THE NEWBORN BLOOD SPOT SCREENING IN THE NETHERLANDS

MONITOR 2016

TNO innovation for life

The Newborn Blood Spot screening program (NBS) was introduced in the Netherlands in 1974. The program 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 public health care or maternity worker. When the baby is admitted to 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

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 (www.neorah.nl) except for the data on congenital hypothyroidism (CH). The diagnostic CH data are registered by TNO. The NEORAH data related to metabolic disorders 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 2016** (Praeventis reference date: 27-03-2017, NEORAH: 21-10-2017, TNO Database: 20-11-2017).

READING GUIDE

In this monitor the colors 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 to improve the results or to get the results to fall within the limits of the target value, can be initiated. Signal- or target values for trends do not exist. Trends which require vigilance, are indicated in orange. Stable trends are indicated in green.

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

- 1st heelprick: the first newborn blood spot collection 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 (insufficient filling) 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.

DIFFERENCE COMPARED TO PREVIOUS MONITORS

The classification and the reference values for cystic fibrosis (CF) have been changed on 01-07-2016. Three mutations are now indicated as 'clinically not relevant' instead of 'clinical relevance unknown'. The reference values for DNA analysis have been liberalised.

WHICH CONDITIONS ARE INCLUDED IN THE SCREENING?

- Congenital adrenal hyperplasia **(CAH)**
- Cystic fibrosis **(CF)**
- Congenital hypothyroidism **(CH)**
- Sickle cell disease **(SCD)**[1]
- Metabolic disorders **(MD)**
  - 3-methylcrotonyl-CoA carboxylase deficiency **(3-MCC)**[2]
  - Biotinidase deficiency **(BIO)**
  - Galactosemia **(GAL)**
  - Glutaric acidemia type 1 **(GA-1)**
  - HMG-CoA lyase deficiency **(HMG)**[2]
  - Isovaleric acidemia **(IVA)**
  - Maple syrup urine disease **(MSUD)**
  - Medium-chain acyl-CoA dehydrogenase deficiency **(MCAD)**
  - Multiple CoA carboxylase deficiency **(MCD)**[2]
  - 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)**[3]

[1] Alpha- and beta-thalassemia are not part of the NBS in 2016: they are considered incidental findings when screening for SCD.
[2] These three conditions are reported altogether under one name: 3-MHM, since they have the same marker.
[3] OCTN2 deficiency is not part of the NBS: it is considered an incidental finding.

More information about all conditions can be found on the RIVM website:
Http://www.rivm.nl/Onderwerpen/H/Hielprik/Hielprik_voor_professionals

PARTICIPATION

In 2016 174,085 children were eligible to participate in the NBS. Newborn blood was collected in 172,754 children. This means that the participation rate is 99.2% which is higher than the target percentage of 99.0% (figure 2).

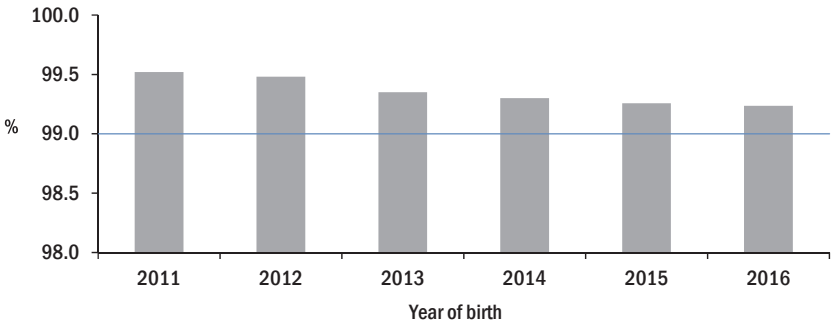

Figure 2
Screening participation according to birth year (2011-2016) (the blue line is the signal value. To support readability the y-axis starts at 98%)

Participation is in decline since 2011. This can be explained by the increase in the number of registered objections by parents against the NBS and the number of children with an unknown reason for non-participation (figure 3). This can partially be explained by improved RIVM-DVP registration of reasons for non-participation since 2008. Previously the group without screening data and no registered explanation as to why, consisted of 800-1000 children annually. Since 2008 the group without screening data has been reduced from 5 permille in 2008 to less than 1 permille (65 children) in 2016.

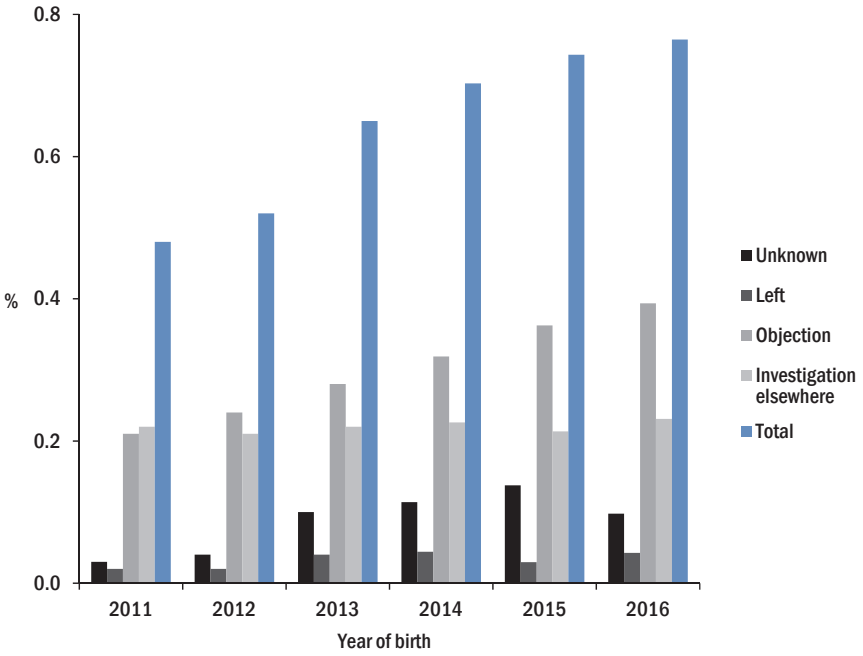

Figure 3
Reasons for non-participation in the screening according to year of birth (2011-2016)

TIMELINESS OF BLOOD COLLECTION

The heelprick is carried out shortly after birth by a screener. Timing of the NBS is crucial. In 2016 the percentage of 1st heelpricks carried out within 168 hours (7 days) after birth, is 98.8%. The minimum target of 99.0% was therefore not reached. This is also the case in the previous years with the exception of the year 2013 (figure 4). In 38% of the children, newborn blood spots were collected in the recommended period between 72-96 hours after birth

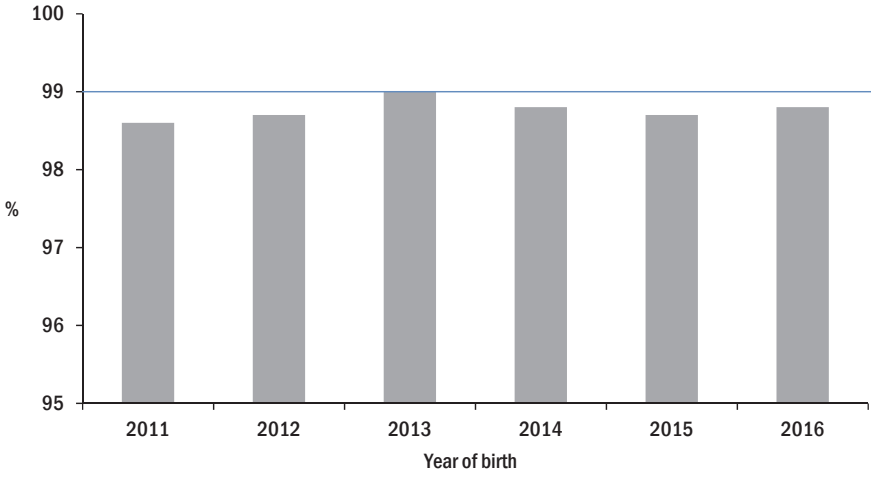

Figure 4
Timeliness of the blood spot collection according to birth year (2011-2016), children born outside the Netherlands are excluded (the blue line indicates the signal value. To support readability the y-axis starts at 95%)

OBJECTIONS AGAINST STORAGE OF NEWBORN BLOOD

In 2016 5.1% of parents objected against the storage of the NBS blood remnants for the purpose of (anonymous) scientific research. This percentage shows a rising trend since 2011 and stabilised in 2015 (figure 5).

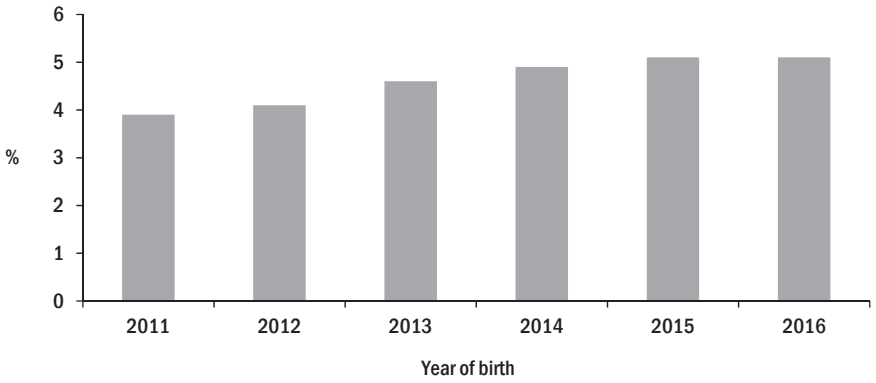

Figure 5
Objection of parents against the storage of NBS remnants for anonymous scientific research, according to birth year (2011-2016)

REPEAT 1ST HEELPRICK

In 2016 some of the blood spot collections needed to be repeated for example because insufficient blood was collected on the blood spot card. The target values have been exceeded in CH, CF, SCD and BIO (table 1).

Table 1
Repeat first heelpricks according to birth year (2011-2016)

% of repeat 1st heelpricks		2011	2012	2013	2014	2015	2016	(number in 2016)	Target value
CAH		0.12	0.08	0.09	0.10	0.09	0.10	(166)	≤0.50
CH		0.36	0.29	0.29	0.38	0.56	0.55	(945)	≤0.50
CF		0.48	0.34	0.33	0.48	0.58	0.61	(1046)	≤0.50
SCD		0.79	0.61	0.58	0.71	0.82	0.82	(1398)	≤0.80
MD	PKU	0.23	0.11	0.11	0.14	0.14	0.18	(319)	≤0.50
	3-MHM	0.27	0.15	0.16	0.17	0.20	0.22	(377)	≤0.50
	BIO	0.47	0.31	0.29	0.42	0.51	0.54	(934)	≤0.50
	GAL	0.38	0.25	0.23	0.31	0.31	0.27	(461)	≤0.50
	GA-1	0.27	0.15	0.16	0.17	0.20	0.22	(377)	≤0.50
	IVA	0.27	0.15	0.16	0.17	0.20	0.22	(377)	≤0.50
	MSUD	0.23	0.11	0.11	0.14	0.18	0.18	(319)	≤0.50
	MCAD	0.27	0.15	0.16	0.17	0.20	0.22	(377)	≤0.50
	TFP/LCHAD	0.27	0.15	0.16	0.17	0.20	0.22	(377)	≤0.50
	TYR-1	0.23	0.11	0.11	0.14	0.18	0.18	(319)	≤0.50
	VLCAD	0.27	0.15	0.14	0.17	0.20	0.22	(377)	≤0.50
	OCTN2	0.23	0.11	0.11	0.14	0.18	0.18	(319)	≤0.50

SECOND HEELPRICK

In 2016 0.078% of the CAH results indicated the need for a 2nd heelprick. This means that the target value for this indicator (≤0.090%) has been reached for that year (table 2).

In 2016 0.53% of the CH results indicated the need for a 2nd heelprick. The target value for this indicator (≤0.50%) has not been reached. The percentage of 2nd heelprick was lower in 2016 when compared to 2015 and 2014. Since 2011 the target value for this indicator was shown to be below 0.50% only in 2011.

Table 2
Second heelprick according to birth year (2011-2016)

		2011	2012	2013	2014	2015	2016	(number in 2016)	Target value
CAH	% of 2nd heelpricks	0.100	0.083	0.096	0.070	0.079	0.078	(135)	≤0.09
CH	% of 2nd heelpricks	0.47	0.53	0.55	0.74	0.82	0.53	(909)	≤0.50

REFERRALS

In 2016 the NBS resulted in 647 referrals (table 3). This gives a referral rate of 0.37% of the total number of screened children in 2016. This is a lower percentage when compared to 2015 and is comparable to the previous years.

Table 3
Referrals according to birth year (2011-2016)[1]

% of referrals		2011	2012	2013	2014	2015	2016	(number in 2016)	Trend
CAH		0.017	0.014	0.024	0.014	0.015	0.015	(27)	stable
CH		0.18	0.20	0.19	0.22	0.31[2]	0.21	(357)	stable
CF		0.028	0.027	0.023	0.019	0.020[3]	0.026	(45)	2016 higher[4]
SCD		0.034	0.042	0.041	0.040	0.027	0.035	(60)	stable
MD	PKU	0.007	0.009	0.009	0.011	0.012	0.012	(20)	stable
	3-MHM	0.004	0.008	0.003	0.004	0.004	0.003	(5)	stable
	BIO	0.033	0.011	0.006	0.007	0.011	0.010	(17)	stable
	GAL	0.044	0.029	0.032	0.035	0.041	0.019	(34)	2016 low[5]
	GA-1	0.008	0.004	0.002	0.001	0.001[6]	0.001	(2)	reduction[7]
	IVA	0.001	0.002	0.001	0.002	0.001	0.004	(7)	2016 high
	MSUD	0.007	0.003	0.005	0.005	0.007[8]	0.012	(20)	2016 high
	MCAD	0.014	0.014	0.013	0.012	0.011	0.012	(20)	stable
	TFP/LCHAD	0.008	0.003	0.001	0.001	0.001	0	(0)	stable
	TYR-1	0.001	0	0.001	0.001	0.002	0.002	(4)	stable
	VLCAD	0.002	0.002	0.009	0.003	0.011[9]	0.005	(9)	stable
	OCTN2	0.007	0.009	0.008	0.006	0.005	0.012	(20)	2016 high
Total referral rate		0.40	0.38	0.37	0.38	0.48	0.37	(647)	

[1] In this table the referrals because of incidental findings (alfa- and beta-thalassaemia and OCTN2), are included.
[2] Includes a child which needed a 2nd heelprick ≥ 60 days after birth. TSH was not abnormal, however criteria belonging to a heelprick carried out <60 days after birth were used, leading to an 'abnormal' result.
[3] Excluding a child with an abnormal result, which died before referral (on day 3 after birth).
[4] Probably as a result of adapted reference values for CF per 01-07-2016 (resulting in more DNA testing and subsequently more referrals).
[5] Possibly as a result of adapted reference values for GALT per 01-07-2015.
[6] Excluding a child with an abnormal result which died before referral (on day 1 after birth).
[7] Possibly as a result of adapted reference values per 01-01-2012 for C5DC (GA-1) from 0.1 µmol/l to 0.70 µmol/l because of a change-over to a different internal standard.
[8] Excluding a child with an abnormal result which died (date unknown) and was not referred.
[9] Results for VLCAD vary by year. Excluding a child with abnormal results which died before referral (3.5 weeks after birth). First heelprick was not classifyable, repeat first heelprick arrived in the laboratory three days before the child's death.

TIMELINESS OF DIAGNOSTICS

In 2016 the target values have been reached for all conditions (table 4).

Table 4
Timeliness of diagnostic results in children born in 2016

	% diagnosed in time	Target value
CAH	100	≥90%<15 days
CH	93	≥90%<15 days
CF excl. MI	97	≥90%<30 days
incl. MI	98	≥90%<30 days
SCD	92	≥90%<12 weeks[1]
MD[2]	98	≥90%<10 days

[1] 42% of children were seen <28 days after birth.
[2] OCTN2 deficiency excluded.

DIAGNOSTIC RESULTS

In 2016, 597 children were referred because of a condition which is part of the screening program. In 176 (29%) cases the condition was confirmed (table 5). Children with a referral because of the incidental finding of alpha-thalassemia or beta-thalassemia (n=30) and OCTN2-deficiency (n=20) are not included in these numbers, because these conditions were not target diseases of the screening program. In 2016 a total of 172,754 children were screened.

In 2016 four children had a false-negative test result. The NBS results of these children were not abnormal, although they were diagnosed with one of the conditions from the screening program at a later stage. In all four children this concerned CF. In three of these children the NBS was carried out in the first half of 2016 and therefore before the reference values were adapted.

Table 5
Diagnostic results of referred children born in 2016[1]

2016		Referred	Diagnosis confirmed	Negative	(Still) unknown	False negative	Missed
CAH		27	8	16[2]	3	0	0
CH		357	71	247	39[3]	0	0
CF		45	29[4]	15[5]	1	4	0
SCD		30	22	1[6]	7	0	0
MD	PKU	20	16	3	1	0	0
	3-MHM	5	2	3[7]	0	0	0
	BIO	17	1	16	0	0	0
	GAL	34	0	32	2	0	0
	GA-1	2	1	1	0	0	0
	IVA	7	2	1	4[8]	0	0
	MSUD	20[9,10]	1	16[9]	3[10]	0	0
	MCAD	20	19	1	0	0	0
	TFP/LCHAD	0	0	0	0	0	0
	TYR-1	4	1	3	0	0	0
	VLCAD	9	3	4	2	0	0
Total		**597**	**176**	**359**	**62**	**4**	**0**

[1] This table does not include referrals for the incidental findings alpha- and beta-thalassaemia and OCTN2.
[2] One of these children was diagnosed with non-classical CAH.
[3] In 7 children a definite diagnosis could not yet be determined. In 12 children the diagnosis has not yet been received (including 2 children who died) and the referral of 20 children was still unknown at the reference date.
[4] Includes 5 children with a meconium ileus.
[5] Includes 1 child with a F508del + R1162L result: counted as a negative result.
[6] Diagnosis aa/a-.
[7] Includes one child diagnosed with betaketothiolase deficiency.
[8] Includes one child which died before referral, and one child which died after referral but before diagnostic investigations were started.
[9] Includes a child that was wrongly referred due to a dirty NBS card.
[10] Includes a child which died before diagnostic investigations were started.

DETECTION RATES

Table 6 shows the detection rates (per 1000 screened children), the positive predictive value (PPV), the sensitivity (Sens) and Specificity (Spec) of the program, based on the numbers of 2016.

The detection rates are comparable to that of previous years since 2011 (stable) in most cases. In case of CF, the detection rate is slightly higher in 2016 when compared to previous years. This can be explained by the change in reference values. The detection rates for SCD, BIO and GAL are lower in 2016 when compared to previous years. In case of BIO, it was a gradual reduction across the last few years, caused by a change in the diagnostic criteria of the paediatricians.

The PPV target values have been reached for CAH (>15%), CH (>15%), CF incl. meconium ileus (MI, >65%), SCD (>90%), PKU (>60%) and MCAD (>70%). The PPV target value for CF excl. MI (>65%) has not been reached.

Target values for sensitivity are 100% for all conditions. In 2016 this target value for CF has not been reached. For all other conditions the target value was reached.

The target values for specificity have been reached for all conditions in 2016.

Table 6
Detection rate, positive predictive value (PPV), sensitivity (Sens) and specificity (Spec) in children born in 2016[1,2]

2016		Detection rate (per 1000)	Trend detection rate 2011-2016[3]	PPV (%)	Sens (%)	Spec (%)
CAH		0.046	stable	33	100	99.991
CH		0.411	stable	22	100	99.857
CF excl. MI		0.139	2016 high	62	86	99.991
incl. MI		0.168	2016 high	66	88	99.991
SCD		0.127	2016 low	96	100	99.999
MD	PKU:	0.093	increase	84	100	99.998
	3-MHM:	0.012	stable		100	99.998
	BIO:	0.006	reduction		100	99.991
	GAL:	0	2016 low		–	99.981
	GA-1:	0.006	stable		100	99.999
	IVA:	0.012	stable		100	99.999
	MSUD:	0.006	stable		100	99.991
	MCAD:	0.006	stable	95	100	99.999
	TFP/LCHAD:	0	stable		–	100
	TYR-1:	0.006	stable		100	99.998
	VLCAD:	0.017	stable		100	99.998
Total[4]		**1.035**		**33**	**98**	**99.792**

[1] In the 2017 evaluation report the PPV, Sens and Spec of several years combined will be calculated.
[2] Incidental finding of alpha- and beta-thalassaemia and OCTN2 are not included in this table.
[3] Data not shown.
[4] Includes children with CF with meconium ileus.

COSTS

The costs of the screening program (excluding diagnostics) were roughly 15.7 million euro in 2016 (Source: Macrokader RIVM-CvB). Screening costs per child are 91 euro. Since 2011, screening costs per child have been rising with an average of 2.8% each year, mainly caused by the indexation of the fees for blood collection and laboratory analysis.

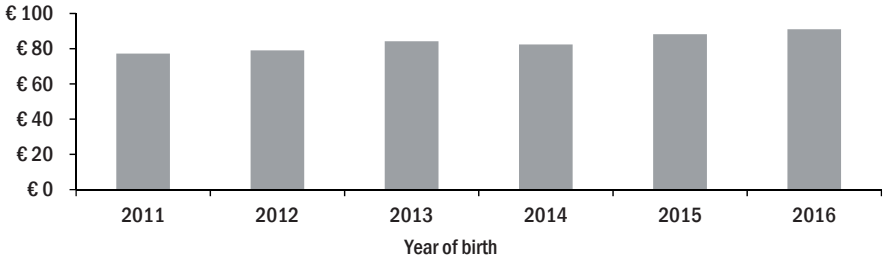

Figure 6
Costs of the screening program per screened child according to birth year (2011-2016)

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 99.2% in 2016.
- The **timeliness** target value of the 1st heelprick was not reached: 98.8% was carried out within 168 hours after birth against a target value of 99.0%. The percentage was also below 99% in the years 2011-2015 with the exception of 2013.
- The rising trend of parents who **object to the storage of blood remnants** for scientific research purposes, seems to have stabilized. Both in 2015 and 2016, 5.1% of the parents objected to storage.
- The target values concerning the percentage of children who needed a **repeat 1st heelprick** were exceeded in the case of CH (0.55%, target value <0.50%), CF (0.61%, target value ≤0.50%), SCD (0.82%, target value ≤0.80%), and BIO (0.54%, target value ≤0.50%).
- The **timeliness of diagnostics** met the target values in 2016.
- The percentage of NBS with **inconclusive CH results** in 2016, was 0.53%. This is considerably more favourable when compared to 2014 (0.74%) and 2015 (0.82%). The target value (0.50%) for this indicator was almost reached in 2016.
- The **positive predictive value** for CF screening excl. MI (62%) did not meet the target value (>65%) in 2016. The other disorders do meet the target values.
- The **sensitivity** of screening for CF was 86% (excluding children with MI) and 88% (including children with MI) in 2016. The target values of 100% were therefore not reached in 2016. The other conditions did reach the target value of 100%.
- All conditions reached the target values in terms of **specificity.**
- The **detection rate** of the total screening program was 1.035 per 1000 children screened, and the program had a positive predictive value of 33%, a sensitivity of 98% and a specificity of 99.792%.
- In 2016 **screening costs** per child (diagnostic costs excluded), were 91 euro: they show a rising trend since 2011 mainly because of the indexation of blood collection and laboratory analysis fees.

RECOMMENDATIONS

- Continue or intensify measures to improve the **timeliness of the 1st heelprick.**
- Gain more insight into the background of **objections against the NBS.**
- Continue or intensify the measures to reduce the high number of **repeat 1st heelprick when screening for CH, CF, SCD and BIO** in so far it concerned an insufficient blood sample.
- Attention to the high number of **2nd heelpricks** when screening for CH.
- Continued attention for **timeliness of registration** of diagnostic data.

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