still uncertain, because many diagnostic data are missing.

The target values for sensitivity and specificity have been reached for all conditions in 2018.

Table 5
Detection rate, positive predictive value (PPV), sensitivity (Sens) and specificity (Spec) in children born in 2018 and the period 2014-2018^{1,2}

	2018				2014-2018				Trend detection rate 2013-2018	
	Detection rate (per 1000)	PPV ³ (%)	Sens (%)	Spec (%)	Detection rate (per 1000)	PPV (%)	Sens (%)	Spec (%)		
CAH	0.053	36	100	99.991	0.044	33	100	99.991	stable	
CH	0.154	20	100	99.939 ⁴	0.378	22	99.385	99.863	reduction	
CF excl. MI	0.119	69	100	99.995	0.011	62	92.079	99.993	stable	
incl. MI	0.142	73	100	99.995	0.134	66	93.496	99.993	stable	
HbP	SCD	0.154	96	100	99.999	0.159	96	100	99.999	stable
	HbH	0	-	99.995	-	-	-	-	-	
	bTM	0.018	-	100	99.997	-	-	-	-	
MD²	PKU	0.095	100	100	100	0.090	90	100	99.999	stable
	3-MHM	0.030	-	100	99.994	0.020	41	100	99.997	stable
	BIO	0.012	-	100	99.989	0.025	21	100	99.991	stable
	GAL	0.018	-	100	99.978	0.008	3	100	99.973	stable
	GA-1	0	-	-	-	0.000	14	100	99.999	stable
	IVA	0.024	-	100	100	0.015	72	100	99.999	stable
	MSUD	0.012	-	100	100	0.006	9	100	99.994	stable
	MCAD	0.113	90	100	99.999	0.110	95	100	99.999	stable
	TFP/LCHAD	0	-	-	99.999	0.004	43	100	100	stable
	TYR-1	0	-	-	99.999	0.005	27	100	99.999	stable
	VLCAD	0.036	-	100	99.997	0.028	40	96.000	99.996	stable
Total		0.861	40	100	99.870	1.035	33	98.775	99.790	

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 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.

⁴ In 2018, 45% (n=112) of the diagnostic data was not delivered. If we assumed that all of these 112 children had a false positive heelprick result, the specificity would be 99.87%. This is still above the target value of 99.84%.

TIMELINESS DIAGNOSTICS

From 2017 onwards, the timeliness of diagnostics has been calculated in the total population of children that have been referred to paediatricians for all diseases. Until 2016, only children with the condition were included in the calculation for CAH, CH and CF.

The target values for the conditions CAH, CH, CF and MD were not achieved in 2018 (Table 6).

Table 6
Timeliness of diagnostic results in children born in 2018

	% < diagnosed in time	Target value
CAH	77	≥90% < 15 days
CH¹	85	≥90% < 15 days
CF all referrals	77	≥90% < 30 days
excl. MI ²	74	≥90% < 30 days
HbP³	91	≥90% < 12 weeks ⁴
MD⁵	76	≥90% < 10 days

¹ CH: For 55% of the referred children the diagnostic data in NEORAH is known. The remaining data (still) needs to be delivered. Therefore, the actual percentage may be different.

² Calculated over all children referred for CF excluding children with meconium ileus.

³ All children referred for HPLC patterns matching with sickle cell disease, HbH-disease and beta-thalassemia.

⁴ 31% of children was seen <28 dagen after birth.

⁵ OCTN2 excluded.

COSTS

The costs of the screening programme (excluding diagnostics) were about 16.6 million euro in 2018 (Source: Final bill NBS, RIVM-CvB). Screening costs per child are 99 euro. Since 2013, screening costs per child have been rising with an average of 3.5% each year, caused mainly by the indexation of the costs for blood collection, the heel prick set and laboratory analysis.

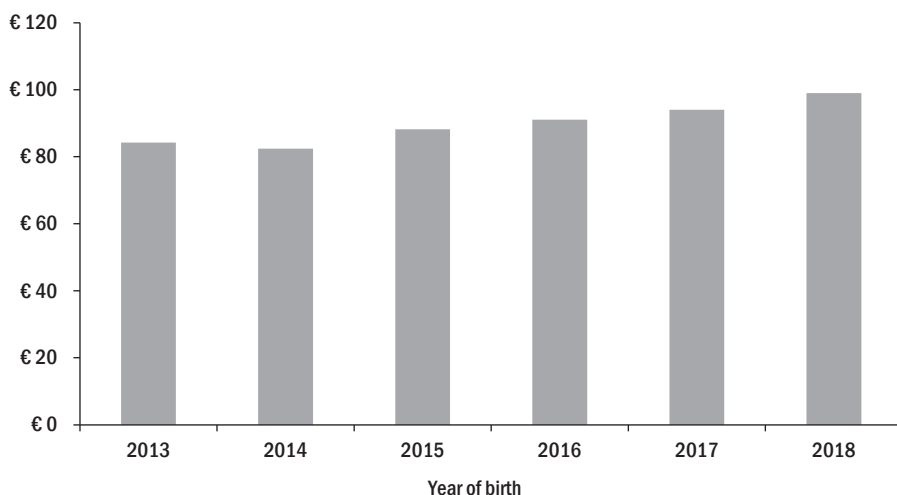


Figure 6
Costs of the screening programme per screened child according to year of birth (2013-2018)

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