Annual Report 2016

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Malformation Monitoring Centre Saxony-Anhalt

Medical Faculty

Otto-von-Guericke-University Magdeburg

SACHSEN-ANHALT

Ministerium für Arbeit, Soziales und Integration

Annual Report 2016
of the Federal State of Saxony-Anhalt
about the frequency of congenital malformations and anomalies as well as chromosomal aberrations

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Introduction

Dear reader,

At the very beginning, I would like to thank all of you who made this report possible through their participation and all of those who are contact persons for the Malformation Monitoring Centre. The active interdisciplinary collaboration for the purpose of continuous malformation reports is an exceptional example in Germany.

The special topic of this year's report addresses the prevalence of malformations of the skeletal. For our federal state, the malformations of extremities and their frequency distribution is in the focus.
When hearing the phrase 'malformation of extremities', one of the first thoughts that strike our mind, is the Contergan-scandal.
„Contergan? Has it not been 50 years ago and long been over? states the ebsite of the "Bundesverband der Contergangeschädigten e.V.". With the tragical teratogenic effect of the medical substance Thalidomid in the beginning of the 1960s, the number of malformations of extremities significantly increased. Later on, findings were obtained that led to a change of thinking in medicine. Not only with regard to the necessary inspection and testing of medications prior to their market entry but also regarding the observation that Postmarketing Surveillance is still irredeemable. Further, the "teratogenic impetus" is one of the reasons for the implementation of a network of surveillance and malformation monitoring systems in Europe and worldwide. These systems aim to detect the possible prevalence of malformations, such as appeared from Contergan. The first malformation monitoring systems have already been established in the 1970s in Australia and Hungary.
These systems provided inspirations for the foundation of the malformation registry here in Magdeburg in 1980.

90 % of the malformations of the skeletal are genetic and about 10% are caused by exogenous impacts, such as radiation, Thalidomid, alcoholism or due to abnormal developments mostly of the extremities and the spine, which are induced by rubella infections. They are characterized by aplasia, hypoplasia, hyperplasia or redundant body parts, such as fingers. .

Since 1993, the Malformation Monitoring Centre has been representing Germany with data from Saxony-Anhalt at the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), an WHO associated institution with 42 malformation registries from 38 countries worldwide. Further information about ICBDSR can be found on: www.icbdsr.com.

Already since 1992 has the Malformation Monitoring Centre Saxony-Anhalt been part of the European network for population-based malformation registration EUROCAT. Since 2015, the EUROCAT central registry is resident at the Joint Research Center (JRC) of the in-house science service of the European Commission in Ispra, Italy.
In the course of the annual conference in June of this year, Dr. A. Rißmann has been elected for the scientific board of the EUROCAT. Further information about EUROCAT can be found on: www.eurocat-network.eu.

I can only again and again stress that the European and worldwide networking and epidemiologic surveillance would not be possible without the dedicated collaboration of each sending clinic. All of the studies ultimately depend on the data. The larger the amount of data is, the more balanced is the interpretation and scientific evaluation.

Finally, I would like to thank the Medical Faculty of the Otto-von-Guericke-University Magdeburg, especially Prof. Dr. H-J. Rothkötter, Dr. J. L. Hülsemann and Dr. K. Stachel, who all actively support the Malformation Monitoring Centre Saxony-Anhalt project.
Yours sincerely

Petra Grimm-Benne
Federal Minister of Labour, Social Affairs and Integration
Saxony-Anhalt

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Abbreviations

AABR	automated auditory brainstem response (Hirnstammaudiometrie)
ASD	atrial septal defect
blt.	bilateral
BMI	Body-Mass-Index
BP	basis prevalence
CI	confidence interval
CNS	central nervous system
dB	dezibel
DD	differential diagnosis
DIV	double inlet ventricle
DORV	double outlet right ventricle
DUP	dilated uropathy
ENT	ears, nose, throat
EUROCAT	European Surveillance of Congenital Anomalies
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss
ICBDSR	International Clearinghouse for Birth Defects Surveillance and Research
ICSI	intracytoplasmatic sperm injection
LB	live births
MCA	multiple congenital anomalies
NHS	newborn hearing screening
n.o.s..	not otherwise specified
n.s.	not specified
NT	nuchal translucency
OR	Odds Ratio (Quotenverhältnis)
P	prevalence
PDA	persistent ductus arteriosus
PFO	persistent foramen ovale
SA	spontaneous abortion
SB	stillbirths
TEOAE	transistory evoked otoacoustic emissions
TOP	termination of pregnancy
VSD	ventricular septal defect
WOG	weeks of gestation

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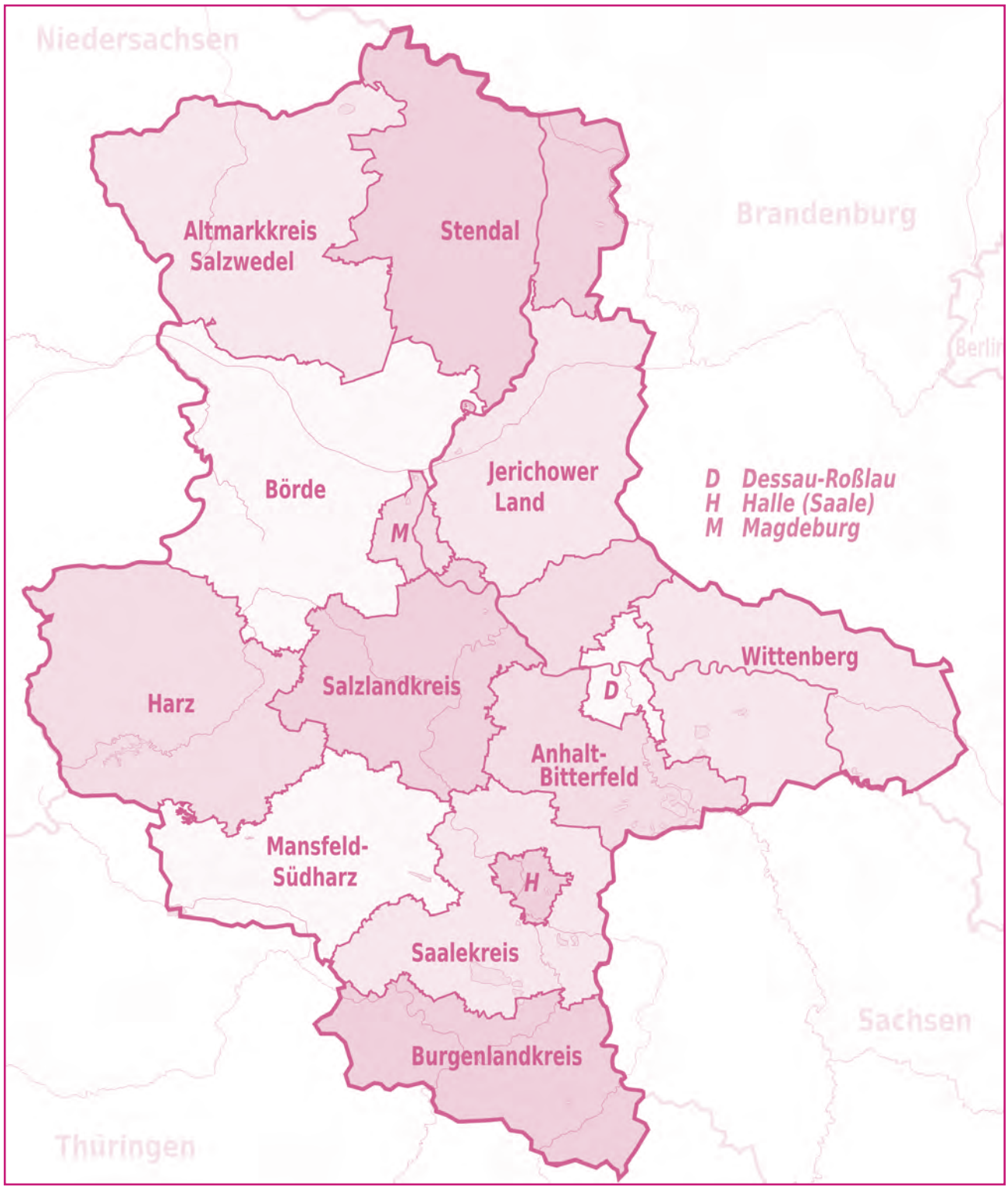
1 Saxony-Anhalt - Registration Area



2 Birth Rate 2016

	Live birth*	Stillbirths*	Spontaneous Abortions (> 16 WOG)	Termination of Pregnancy for fetal anomaly following prenatal diagnosis	Total	*Live births***	*Stillbirths***
Altmarkkreis Salzwedel	714	2	-	3	**719**	*706*	*1*
Anhalt-Bitterfeld	1,184	5	2	3	**1,194**	*1,199*	*1*
Börde	1,408	4	2	15	**1,429**	*1,432*	*4*
Burgenlandkreis	1,447	5	-	3	**1,455**	*1,437*	*3*
Dessau-Roßlau	627	2	-	1	**630**	*630*	*3*
Halle	2,251	9	1	10	**2,271**	*2,288*	*6*
Harz	1,520	8	-	9	**1,537**	*1,545*	*8*
Jerichower Land	709	2	-	4	**715**	*718*	*4*
Magdeburg	2,371	7	14	13	**2,405**	*2,401*	*11*
Mansfeld-Südharz	979	4	-	3	**986**	*977*	*2*
Saalekreis	1,536	6	-	8	**1,550**	*1,505*	*2*
Salzlandkreis	1,475	4	4	5	**1,488**	*1,483*	*2*
Stendal	875	4	1	3	**883**	*885*	*2*
Wittenberg	868	4	-	-	**872**	*887*	*5*
Unknown district in Saxony-Anhalt n.o.s.	-	-	-	1	**1**	-	-
Major cities: Dessau-Roßlau, Halle, Magdeburg	5,249	18	15	24	**5,306**	*5,319*	*20*
Districts, in total	12,715	48	9	56	**12,828**	*12,774*	*34*
Saxony-Anhalt	**17,964**	**66**	**24**	**81**	**18,135**	*18,093*	*54*

* of the Malformation Monitoring Centre for the Annual Report 2016 used extrapolated numbers, effective 01.11.2017
** Source: © * Federal Statistical Office Saxony-Anhalt, Halle (Saale), preliminary numbers of 15.11.2017

The evaluations in the annual report are based on the birth rate of the federal state Saxony-Anhalt. For the data on malformations, the deadline is at the beginning of August, for the birth rate at the beginning of September. In the monthly bulletin issued in October by the Federal Statistical Office Saxony-Anhalt (26.10.2017), a preliminary number of 16,591 live births (sorted by districts) is stated for the time period from January until November 2016.

In order to secure an in time preperation of the report for the year following this birth year, a total number of births had to be projected at the beginning of November for the determination of a prevalence. The Malformation Monitoring Centre projected the total number of births to be 17,964 live births by using numbers from the Statistical Office for January to November 2016 and a trend from the previous 12 years in Saxony-Anhalt (2nd column).
On November 15, 2017, the Statistical Office published the preliminary number of live births according to districts for 2016 (7th column). The deviation amounts to 0.71 %.

We received a differentiation by sex as well as data on stillbirths from the Statistical Office on November 16, 2017. Hence, the expected values with regard to numbers of the previous years (2004-2015) for stillbirths in 2016 were used (rounded to integral numbers, 3rd column).

3 Participating Institutions of the Region 2016

3.1 Maternity units / paediatric units / paediatric surgery / paedia tric cardiology (ordered by location)

- AMEOS Klinikum Aschersleben
- Gesundheitszentrum Bitterfeld/Wolfen
- HELIOS Klinik Jerichower Land Burg
- Städtisches Klinikum Dessau
- Altmark-Klinikum Krankenhaus Gardelegen
- AMEOS Klinikum Halberstadt
- Krankenhaus St. Elisabeth und St. Barbara Halle
- Universitätsklinikum Halle (Saale)
- HELIOS Klinik Köthen
- Herzzentrum Leipzig - Universitätsklinik, Klinik für Kinderkardiologie *(outside of Saxony-Anhalt)*
- Krankenhaus St. Marienstift Magdeburg
- Klinikum Magdeburg
- Universitätsklinikum Magdeburg A.ö.R.
- Carl-von-Basedow-Klinikum Saalekreis Merseburg
- Harzklinikum Dorothea Christiane Erxleben Klinikum Quedlinburg
- Altmark-Klinikum Krankenhaus Salzwedel
- HELIOS Klinik Sangerhausen
- AMEOS Klinikum Schönebeck
- Johanniter-Krankenhaus Genthin-Stendal
- Asklepios Klinik Weißenfels
- Harzklinikum Dorothea Christiane Erxleben Klinikum Wernigerode
- Georgius-Agricola Klinikum Zeitz
- HELIOS Klinik Zerbst/Anhalt

3.2 Institutions of pre- and postnatal diagnostics (ordered by location)

- Dipl. Heilpädagogin Schlote, Glindenberg/Magdeburg
- Dr. Perlitz, Fachärztin für Frauenheilkunde und Geburtshilfe, Haldensleben
- PD Dr. Hahmann, Facharzt für Frauenheilkunde und Geburtshilfe, Halle
- Krankenhaus St. Elisabeth und St. Barbara Halle, Pränatale Ultraschalldiagnostik: CA Dr. Seeger / OÄ Dr. Radusch
- Dr. Altus, Fachärztin für Humangenetik, Magdeburg
- Dr. Karstedt, Facharzt für Kinder- und Jugendmedizin, Kinderkardiologie, Magdeburg
- Dr. Karsten, Facharzt für Frauenheilkunde und Geburtshilfe, Magdeburg
- Klinikum Magdeburg, Pränatale Ultraschalldiagnostik: OÄ Dr. Schleef
- Universitätsklinkum Magdeburg A.ö.R., Institut für Humangenetik
- Universitätsklinkum Magdeburg A.ö.R., Universitätsfrauenklinik, Pränatale Ultraschalldiagnostik: OÄ Dr. Gerloff
- Universitätsklinkum Magdeburg A.ö.R., Institut für Klinische Chemie, Screeninglabor
- Trackingstelle Neugeborenenhörscreening Sachsen-Anhalt, Magdeburg
- Dr. Welger, Fachärztin für Frauenheilkunde und Geburtshilfe, Magdeburg
- Dipl.-Med. Fiedler und Giesecke, Fachärzte für Orthopädie, Merseburg
- Dr. Schneider, Facharzt für Frauenheilkunde und Geburtshilfe, Naumburg
- Altmark-Klinikum Krankenhaus Salzwedel, Pränatale Ultraschalldiagnostik: CA Dr. Müller
- Harzklinikum Dorothea Christiane Erxleben Klinikum Wernigerode, Pränatale Ultraschalldiagnostik: OÄ Dr. Schulze

3.3 Pathological-anatomical institutes (ordered by location)

- Institut für Pathologie Dr. Taege, Dr. Bilkenroth und Dr. Irmscher, Eisleben
- Universitätsklinikum Halle (Saale), Institut für Pathologie
- Klinikum Magdeburg, Institut für Pathologie
- Universitätsklinikum Magdeburg A.ö.R., Institut für Pathologie
- Praxis für Pathologie PD Dr. Schultz, Dr. Lüders, Dr. Hainz, Stendal
- Institut für Pathologie Dr. Meier, Weißenfels

4 Malformation Registration in Saxony-Anhalt

4.1 General Information

To begin with, we would like to thank all sending institutions for the active interdisciplinary collaboration for the purposes of continuous malformation reports.

This year's special topic of the Annual Report is the prevalence of malformations of the skeletal. Thus, malformations of extremities and their frequency distribution in our federal state are particularly in the focus.
There is one word which is also connected to malformations of the extremities by non-professionals – Thalodomid (Contergan©). Contergan? Has it not been 50 years ago and long been over? states the website of the "Bundesverband der Contergangeschädigten e.V.".
With the tragical teratogenic effect of the medical substance Thalidomid in the beginning of the 1960s, the number of malformations of extremities significantly increased.
Later on, findings were obtained that led to a change of thinking in medicine. Not only with regard to the necessary inspection and testing of medications prior to their market entry but also regarding the observation that Postmarketing Surveillance is still irredeemable. Further, the "teratogenic impetus" is one of the reasons for the implementation of a network of surveillance and malformation monitoring systems in Europe and worldwide (the first have already been established in the 1970s in Australia and Hungary). These systems aim to detect the possible prevalence of malformations, such as appeared from Contergan.
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Already since 1992 has the Malformation Monitoring Centre Saxony-Anhalt been part of the European network for population-based malformation registration EUROCAT (European Surveillance of Congenital Anomalies).
Since 2015, the EUROCAT central registry is resident at the Joint Research Center (JRC) of the in-house science service of the European Commission in Ispra, Italy.
In the course of the annual conference in June 2017, Dr. A. Rißmann has been elected for the scientific board of the EUROCAT. Further information about the EUROCAT can be found on: www.eurocat-network.eu.
We can only again and again stress that the European and worldwide networking and epidemiologic surveillance would not be possible without the dedicated collaboration of each sending institution.

This national project for malformation data acquisition is only possible due to the consistent support of the Ministry of Employment and Social Affairs of the Federal State of Saxony-Anhalt. At this point we would like to thank especially our persons in charge in the Ministry Dr. Dr. R. Nehring and Dr. H. Willer and Mr. M. Schiener.

Additionally, we would like to thank our colleagues at the Medical Faculty of the Otto-von-Guericke University for their organisational support within the project of the Malformation Monitoring Centre Saxony-Anhalt. We would like to thank particularly Dr. K. Stachel, Dr. J. L. Hülsemann and Prof. Dr. med. H.-J. Rothkötter.

4.2 Registration and Analysis

The present report contains data about infants of the Federal State of Saxony-Anhalt with congenital malformations and chromosomal disorders in relation to the mother's place of residence during pregnancy, respectively at birth.

The total number of "births" includes
- live births,
- stillbirths,
- terminations of pregnancy after prenatal diagnostics (all weeks of gest.) sowie
- spontaneous abortions (>16 weeks of gest.)

and forms basis for the annual prevalence calculation.

The expected date of delivery is used as basis for analysing the termination of pregnancy, e.g. 2014 is considered the year of birth although some terminations of pregnancy after prenatal diagnostics took place at the end of 2013. This method is common on an international scale.

In contrast, the time of delivery of spontaneous abortions is not corrected as the abortion is registered in the month when it actually took place.

The data of live births and stillbirths is provided annually by the Statistical Office of Halle. The outlined percentage indications and prevalences are rounded.

All data transmitted to the Monitoring of Congenital Malformations is medically controlled upon receipt and the diagnoses are encoded according to ICD-10 and according to another extension (Adaptation of the Royal College of Pediatrics and Child Health). Details about the intake of medication during pregnancy are registered by using the internationally recommended ATC codes.

The total number of infants with major malformations as well as the geographical distribution of appearance in the big cities and districts is outlined in chapter 7 and 8 (German version).
Infants with only minor malformations or rather norm variations are not evaluated separately since this data is only collected incompletely in the end. Chapter 11 outlines the most frequent single diagnoses of major malformations registered in 2014. Similar to the previous years we analysed the reported pathological prenatal screening results separately in Chapter 10 (German version).

Chapter 12 contains again the analysis of the so-called indicator birth defects. As we have presented data in this way for a number of years, it is possible to evaluate the current prevalences of 2014 in comparison to the last 12 years (2002-2013). Here, a **total number of 207,910 births** forms basis for the **basis prevalence** calculation **2004 to 2015**.

The graphical presentation of the annual prevalences allows to identify frequent appearances and gives a good overview about rarely appearing indicator births defects. The exact calculation of confidence levels is based on the binominal distribution with a confidence probability of 95%. To discover a certain trend the percentage change of an indicator malformation prevalence is illustrated as well during the publishing time of the Annual Report (Chapter 12.37).

Chapter 13 (German version) outlines data regarding genetically caused diseases, chromosomal disorders, sequences, associations, complexes and embryopathies. Chapter 14 (German version) contains an analysis of malformation caused terminations of pregnancy.

As usual, the Newborn hearing screening forms part of the Report of the Malformation Monitoring Centre Saxony-Anhalt and is outlined in chapter 18.
Chapter 19 presents the Annual Report of the department of newborn screening in Saxony-Anhalt with data regarding congenital metabolic disorders and endocrinopathies.

4.3 Data Quality and Completeness/Reporting Procedure

The scientific work of the Malformation Monitoring Centre Saxony-Anhalt and the current annual report are based on a database. The data has been sent to the Malformation Monitoring Centre by the maternity and pediatric clinics resp. by institutions of pre- and postnatal diagnostics, which are mentioned in chapter 5.2 (German version). This database already contains data of 37 years. We were able to collect **2,055 records** about the newborns and fetuses of the **birth year 2016**, which is equal to 11 % of all born in Saxony-Anhalt. After the publication of last year's Annual Report, the number of births and corresponding data records for 2015 increased from 1,825 to 1,855.

We received **2,339 reports** for the **birth year 2016**. In 10.8% of all cases we received information from different institutions. Receiving these double-reports helps to reconfirm a diagnosis or to classify complex malformations exactly.

Continuously high reporting rates in respect to the number of births per clinic are obtained for long years from the AMEOS Klinikum Schönebeck, HELIOS Klinik Köthen and the hospital St. Marienstift Magdeburg. A remarkly high increase of the reporting rate compared to last year has been realized by the Johanniter-Krankenhaus Genthin-Stendal It was to expect, with regard to their birth rates, that the Saale-Unstrut Klinikum Naumburg would report 13 children or fetuses with major malformations; the Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg was expected to report 25 with regard to their birth rates.

The quality of the Annual Report is influenced by the significance of the related statistics, which in turns is dependent on the continouosly high quality level of the data. Therefore, it is of importance to receive correct and detailed diagnosis desciptions on the reports as well as to collect all incoming questions. The data quality remained also in 2016 on a high level thanks to the excellent work and dedication of all our senders. We received important information nearly in all cases: gender 98.4 %, maternal age 99.6 % and district 99.9 %. The births weight was not reported in 70 cases (3.4 %), of which 47 were terminations of pregnancy. The head circumference, a significant factor for the assessment of a microcephaly, was missing for 346 children (18.3 % of the non-deceased live births).

We kindly ask again all reporting institutions in Saxony-Anhalt to describe every diagnosed malformation as detailed as possible and to mention also additional malformations. It is a positive development that only five of the fetuses of the birth year 2016 (2015: 4 fetuses), which have been prenatally diagnosed with an indicator malformation (chapter 10 (German version)), could not have been matched to a postnatal report. If the confirmation of the report is missing or unclear, it cannot be considered for the statistics of the indicator malformations (chapter 12).

We receive two thirds of malformation registrations and indications of control cases by means of the **"green documentation sheets"**, which we provide free of charge to the reporting institutions. Documentation sheets may be ordered at any time by phone +49 391-6714174 or e-mail to monz@med.ovgu.de

Additionally, it is also possible to report on so-called **"white documentation sheets"**. This form serves to register a minimum data set. The indication of the above mentioned information and possible risk factors like intake of medication or family histories and an exact description of the malformation and corresponding symptoms are important here.

Both documentation sheets are also available for download on our homepage **www.angeborene-fehlbildungen.com.** It is possible to complete them manually or to enter the data directly into the PDF file, print it out and send it back to us. Mostly, we receive the reports by mail on our documentation form sheets. With some institutions, we established the transmission of reports via Fax. Our **fax number** is **+49 391-6714176**.

We will be at your disposal for answering any further questions about the reporting procedure and congenital malformations in general.

6 Sex Ratio

Sex ratio of all live births and stillbirths in Saxony-Anhalt (estimated numbers for the Annual Report 2016 applying information of the Statistical Office Halle)

male	9.274	live births and stillbirths
female	8.756	live births and stillbirths
total	18.030	live births and stillbirths

Sex ration m : f = 1.06

The Statistical Office provided from January to November 2016 a preliminary number of 16,591 live births, of which 8,534 were male und 8,057 female (sex ratio m : f = 1,06).

By using the preliminary numbers of live births in the districts from January to November 2016 from the Statistical Office and the tendency of the past 12 years in Saxony-Anhalt, a total number of 17,964 live born children (9,240 male and 8,724 female) was estimated. For the Annual Report of 2016, an expected value of 66 stillbirths (34 male and 32 female) was used.

For 2016 the Malformations Monitoring Centre received 1,052 reports of newborns with major or minor malformations. Compared to the year 2015 (895 births), in 2016 the number of newborns with malformations increased by 157.

This was in the year 2016 for the major malformations more noticeably than in the year 2015 (m : f = 1.08). For the newborns with minor malformations, androtropism was distinctly less frequent than in 2015 (m : f = 1.40).

Sex ratio of all births with major malformations (including abortions)

male	353	births
female	292	births
uncertain	3	births
unknown	25	births
total	673	births

Sex ratio m : f = 1.34

Sex ratio pf all births with only minor malformations and anomalies

male	215	births
female	164	births
total	379	births

Sex ratio m : w = 1.50

11 Organ System Involvement in Infants and Foetuses with Major Malformations

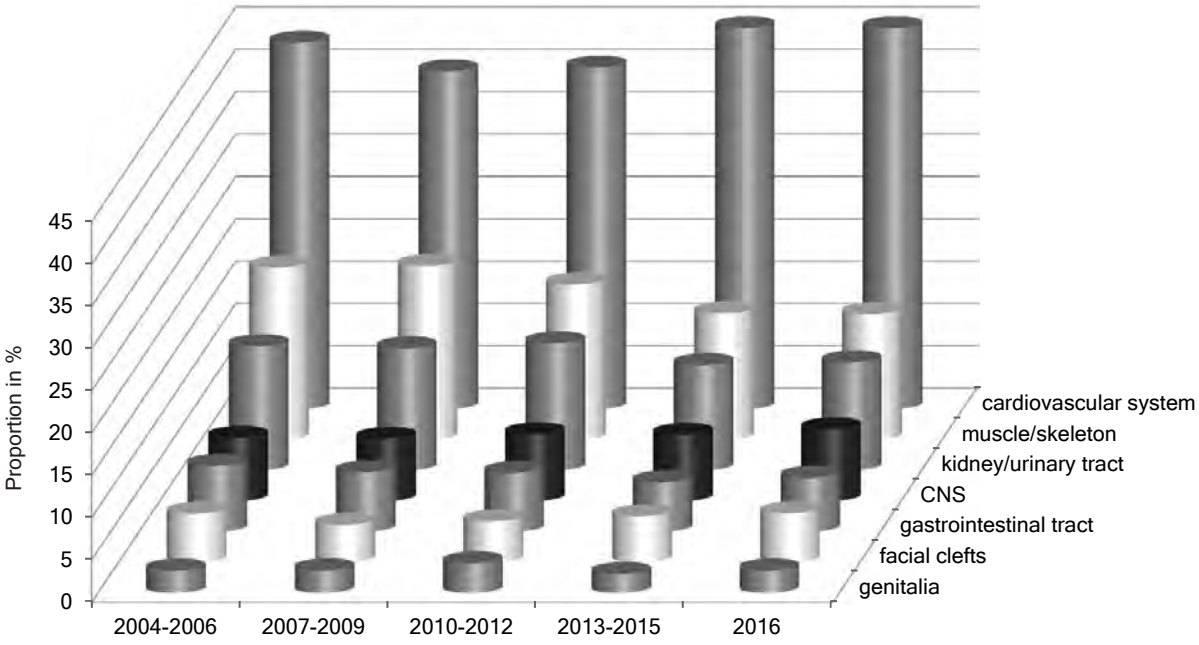


Fig. 5: Organ system involvement in major malformations (grouped)

The prevalence with which the different organ systems are affected by major malformations, is presented in chapter 11.
In Saxony-Anhalt, 763 newborns with major malformations were reported in 2016. Within these, 293 newborns showed more than one major malformation, thus multiple mentions are possible.
The diagram only displays the stated malformations in the selected organ systems of newborns.
The data from year 2016 are illustrated separately. For the previous years, beginning 2004, data of three years is grouped in figure 5. The prevalence of malformations in the selected organ systems has stayed in the same order almost without any changes since 2004.

The cardiovascular system was, as expected, again in 2016 the organ system that showed the highest number of malformations. 45.68 % of the by malformations affected persons showed this malformation in 2016 compared to the years 2013 to 2015 (45.39 &) with an almost equal proportion.

The proportion of affected persons with major malformations of the muscle and skeleton system decreased again, just like in the previous years (2016: 14.86 %; 2013-2015: 14.96 %; 2010-2013: 18.38 %).

A slight increase in the prevalence of malformations in the kidney and urinary tract became apparent in the year 2016 (12.78 %) compared to 2013 to 2015 (12.48 %). However, this year's proportion did not reach the all time high of 2010 to 2012 (15.04 %).
Proportionally, there have been more malformations of the CNS detected in 2016 (8.47 %) compared to the years 2013-2015 (7.84 %) or 2010-2012 (7.91 %). This year's percentage lies above the since 2004 calculated average proportions (see diagram). This development needs to be further monitored.
After the relatively low proportion of malformations of the gastrointestinal tract in the years 2013 to 2015, the percentage for 2016 (6.40 %) increases again and almost reaches the numbers of previous years (2010-2012: 6.96 %; 2007-2009: 7.03 %)
Facials clefts occurred again more frequently (2016: 5.80 %; 2013-2015: 5.47 %).
With 2.68 % of all newborns with major malformations, the malformations of the genitalia have become more frequent again, after they've been less frequent in 2013 to 2015 (2.26 %). However, they did not exceed the high of 2010 to 2012 (3.51 %).

The most frequent single diagnoses 2016 (only major malformations)

	ICD-10	Diagnosis	Infants/Foetuses 2016		Infants/Foetuses 2004-2015 Prevalence /10.000**
			Number	Pravalence /10.000*	
1.	Q21.1	Atrial septal defect (inclusive persistent foramen ovale/PFO)	204	112.5	82.9
2.	Q21.0	Ventricular septal defect	79	43.6	46.6
3.	Q62.3	Other obstructive defects of renal pelvis and ureter (dilated uropathy grade II-IV)	45	24.8	17.4
4.	H90.	Conductive and sensorineural hearing loss	42	23.2	17.4 (22.2#)
5.	Q66.0	Pes equinovarus congenitus (clubfoot)	32	17.6	16.1
6.	Q90.	Down syndrome (trisomy 21)	24	13.2	18.1
7.	Q37.	Cleft palate with cleft lip	21	11.6	11.0
8.	Q62.1	Stenosis and atresia of ureter	20	11.0	7.7
9.	Q62.2	Congenital megaureter	19	10.5	8.1
10.	Q69.	Polydactyly (pre- and postaxial)	17	9.4	12.1
11.	Q21.2	Atrioventricular septal defect	12	6.6	4.5
12.	Q25.0	Patent ductus arteriosus	11	6.1	9.8
	Q63.0	Accessory kidney	11	6.1	7.2
	Q22.1	Pulmonary valve stenosis	11	6.1	6.8
	Q61.4	Renal dysplasia	11	6.1	6.0
	Q25.1	Coactartion of aorta	11	6.1	5.2
	Q23.3	Congenital mitral insufficiency	11	6.1	4.9
	Q35.1 Q35.5 Q35.9	Cleft palate	11	6.1	3.8
	Q02	Microcephaly	11	6.1	3.2
13.	Q05	Spina bifida	9	5.0	5.8
	Q21.3	Tetralogy of Fallot	9	5.0	3.6
	Q20.3	Discordant ventriculoarterial connection	9	5.0	3.4
	Q79.2	Omphalocele	9	5.0	3.3
	Q60.6	Potter sequence	9	5.0	2.3

* based on 18,135 newborns

** based on 207,910 newborns

\# 2007-2015 (since 2007 data is synchronised with the newborn hearing screening tracking centre)

The table presented on the previous page shows the most frequently registered major single diagnoses in Saxony-Anhalt. Therefore, the current and the basis prevalance, respectively, are denoted. The prevalence for the year 2016 is based on 18,135 births, while the baisc prevalance (2004 to 2015) is based on 207,910 births.

By far the cardiovascular system is most frequently affected by malformations. Just like every year, the ASD (2016: 112.5 per 10,000 births) can be found in the first row. It occured with more than one percent more often than in the years 2004 to 2015 (82,9 per 10,000 births, CI 79.0 to 86.9). Since about 2010, more cardiac malformations were reported in detail. As a result, a seperated count for some cardiac malformations, such as the atrioventricular septal defect (2016: 6.6 per 10,000 births, 2004-2015: 4.5 per 10,000 births, CI 3.6 to 5.6), the congenital mitral insufficiency (2016: 6.1 per 10,000 births, 2004-2015: 4.9 per 10,000 births, CI 4.0 to 5.9), the tetralogy of Fallot and the discordant ventriculoarterial connection (2016 respectively: 5.0 per 10,000 births) shows higher pravalence than over the years 2004 to 2015.

As usually, the VSD (2016 43.6 per 10,000) ranks second in the list of frequencies of the single diagnoses. It occured a little less frequently in 2016 than in previous years (2004-2015: 46.6 per 10,000 births, CI 43.8 to 49.6).Likewise, less frequently than on average, similar to in the previous year, a PDA (2016: 6.1; 2015: 7.4 per 10,000 newoborns) was reported. Coactartion of aorta and pulmonary valve stenosis (likewise, respectively 6.1 per 10,000 births) showed simalar frequencies as the basis prevalence in 2016.

Ranked third place, after four years in the fourth place and more frequently than expected is the dilated uropathy from grade II (2016: 24.8 per 10,000 births; 2004-2015: 22.2 per 10,000 births, CI 20.3 to 24.3). Moreover, three more malformations of the urinary tract system, the stenosis and atresia of ureter (2016: 11.0 per 10,000 births, 2004-2015: 7.7 per 10,000 births, CI 6.6 to 9.0), the congenital megaureter (2016: 10.5 per 10,000 births, 2004-2015: 8.1 per 10,000 births, CI 7.0 to 9.4) and the Potter sequence (2016: 5.0 per 10,000 births, 2004-2015: 2.3 per 10,000 births, CI 1.7 to 3.1) were observed more often than usually. With, repectively, 6.1 per 10,000 births in 2016, a typical number of renal dysplasia was reported and an accessory kidney was slightly less frequent than typically.

This year, in the fourth place was a conductive and sensorineural hearing loss (2016: 23.2 per 10,000 births). In 2007, the Newborn Hearing Screening was introduced in Saxony-Anhalt. The subsequent increase of the prevalance, which shows the influence of the Hearing Screening on the detection and reporting rate, is not captured by the pravalence of the interval from 2004 to 2015 of 17.4 per 10,000 births (CI 15.7 to 19.3). Until 2006, the observed prevalence was significantly below 10.0 and then increased to 21.9 per 10,000 births (2007-2015: 156,004 births, CI 19.7 to 24.3).

On rank five, in the reference range of the basis prevalence, is the pes equinovarus congenitus (clubfoot) (2016: 17.6 per 10,000 births; 2004-2015: 16.1 per 10,000 births, CI 14.5 to 17.9).

The Down-syndrome (2016: 13.2 per 10,000 births) was significantly less frequent than on average (2004-2015: 18.1 per 10,000 births, CI 16.4 to 20.0). For all reported years, only in 2005 with 12.1 per 10,000 births, the prevalanece value was smaller than in this year.

The cleft lip and palate as well as the indicator malformation cleft lip and cleft lip and palate, to which this malformation belongs, occured with a frequency in the expected interval (2016: 11.6 per 10,000 births, 2004-2015: 11.0 per 10,000 births, CI 9.6 to 12.5).

The tenth rank in 2016 is taken by polydactyly (2016: 9.4 per 10,000 births, 2004-2015: 12.1 per 10,000 births, CI 10.7 to 13.7). The frequency of polydactyly, which includes the more rare preaxial polydactyly (indicator malformation) as well as the postaxial polydactyly, is below the expetcted value.

On rank 12 (2016: 6.1 per 10,000 births), and, respectively, above the average prevalance from 2004 to 2015 are the two indicator malformations cleft palate (2004-2015: 3.8 per 10,000 births, CI 3.0 to 4.8) and microcephaly (2004-2015: 3.2 per 10,000 births, CI 2.4 to 4.1). A higher prevalance of cleft palates was observed in 2006 (6.4 per 10,000 births) for the last time. This year's prevalence of microcephaly exceeds the expected value by far.
For newborns, microcephaly is defined by statistical values of the head circumference; however, it appears often only with the development of the brain in the first months of life. After a reassessment, when applying lower boundary values (2 standard deviations instead of the 3rd percentile), and the strict consideration of the maturity of the child, the number of head circumferences decreased compared to the ones which were evaluated as microcephaly by applying the old boundary values. Nonetheless, the high values in the past five years are noticeable. Presumably, the increase in the prevalence is only a seemingly increase and based on the sensitization of this malformation through discussions about the Zika virus and the, therefore, following additional information on the clinical course in the first year of life.

Rank 13 of the frequency list (2016: 5.0 per 10,000 births) is occupied by two indicator malformations. The prevalence of spina bifida is within the domain of the conficence interval (2004-2015: 5.8 per 10,000 births, CI 4.9 to 6.9). The abdominal wall defect omphalocele was diagnozed a little more frequently than in the previous years (2004-2015: 3.3 per 10,000 births, CI 2.5 to 4.2).

Anencephalia and the Turner-syndrome, both just not listed in the table anymore, appeared in 2016 with a prevalence of 4.4 and 3.9, respectively, per 10,000 births approximately twice as often as was expected (2004-2015: 2.1 per 10,000 births, CI 1.5 to 2.8).

12 Indicator Defects of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

12.0 Definitions

1. Neural tube defects: common congenital malformations that occur when the neural tube fails to achieve proper closure during early embryogenesis, resulting in defective development of the associated vertebral arches.
Synonyms: Spina bifida, anencephaly, NTD.

2. Anencephaly: a congenital malformation characterized by the total or partial absence of the cranial vault, the covering skin, and the brain missing or reduced to small mass. Inclusive craniorachischisis. Inclusive infants with iniencephaly and other neural tube defects as Encephalocele or open spina bifida, when associated with anencephaly. Exclusive acephaly, that is, absence of head observed in amorphous acardiac twins.

3. Spina bifida: a family of congenital malformation defects in the closure of the spinal column characterized by herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine. Inclusive meningocele, meningomyelocele, myelocele, myelomeningocele, rachischisis. Spina bifida is not counted when present with anencephaly. Exclusive spina bifida occulta, sacrococcygeal teratoma without dysraphism.

4. Encephalocele: a congenital malformation characterized by herniation of the brain and/or meninges through a defect in the skull. Encephalocele is not counted when present with spina bifida.

5. Microcephaly: a congenitally small cranium, defined by an occipito frontal circumference (OFC) 3 standard deviation below the age and sex appropriate distribution curves (see growth charts Voigt et al. 2014, chapter 25).
Exclusive microcephaly associated with anencephaly or encephalocele.

6. Congenital Hydrocephaly: a congenital malformation characterized by dilatation of the cerebral ventricles, not associated with a primary brain atrophy, with or without enlargement of the head, and diagnosed at birth. Not counted when present with encephalocele or spina bifida. Exclusive macrocephaly without dilatation of ventricular system, skull of macerated fetus, hydranencephaly, holoprosencephaly, and postnatally acquired hydrocephalus.

7. Arhinencephaly/holoprosencephaly: a congenital malformation of the brain, characterized by various degrees of incomplete lobation of the brain hemispheres. Olfactory nerve tract may be absent. Holoprosencephaly includes cyclopia, ethmocephaly, cebocephaly, and premaxillary agenesis.

8. Anophthalmos/microphthalmos: apparently absent or small eyes. Some normal adnexal elements and eyelids are usually present. In microphthalmia, the corneal diameter is usually less than 10 mm. and the antero posterior diameter of the globe is less than 20 mm.

9. Anotia/Microtia: a congenital malformation characterized by absent parts of the pinna (with or without atresia of the ear canal) commonly expressed in grades (I - IV) of which the extreme form (grade V) is anotia, absence of pinna. Exclusive small, normally shaped ears, imperforate auditory meatus with a normal pinna, dysplastic and low set ears.

10. Tetralogy of Fallot: a condition characterized by ventricular septal defect, overriding aorta, infundibular pulmonary stenosis, and often right ventricular hypertrophy.

11. Transposition of great vessels (TGV): a cardiac defect where the aorta exits from the right ventricle and the pulmonary artery from the left ventricle, with or without other cardiac defects. Inclusive double outlet ventricle so called corrected transposition.

12. Hypoplastic left heart syndrome: a cardiac defect with a hypoplastic left ventricle, associated with aortic and/or mitral valve atresia, with or without other cardiac defect.

13. Coarctation of the aorta: an obstruction in the descending aorta, almost invariably at the insertion of the ductus arteriosus.

14. Cleft lip with or without cleft palate: a congenital malformation characterized by partial or complete clefting of the upper lip, with or without clefting of the alveolar ridge or the hard palate. Exclusive midline cleft of upper or lower lip and oblique facial fissure (going towards the eye).

15. Cleft palate without cleft lip: a congenital malformation characterized by a closure defect of the hard and/or soft palate behind the foramen incisivum without cleft lip. Inclusive submucous cleft palate. Exclusive cleft palate with cleft lip, cleft uvula, functional short palate, and high narrow palate.

16. Choanal atresia, bilateral: congenital obstruction (membraneous or osseous) of the posterior choana or choanae. Exclusive choanal stenosis and congestion of nasal mucosa.

17. Oesophageal atresia/stenosisl: a congenital malformation characterized by absence of continuity or narrowing of the esophagus, with or without tracheal fistula. Inclusive Tracheoesophageal fistula with or without mention of atresia or stenosis of oesophagus.

18. Small intestine atresia/stenosis: complete or partial occlusion of the lumen of a segment of the small intestine. It can involve a single area or multiples areas of the jejunum or ileum. Exclusive duodenal atresia

19. Anorectal atresia/stenosis: a congenital malformation characterized by absence of continuity of the anorectal canal or of communication between rectum and anus, or narrowing of anal canal, with or without fistula to neighbouring organs. Exclusive mild stenosis which does not need correction, and ectopic anus.

20. Undescended testis: bilateral undescended testes in at term newborn or at least unilateral undescended testis in males more than 1 year of age. Exclusive retractrile testis.

21. Hypospadias: a congenital malformation characterized by the opening of the urethra on the ventral side of the penis, distally to the sulcus. Incl. penile, scrotal, and perineal hypospadias. Exclusive glandular or first degree hypospadias and ambiguous genitalia (intersex or pseudohermaphroditism).

22. Epispadias: a congenital malformation characterized by the opening of the urethra on the dorsal surface of the penis. Not counted when part of exstrophy of the bladder.

23. Indeterminate sex: genital ambiguity at birth that does not readily allow for phenotypic sex determination. Incl. male or female true or pseudohermaphroditism.

24. Potter sequence: a congenital malformation characterized by complete absence of kidneys bilaterally or severely dysplastic kidneys.

25. Renal agenesis, unilateral: a congenital malformation characterized by complete absence of one kidney unilaterally. Exclusive unilateral dysplastic kidney.

26. Cystic kidney: a congenital malformation characterized by multiple cysts in the kidney. Inclusive infantile polycystic kidney, multicystic kidney, other forms of cystic kidney and unspecified cystic kidney. Exclusive single kidney cyst.

27. Bladder exstrophy: complex malformation characterized by a defect in the closure of the lower abdominal wall and bladder. Bladder opens in the ventral wall of the abdomen between the umbilicus and the symphysis pubis. It is often associated with epispadias and structural anomalies of the pubic bones.

28. Polydactyly, preaxial: extra digit(s) on the radial side of the upper limb or the tibial side of the lower limb. It can affect the hand, the foot, or both.

29. Limb reduction defects: a congenital malformation characterized by total or partial absence or severe hypoplasia of skeletal structures of the limbs. Inclusive femoral hypoplasia. Exclusive mild hypoplasia with normal shape of skeletal parts, brachydactyly, finger or toe reduction directly associated with syndactyly, general skeletal dysplasia and sirenomelia.

30. Diaphragmatic hernia: a congenital malformation characterized by herniation into the thorax of abdominal contents through a defect of the diaphragm. Inclusive total absence of the diaphragm. Exclusive hiatus hernia, eventration and phrenic palsy.

31. Omphalocele: a congenital malformation characterized by herniation of abdominal contents through the umbilical insertion and covered by a membrane which may or may not be intact. Exclusive gastroschisis (para umbilical hernia), a or hypoplasia of abdominal muscles, skin covere umbilical hernia.

32. Gastroschisis: a congenital malformation characterized by visceral herniation through a right side abdominal wall defect to an intact umbilical cord and not covered by a membrane. Exclusive hypoplasia of abdominal muscles, skin covered umbilical hernia, omphalocele.

33. Prune belly sequence: a complex congenital malformation characterized by deficient abdominal muscle and urinary obstruction/distension. It can be caused by urethral obstruction secondary to posterior urethral valves or urethral atresia. In the affected fetus the deficiency of the abdominal muscle may not be evident. It can be associated with undescended testes, clubfoot, and limb deficiencies.

34. Down syndrome (Trisomy 21): a congenital chromosomal malformation syndrome characterized by a well known pattern of minor and major anomalies and associated with excess chromosomal 21 material. Inclusive trisomy mosaicism and translocations of chromosome 21.

35. Patau syndrome (Trisomy 13): a congenital chromosomal malformation syndrome associated with extra chromosome 13 material. Inclusive translocation and mosaic trisomy 13.

36. Edwards syndrome (Trisomy 18): a congenital chromosomal malformation syndrome associated with extra chromosome 18 material. Inclusive translocation and mosaic trisomy 18.

Note:

The prevalences we calculated in the following chapters are population-based. The value indicates the number of births with malformations born in the observed population with reference to the total number of births in this population. Since 2000, the prevalence calculations are only referring to children whose mothers have their residence in Saxony-Anhalt. Between 1996-1999, the registration area of the Monitoring of Congenital Malformations did not cover the entire area of Saxony-Anhalt (1996/1997: 14, 1998: 15, 1999: 16 of 21 districts). The calculation of the basis prevalences (2004-2015) is based on a total number of 207,910 births.

The analysis of the indicator malformations is conducted with regard to the diagnoses. It is possible that one child has more than one indicator malformation. Therefore, the summarization of all indicator malformations might be higher than the total number of births with an indicator malformation.

12.1 Neural tube defects (Q00./Q01./Q05.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Halle 5 x Magdeburg	6	11.3	↔
Districts: 1 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 2 x Burgenlandkreis 6 x Börde 2 x Harz 3 x Jerichower Land 1 x Stendal	16	12.5	↑
Saxony-Anhalt	**22**	**12.1**	↑

Neural tube defects (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	9.76	7.35 - 12.70
Districts	8.91	7.56 - 10.48
Region	9.14	7.95 - 10.49
EUROCAT	10.25	10.03 - 10.48
		3.43 S Portugal* 20.19 Isle de la Reunion (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

Neural tube defects contain three malformations of the CNS: Anencephaly, Spina bifida und Encephalocele.
In 2016, eight anencephalies, nine spina bifidas and five encephaloceles were reported. While for spina bifida, which usually accounts for about 60 % of the neural tube defects, a prevalence within the confidence interval of the basis prevalence was noticeable, the other two entities showed a prevalence significantly above the expected value.
Hence, the resulting **prevalence** in 2016 for neural tube defects amounts to **12.1 per 10,000 births** and is above the upper confidence limit of the calculated basis prevalence (2004-2015: 9.14 per 10,000 births).

For Europe, EUROCAT states a basis prevalence of 10.25 per 10,000 births. The value for Saxony-Anhalt in 2016 can be considered as significantly high but yet, does not reach the maximum values of other registries.

In five cases, the infants were live births. The prevalence of live births with neural tube defect of 2.7 per 10,000 births is equal to the time period of 2004 to 2015 (2.7 per 10,000 births). The largest proportion consists, respectively, of terminations of pregnancy (2016: 73 %, 2004-2015: 68 % of births with neural tube defect).

additional information:

Pregnancy outcome	5 x live births 1 x spontaneous abortion 16 x termination of pregnancy
Sex	5 x male 9 x female 8 x no indication
Number of isolated malformations/MCA	11 x MCA 11 x isolated

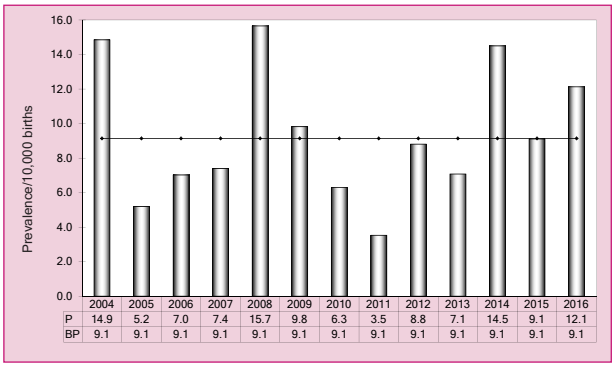


Fig. 6: Development of prevalence/10,000 births with neural tube defects in the registration area since 2004

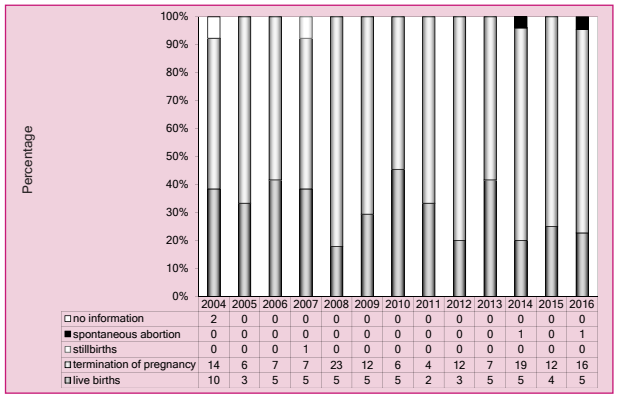


Fig. 7: Pregnancy outcomes of neural tube defects in the registration area since 2004

In 2016, one neural tube defect per 824 births was registered in Saxony-Anhalt.

12.2 Anencephaly (Q00.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Halle 3 x Magdeburg	4	7.5	↑
Districts: 1 x Anhalt-Bitterfeld 1 x Burgenlandkreis 2 x Börde	4	3.1	↔
Saxony-Anhalt	**8**	**4.4**	↑

Anencephaly (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	1.60	0.73 - 3.03
Districts	2.24	1.55 - 3.13
Region	2.07	1.50 - 2.79
EUROCAT	3.89	3.76 - 4.03
		0.99 Wielkopolska (Poland)* 7.38 Isle de la Reunion (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

We registered eight births with anencephaly in Saxony-Anhalt in 2016. Hence, anencephaly takes place 14 in the ranking of the most frequent malformations.
The **12-month prevalence** of **4.4 per 10,000 births** is highly above the confidence interval of the basis pravelence (2.07 per 10,000 births, CI 1.50 - 2.79). Due to the small numbers, such deviations are not unusual. In the years 2003, 2008, and 2014 also eight and nine, respectively, anencephalies were observed in Saxony-Anhalt.

Compared to the pravalences denoted by EUROCAT, this year's value is above the European median (3.89 per 10,000 births), though other regions still exceed this value.

In one case with a complex malformation, a spontaneous abortion occured in the 24th week of gestation.
For all seven terminations of pregnancy, the anencephaly was detected between the 10th and 19th WOG in the prenatal ultrasound and the pregnancies were terminated between the 14th and 20th WOG.

additional information:

Pregnancy outcome	1 x spontaneous abortion 7 x termination of pregnancy
Sex	1 x male 4 x female 3 x no indication
Number of isolated malformations/MCA	4 x MCA 4 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Amniotic band between the inside of the right lower forearm and the occipital region, bilateral anophthalmia, rudimentary nose, median cleft palate and mandibular cleft, mandibular micrognathia, peremal symrachydactyly of the left hand and right foot (each with aplasia of middle and end pharynx of digiti IV), brachyphalangia of the hand and clubfoot on the right, hypoplasia of the lungs and heart, craniofacial dysmorphism with hypertelorism and laterally displaced eyelids
- Omphalocele, deep-seated ears
- 2 x hypoplastic adrenal glands

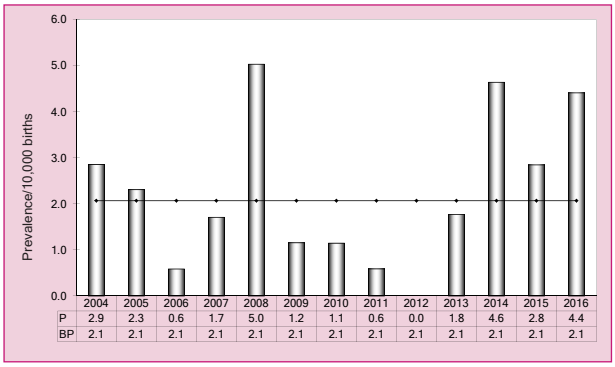


Fig. 8: Development of prevalence/10,000 births with anencephaly in the registration area since 2004

In 2016, one anencephaly per 2,267 births was registered in Saxony-Anhalt.

12.3 Spina bifida (Q05.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities	0	0.0	↓
Districts: 1 x Altmarkkreis Salzwedel 1 x Burgenlandkreis 2 x Börde 1 x Harz 3 x Jerichower Land 1 x Stendal	9	7.0	↗
Saxony-Anhalt	**9**	**5.0**	↔

Spina bifida (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	6.56	4.62 - 9.05
Districts	5.54	4.42 - 6.86
Region	5.82	4.89 - 6.91
EUROCAT	5.12	4.97 - 5.28
		1.81 S Portugal* 10.58 Isle de la Reunion (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

Three live births and six terminations of pregnancy were affected by Spina bifida in Jahr 2016.
The observed prevalence of 5.0 per 10,000 births is within the calculated basis prevalence for the past 12 years of 5.82 per 10,000 births in Saxony-Anhalt as well as the Europe-wide prevalence given by EUROCAT (5.12 per 10,000 births).

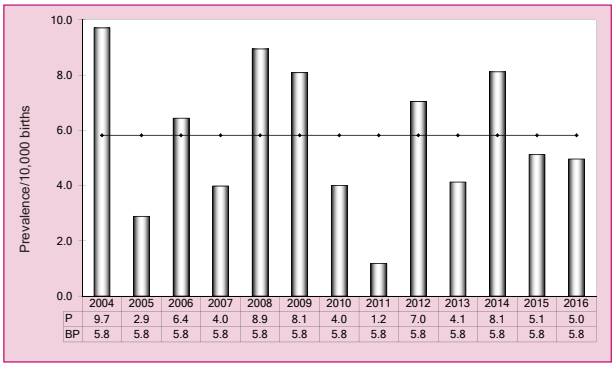
zusätzliche Angaben:

Pregnancy outcome	3 x live births 6 x termination of pregnancy
Sex	3 x male 4 x female 2 x no indication
Number of isolated malformations/MCA	6 x MCA 3 x isolated

For the three live births, one time each a lumbosacral and a lumbar spina bifida (both with an Arnold-Chiari syndrome) and one thoracic spina bifida (with Fetopathia diabetica) were reported. The proportion of live birth in this year (33 %) is a little lower than from 2004 to 2015 (39 %), while the proportion of terminations of pregnancy is correspondingly higher. A maximum of 92 % (2012) of the pregnancies with spina bifida were terminated prior to maturity.
For three terminations of pregnancy in 2016 a spina bifida as well as a hydrocephaly occured.

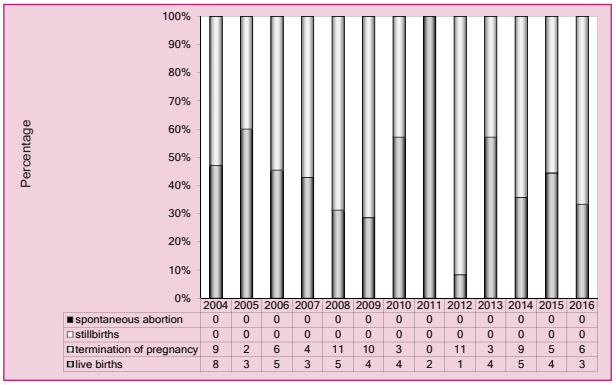
Malformation combinations (MCA) or superordinated syndromes detected:

- Meckel-Gruber syndrome with: Potter sequence, post-axial hexadactyly on the hands and feet, dysmorphism in the skull, mandibular micrognathia, broad nasal root, deep-seated ears
- Body-Stalk anomaly with: Ectopia cordis
- Vertebral arch hypoplasia (bones 1/2), crevice vertebrae (bones 1-4), dermal sinus, Fetopathia diabetica
- 3 x Arnold-Chiari syndrome



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	9.7	2.9	6.4	4.0	8.9	8.1	4.0	1.2	7.0	4.1	8.1	5.1	5.0
BP	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8

Fig. 9: Development of prevalence/10,000 births with spina bifida in the registration area since 2004



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
spontaneous abortion	0	0	0	0	0	0	0	0	0	0	0	0	0
stillbirths	0	0	0	0	0	0	0	0	0	0	0	0	0
termination of pregnancy	9	2	6	4	11	10	3	0	11	3	9	5	6
live births	8	3	5	3	5	4	4	2	1	4	5	4	3

Fig. 10: Pregnancy outcomes of spina bifida in the registration area since 2004

In 2016, one spina bifida per 2,015 births was registered in Saxony-Anhalt.

12.4 Encephalocele (Q01.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 2 x Magdeburg	2	3.8	↗
Districts: 2 x Börde 1 x Harz	3	2.3	↑
Saxony-Anhalt	**5**	**2.8**	↑

Encephalocele (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	1.60	0.73 - 3.03
Districts	1.12	0.65 - 1.80
Region	1.25	0.82 - 1.83
EUROCAT	1.24	1.16 - 1.32
		0.27 S Portugal* 2.83 Mainz (Germany)**

*/** centres with lowest resp. highest prevalence/10,000 births

For all five births in 2016, an occipital encephalocele occured. The prevalence of 2.8 per 10,000 births is above the confidence limits of the basis prevalence in Saxony-Anhalt (1.25 per 10,000 births). For all reported years, the number of cases was below five at all times; the maximum value of the prevalence was reached in 2004 with 2.3 per 10,000 births.

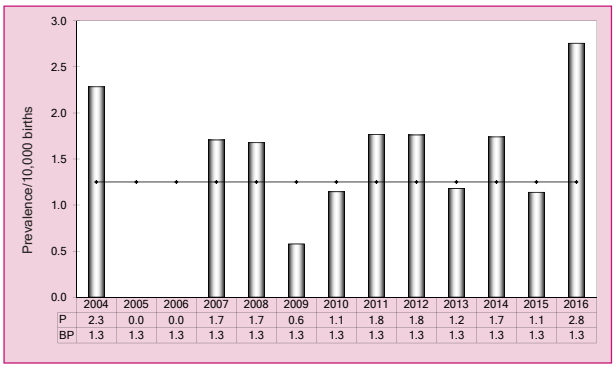
Compared to the Eruope-wide values from 2004 to 2015, this year's prevalence in Saxony-Anhalt is above the upper confidence limit and slightly below the maximum value from the Mainzer registry. Ein Lebendgeborenes wurde am 2. Lebenstag operiert, das andere nach etwa fünf Monaten.
The abortions took place in the 13th, 14th, and 17th WOG.

additional information:

Pregnancy outcome	2 x live births 3 x termination of pregnancy
Sex	1 x male 1 x female 3 x no indication
Number of isolated malformations/MCA	1 x MCA 4 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- Meckel-Gruber syndrome with: Potter sequence, Dandy-Walker syndrome



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	2.3	0.0	0.0	1.7	1.7	0.6	1.1	1.8	1.8	1.2	1.7	1.1	2.8
BP	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3

Fig. 11: Development of prevalence/10,000 births with encephalocele in the registration area since 2004

In 2016, one encephalocele per 3,627 births was registered in Saxony-Anhalt.

12.5 Microcephaly (Q02.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 1 x Halle 1 x Magdeburg	2	3.8	↔
Districts: 1 x Altmarkkreis Salzwedel 1 x Burgenlandkreis 1 x Börde 1 x Harz 4 x Salzlandkreis 1 x Stendal	9	7.0	↑
Saxony-Anhalt	**11**	**6.1**	↑

Microcephaly (2004 to 2015)			
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births	
Cities	4.26	2.73 - 6.33	
Districts	2.77	2.00 - 3.75	
Region	3.17	2.46 - 4.04	
EUROCAT	2.75	2.64 - 2.87	
		0.46 Norway*	
		11.96 Saxony-Anhalt (Germany)**	

*/** centres with lowest resp. highest prevalence/10,000 births

In 2016, eleven births were diagnosed with microcephaly. The yearly prevalence of 6.1 per 10,000 births has been above the prevalence of the reported time period since 2012 (3.17 per 10,000 births). An increasing tendency is noticeable (chapter 12.37).

Likewise, the comparison to European numbers (2.75 per 10,000 births) shows that the value in Saxony-Anhalt is high.

additional information:

Pregnancy outcome	10 x live births 1 x stillbirth
Sex	7 x male 4 x female
Number of isolated malformations/MCA	10 x MCA 1 x isolated

Except for one stillbirth in the 26th WOG, all children were born alive.

The diagnosis microcephaly can only be made by evaluating the measued head circumference in relation to the gestational age and sex of the newborn. Therefore, the Monitoring of Congenital Malformations uses the internationally accepted percentile curves that were published in the INTERGROWTH-21st-Project-Study in 2016. Only in the course of the first year of life, the diagnosis can be verified by taking into account the non-development of the brain and cranial. Through the focus on the malformation microcephaly, which is due to the Zika virus, more and more reports reached us since the zika virus outbreak in 2015. This more realistic depiction of the frequency is presumably reflected in the statistics.

Malformation combinations (MCA) or superordinated syndromes detected:

- Down syndrome with: tetralogy of Fallot, haemodynamically effective PDA in a full-term infant, bilateral conductive hearing loss (left 30-55 dB, right 20-65 dB), craniofacial dysmorphism
- CATCH 22 with: CHARGE association, bilateral cleft palate with cleft lip, right-side microphthalmos, bilateral coloboma of optic disc, tetralogy of Fallot, PFO, and non-hemodynamically effective PDA at full-term infant, hypothyroidism, deep-seated ears, and dysplastic right ear
- Holoprosencephaly, coloboma, VSD
- Jacobsen syndrome with: duodenal atresia, pancreas anulare, horseshoe kidney, pelvic kidney, combined hearing impairment (bilateral 40 dB), blepharophimosis, bilaterally retarded hip maturity and clinodactyly of the fifth fingers, septum pellucidum cyst, craniofacial dysmorphism
- Dextro-transposition of the aorta, epilepsy
- Bilateral optic atrophy, glaucoma and rotational nystagmus, mandibular retrognathia, craniofacial dysmorphism, internal epicanthus
- Brain atrophy, AVSD, most severe joint contractures
- Duplex right kidney, right-side DUP II. degree, left hydrocele
- Nesidioblastosis, bilateral hydrocele and inguinal Hernia at preterm infant
- Early syphilis

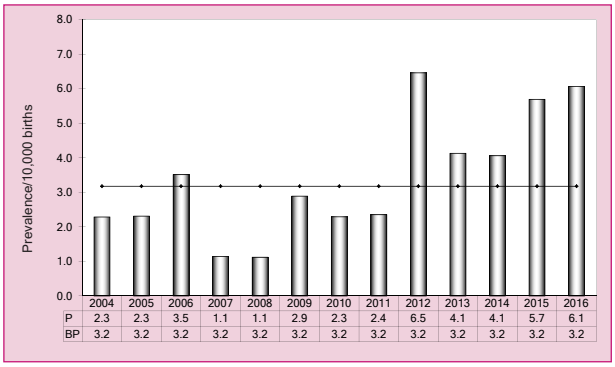


Fig. 12: Development of prevalence/10,000 births with microcephaly in the registration area since 2002

In 2016, one microcephaly per 1,649 births was registered in Saxony-Anhalt.

12.6 Congenital Hydrocephaly (Q03.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 3 x Magdeburg	3	5.7	↔
Districts: 1 x Börde 1 x Harz 1 x Salzlandkreis	3	2.3	↓
Saxony-Anhalt	**6**	**3.3**	↓

Congenital Hydrocephaly (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	7.10	5.07 - 9.66
Districts	5.01	3.95 - 6.28
Region	5.58	4.67 - 6.65
EUROCAT	5.74	5.57 - 5.91
		1.63 S Portugal* 13.69 Paris (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

A hydrocephaly was registered six times in Saxony-Anhalt in 2016. Hydrocephalies in combination with neural tube defects are not counted here.
From 2004 to 2015, the prevalence results in 5.58 per 10,000 births. The prevalence in 2016 of 3.3 per 10,000 births significantly comes below the confidence interval. Within all reported years, the yearly prevalence (2008: 2.8 per 10,000 births) is lower than in this year.

In comparision to European EUROCAT data, this year's prevalence can be assessed as low.

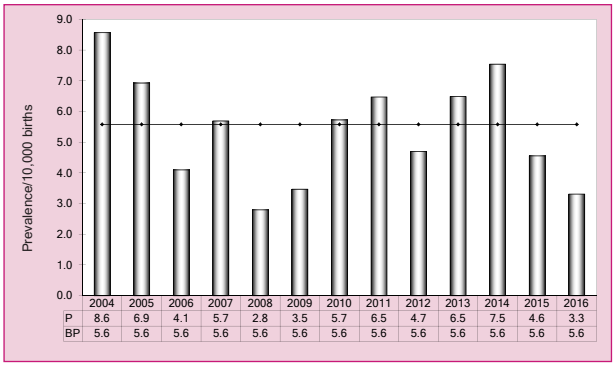
additional information:

Pregnancy outcome	2 x live births 1 x live birth, deceased within 7 days 3 x termination of pregnancy
Sex	2 x male 2 x female 2 x no indication
Number of isolated malformations/MCA	4 x MCA 2 x isolated

Out of three live births with hydrocephaly, one child deceased on the second day of life.
The three fetuses, for which the pregnancy was terminated prior to maturity, showed additonal major malformations: Edwards syndrome, Lissencephaly and Dandy-Walker syndrome.

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome with: VSD, atypical location of the coronary vessels, mandibular retrognathia, bilaterally overlapping fingers, deep-seated ears
- Cerebellar hypoplasia, right-side anophthalmia, left-side microphthalmia, midface hypoplasia, ASD II, dilated brain ventricle, septum pellucidum cyst, broad nasal root, shortened palpebral fissure, plexus cyst, PFO at preterm infant
- Pyruvate dehydrogenase deficiency, corpus callosum agenesis, cerebellar hypoplasia, median cleft palate, glandular hypospadias, clubfoot right-side, rocker bottom foot left, joint contractures, bilaterally dislocated wrists and pulmonary hypoplasia, spina bifida occulta, hepatomegaly, dorsal hooded foreskin, non-hemodynamically effective PDA at preterm infant, mandibular micrognathia and retrognathia, deep-seated ears, narrow palpebral fissure, prominent forehead
- Corpus callosum agenesis, lissencephaly, cerebellar hypoplasia



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	8.6	6.9	4.1	5.7	2.8	3.5	5.7	6.5	4.7	6.5	7.5	4.6	3.3
BP	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6

Fig. 13: Development of prevalence/10,000 births with congenital hydrocephaly in the registration area since 2004

In 2016, one congenital hydrocephalus per 1,649 births was registered in Saxony-Anhalt.

12.7 Arhinencephaly/Holoprosencephaly (Q04.1/Q04.2)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 3 x Halle	3	5.7	↑
Districts: 2 x Burgenlandkreis 1 x Harz 1 x Saalekreis	4	3.1	↑
Saxony-Anhalt	**7**	**3.9**	↑

Arhinencephaly/Holoprosencephaly (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	2.66	1.49 - 4.39
Districts	1.12	0.65 - 1.80
Region	1.54	1.05 - 2.17
EUROCAT	1.44	1.35 - 1.52
		0.22 Malta* 2.92 Isle de la Reunion (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

The indicator malformation arhinencephaly/holoprosencephaly is with a basis prevalence of 1.54 per 10,000 births a rather rare malformation. In 2016, with a **yearly prevalence** of **3.9 per 10,000 births**, it ranked on place 15 in the list of the most frequent malformations.
The prevalence in 2016 is above the calculated confidenz interval; however, the range of the prevalance is large (extreme values: 0.0 (2008; 2014) and 4.6 (2010) per 10,000 births).

In contrast to EUROCAT data, the prevalence in Saxony-Anhalt in 2016 is above the confidence interval of the European registry.

additional information:

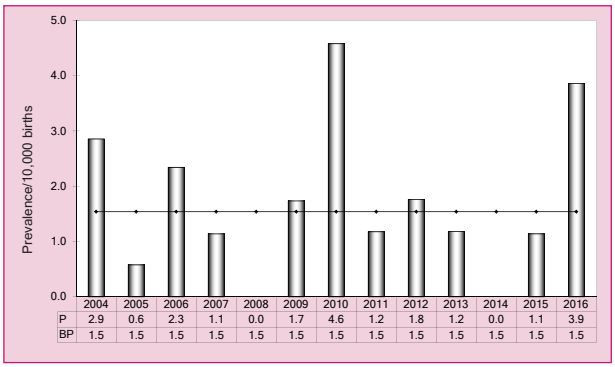
Pregnancy outcome	2 x live births 5 x termination of pregnancy
Sex	3 x male 3 x female 1 x no indication
Number of isolated malformations/MCA	6 x MCA 1 x isolated

All seven births were affected by holoprosencephaly. An arhincencephaly was diagnosed for the last time in 2012, a cyclopia in 2010.

Two children with holoprosencephaly were born alive. Except for one termination of pregnancy, for which prenatally more malformations were observed but postnatally have not been affirmed, all other affected fetuses showed additional major malformations.

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome with: omphalocele, horseshoe kidney, clubhands, craniofacial dysmorphism, deep-seated ears
- Edwards syndrome with: Omphalocele, VSD
- Treacher-Collins syndrome with: DORV, pulmonary valve stenosis, azygos drainage, coronary anomaly, wedge-shaped vertebrae (bones T 4-5), corpus callosum agenesis, septum pellucidum agenesis, transverse cleft lip, macrostomy, PFO, and non-hemodynamically effective PDA at preterm infant
- Microcephaly, coloboma, VSD
- cerebellar hypoplasia, clubfeet, bitateral DUP
- Corpus callosum agenesis



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	2.9	0.6	2.3	1.1	0.0	1.7	4.6	1.2	1.8	1.2	0.0	1.1	3.9
BP	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

Fig. 14: Development of prevalence/10,000 births with arhinencephaly/holoprosencephaly in the registration area since 2004

In 2016, one child/foetus with arhinencephaly/holoprosencephaly per 2,591 births was registered in Saxony- Anhalt

12.8 Anophthalmos/Microphthalmos (Q11.0/Q11.1/Q11.2)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 1 x Halle 3 x Magdeburg	4	7.5	↑
Districts	0	0.0	↓
Saxony-Anhalt	**4**	**2.2**	↑

Anophthalmos/Microphthalmos (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	1.06	0.39 - 2.32
Districts	0.66	0.32 - 1.21
Region	0.77	0.44 - 1.25
EUROCAT	0.98	0.91 - 1.05
		0.27 Hainaut (Belgium)* 2.07 Ukraine**

*/** centres with lowest resp. highest prevalence/10,000 births

The anophthalmos/microphthalmos is a very rare malformation. It occured in 2016 with a **prevalence** of **2.2 per 10,000 births** and was reported with with four cases this year above the basis prevalence.
Since 2000, it was only observed once with the same frequency, but at a lower birth rate in 2010.

The prevalence for Europe from 2004 to 2015 is still below the one for Saxony-Anhalt; therefore, the yearly prevalence in 2016 is in comparison rather high. It also exceeds the denoted maximum prevalence of Ukraine.

additional information:

Pregnancy outcome	3 x live births 1 x spontaneous abortion
Sex	3 x male 1 x female
Number of isolated malformations/MCA	4 x MCA

Three children were born alive. For one foetus with fibrous amniotic bands, the pregnancy terminated spontaneously in the 24th WOG.

Malformation combinations (MCA) or superordinated syndromes detected:

- Fibrous amniotic band between the inside of the right forearm and occipital region, craniorachischisis with meningoencephalocele, rudimentary nose, median cleft palate and mandibular cleft, mandibular micrognathia, peromeleous form of symbrachydactyly of the left hand and right foot (each with aplasia of the middle and end phalanx of the digiti I-V, brachyphalangia of the hand and clubfoot right-side) hypoplasia of the lung and heart, craniofacial dysmorphism with hypertelorism and laterally displaced eyelids
- CATCH 22 with: CHARGE association, microcephaly, bilateral cleft palate with cleft lip and colostomy of the papilla, Fallot tetralogy, PFO and nonhemodynamically effective PDA at full-term infant, hypothyroidism, deep-seated ears and dysplastic right ear
- Dandy-Walker syndrome, cerebellar hypoplasia, midface hypoplasia, ASD II, dilated brain ventricle, septum pellucidum cyst, broad nasal root, shortened cleft palate, plexus cyst, PFO at preterm infant
- Klippel-Trénaunay-Weber syndrome with: intrahepatic bile duct atresia, duplex right kidney

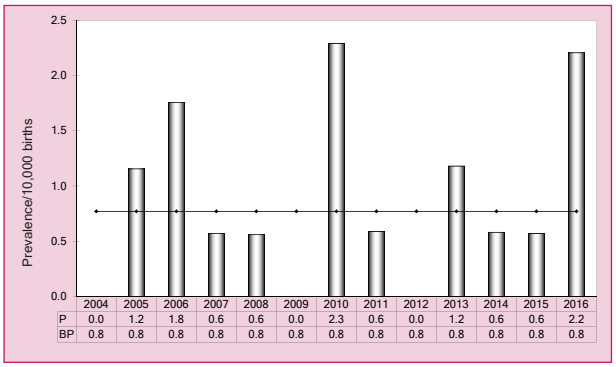


Fig. 15: Development of prevalence/10,000 births with anophthalmos/microphthalmos in the registration area since 2004

In 2016, one child/foetus with anophthalmos / microphthalmos per 4,534 births was registered in Saxony- Anhalt

12.9 Microtia/Anotia (Q16.0/Q17.2)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 2 x Halle 2 x Magdeburg	4	7.5	↑
Districts	0	0.0	↓
Saxony-Anhalt	**4**	**2.2**	↔

Microtia/Anotia (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	2.13	1.10 - 3.72
districts	2.11	1.44 - 2.98
Region	2.12	1.54 - 2.84
EUROCAT	keine Angaben	keine Angaben

The basis prevalence of microtia/anotia accounts to 2.12 per 10,000 births. With a **prevalence** of **2.2 per 10,000 births**, the value for 2016 is within a normal range.

For one child, the microtia affected both ears. The indicator malformation twice got detected as part of the Goldenhar syndrome. For each of the four children with microtia/anotia also a conductive hearing loss was present.

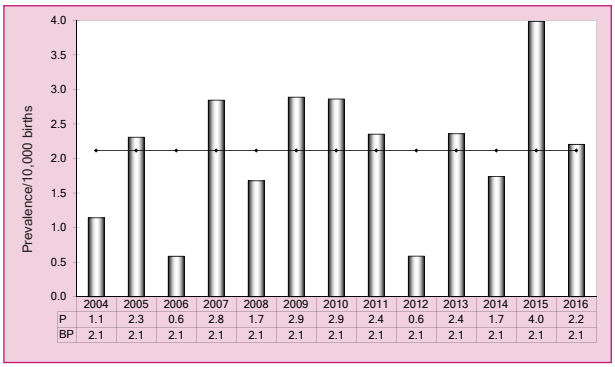
No EUROCAT data are available for this indicator malformation.
The European registries state a significantly lower prevalence for anotia (2004-2015) with 0.26 per 10,000 births.
In 2016, there is one reported case of anotia in Saxony-Anhalt. This is equal to a prevalence of 0.55 per 10,000 births. For the observed years from 2004 to 2015, this amounted to a prevalence for anotia of 0.38 per 10,000 births in Saxony-Anhalt.

additional information:

Pregnancy outcome	4 x live births
Sex	3 x male 1 x female
Number of isolated malformations/MCA	4 x MCA

Malformation combinations (MCA) or superordinated syndromes detected:

- Goldenhar syndrome with: auditory atresia, conductive hearing loss and auricular appendage left, mandibular and maxillary micrognathia
- Goldenhar syndrome with: auditory atresia, conductive hearing loss and hypoplasia of the depressor anguli oris left
- 2 x auditory atresia and conductive hearing loss (1 x bilateral, 1 x right side)



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	1.1	2.3	0.6	2.8	1.7	2.9	2.9	2.4	0.6	2.4	1.7	4.0	2.2
BP	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1

Fig. 16: Development of prevalence/10,000 births with microtia/anotia in the registration area since 2004

In 2016, one child with microtia/anotia per 4,534 was registered in Saxony-Anhalt.

12.10 Tetralogy of Fallot (Q21.3)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 1 x Halle 2 x Magdeburg	3	5.7	↔
Districts: 1 x Burgenlandkreis 2 x Börde 1 x Saalekreis 1 x Salzlandkreis 1 x Stendal	6	4.7	↗
Saxony-Anhalt	**9**	**5.0**	↗

Tetralogy of Fallot (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	3.90	2.45 - 5.91
Districts	3.50	2.62 - 4.57
Region	3.61	2.84 - 4.52
EUROCAT	3.34	3.21 - 3.47
		2.03 S Portugal* 5.10 Mainz (Germany)**

*/** centres with lowest resp. highest prevalence/10,000 births

The Tetralogy of Fallot is a complex malformation that is composed by four cardiac malformations: pulmonary stenosis, VSD, overriding aorta und right ventricular hypertrophy. The indicator malformation was observed 9 times in Saxony-Anhalt in 2016. This is equal to a **prevalence** of **5.0 per 10,000 births**. Compared to the basis prevalence of 3.61 per 10,000 births, this indicates a slight increase.

Also a comparison with the prevalence of EUROCAT shows a value above the confidence interval, yet still slightly below the maximum value of the Mainzer registry.

additional information:

Pregnancy outcome	7 x live births 2 x termination of pregnancy
Sex	6 x male 2 x female 1 x no indication
Number of isolated malformations/MCA	7 x MCA 2 x isolated

For one fetus with Patau syndrome and one with Down syndrome, the pregnancy was terminated in the 13th WOG and in the 19th WOG, respectively.

The Tetralogy of Fallot affects more often boys. In 2016, a sex ratio of m : f of 3 : 1 showed a significant androtropism.

Malformation combinations (MCA) or superordinated syndromes detected:

- 2 x Down syndrome (1 x with: microcephaly, haemodynamically effective PDA at full-term infant, conductive hearing loss left-sided 30-55 dB and right-sided 20-65 dB, craniofacial dysmorphism)
- Patau syndrome with: Omphalocele, cleft palate with cleft lip
- CATCH 22 with: CHARGE association, microcephaly, bilateral cleft palate with cleft lip, right ophthalmoscope, bilateral coloboma of te papilla, PFO and non-hemodynamically effective PDA at full-term infant, hypothyroidism, deep-seated ears and dysplastic right ear
- ASD II, PFO at full-term infant, megaureter and ureteral stenosis right
- Persistent left vena cava superior, PFO and non hae modynamically effective PDA at full-term infant
- Coronary anomaly, PFO at full-term infant

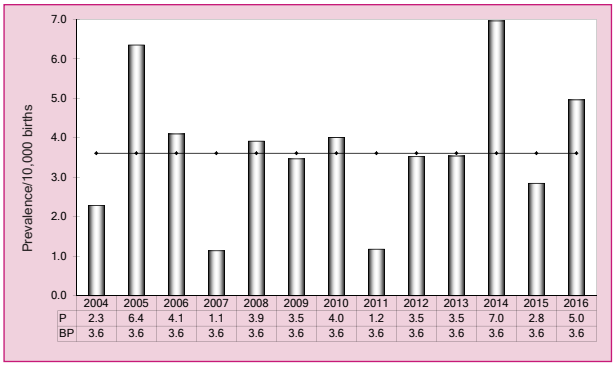


Fig. 17: Development of prevalence/10,000 births with tetralogy of Fallot in the registration area since 2004

In 2016, one tetralogy of Fallot per 2,015 births was registered in Saxony-Anhalt.

12.11 Transposition of Great Vessels - TGV (Q20.1/Q20.3)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 1 x Dessau-Roßlau 1 x Magdeburg	2	3.8	↔
Districts: 3 x Burgenlandkreis 1 x Börde 1 x Jerichower Land 1 x Saalekreis 1 x Salzlandkreis 1 x Stendal 1 x Wittenberg	9	7.0	↑
Saxony-Anhalt	**11**	**6.1**	↑

Transposition of Great Vessels (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	5.15	3.45 - 7.39
Districts	3.76	2.85 - 4.87
Region	4.14	3.31 - 5.11
EUROCAT (Q20.3)	3.45	3.32 - 3.58
		1.36 S Portugal* 4.87 Malta**

*/** centres with lowest resp. highest prevalence/10,000 births

The Transposition of Great Vessels (TGV) is characterized by the congenital transposition of the from the heart outbound going Vessels, including the rare DORV (Double Outlet Right Ventricle, Q20.1).
The indicator malformation appeared in Saxony-Anhalt in 2016 with a **prevalence** of **6.1 per 10,000 births**, which is the highest value for the whole reported time period. The upper bound of the confidence interval of the basis prevalence with 4.14 per 10,000 births is exceeded significantly.

As prevalence of TGV, the European registries state 3.45 per 10,000 births. Likewise, this value is significantly lower than the frequency which was observed in Saxony-Anhalt in 2016. The computetd prevalences, however, are only conditionally comparable, since the EUROCAT prevalence does not include DORV.

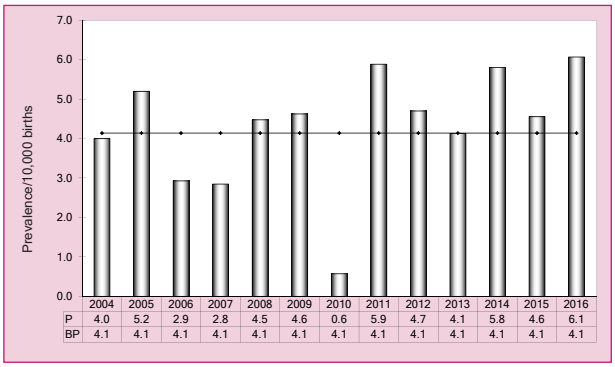
additional information:

Pregnancy outcome	11 x live births
Sex	4 x male 7 x female
Number of isolated malformations/MCA	11 x MCA

All 11 children were born alive. Most of these children underwent surgery at the Deutsches Herzzentrum in Leipzig. Five of these children were prenatally transferred to Leipzig for it.

Malformation combinations (MCA) or superordinated syndromes detected:

- Treacher-Collins syndrome with: holoprosencephaly, pulmonary valve stenosis, azygosdrainage, coronary anomaly, wedge-shaped vertebrae (bones T 4-5), corpus callosum agenesis, septum pellucidum agenesis, transverse lip cleft, macrostomy, PFO and non-hemodynamically effective PDA at preterm infant
- Microcephaly, epilepsy
- preductal aortic coarctation, common ventricle, VSD, PFO at full-term infant, bronchus stenosis and plexus cyst on the left
- Atresia of the aorta, DIV
- 4 x ASD II (1 x with coronary anomaly, 1 x with PFO at full-term infant)
- VSD, pulmonary valve stenosis, thrombus in the vena cava inferior, PFO at preterm infant
- VSD, coronary anomaly, PFO at full-term infant
- VSD



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	4.0	5.2	2.9	2.8	4.5	4.6	0.6	5.9	4.7	4.1	5.8	4.6	6.1
BP	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1

Fig. 18: Development of prevalence/10,000 births with transposition of great vessels in the registration area since 2004

In 2016, one transposition of great vessels per 1,649 births was registered in Saxony-Anhalt.

12.12 Hypoplastic Left Heart Syndrome (Q23.4)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 1 x Halle 1 x Magdeburg	2	3.8	↔
Districts: 1 x Harz 1 x Stendal 2 x Wittenberg	4	3.1	↔
Saxony-Anhalt	**6**	**3.3**	↔

Hypoplastic Left Heart Syndrome (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	2.66	1.49 - 4.39
Districts	2.64	1.89 - 3.39
Region	2.65	1.99 - 3.44
EUROCAT	2.77	2.65 - 2.89
		0.72 S Portugal* 4.40 Styria (Austria)**

*/** centres with lowest resp. highest prevalence/10,000 births

The **yearly prevalence** of **3.3 per 10,000 births** for the hypoplastic left heart syndrome in Saxony-Anhalt in 2016 is within the median range of the calculated basis prevalence from 2004 to 2015. The minimum for the hypoplastic left heart syndrome in the reported years was at 0.6 (2010) and the maximum at 5.0 per 10,000 births (2008).

A comparison to the Europe-wide detected prevalences shows that the prevalence in Saxony-Anhalt in 2016 is within the upper third of the EUROCAT registry and slightly above the European basis prevalence, respectively.

additional information:

Pregnancy outcome	4 x live births 1 x live births, deceased until 7th day 1 x termination of pregnancy
Sex	4 x male 2 x female
Number of isolated malformations/MCA	3 x MCA 3 x isolated

One of the five children born with hypoplastic left heart syndrome deceased within the first week of life. For one foetus, the prenatal ultrasound showed a finding in the 21st WOG and the pregnancy was, subsequently, terminated in the 22nd WOG.

Malformation combinations (MCA) or superordinated syndromes detected:

- Pulmonary atresia
- 2 x AVSD

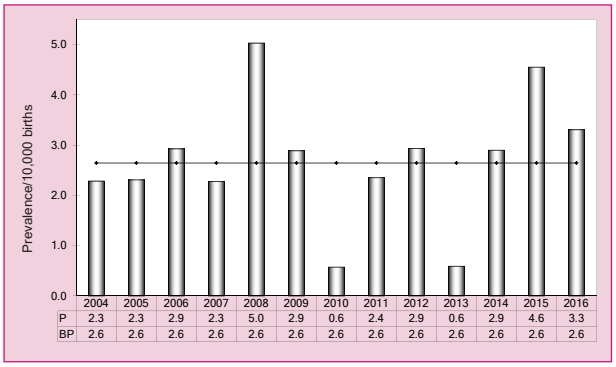


Fig. 19: Development of prevalence/10,000 births with hypoplastic left heart syndrome in the registration area since 2004

In 2016, one child with a hypolastic left heart syndrome per 3,023 births was registered in Saxony-Anhalt.

12.13 Coarctation of Aorta (Q25.1)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities 2 x Dessau-Roßlau 1 x Halle 1 x Magdeburg	4	7.5	↗
Districts: 2 x Burgenlandkreis 1 x Mansfeld-Südharz 1 x Saalekreis 2 x Salzlandkreis 1 x Stendal	7	5.5	↔
Saxony-Anhalt	**11**	**6.1**	↔

Coarctation of Aorta (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	4.61	3.01 - 6.76
Districts	5.41	4.47 - 6.91
Region	5.19	4.32 - 6.23
EUROCAT	3.84	3.71 - 3.98
		1.23 Zagreb (Croatia)* 6.23 Styria (Austria)**

*/** centres with lowest resp. highest prevalence/10,000 births

We registered eleven cases with coarctation of aorta in 2016. The prevalence of 6.1 per 10,000 births remained within the confidence interval of the basis prevalence.

The prevalence in 2016 as well as the basis prevalence for Saxony-Anhalt are above the basis prevalence stated by EUROCAT. The maximum value of the registry in Styria (Austria), however, is not exceeded.

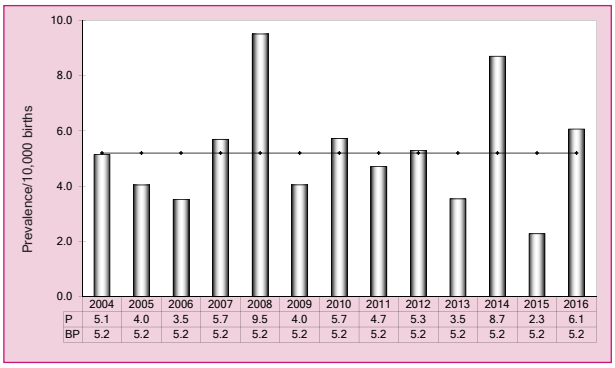
additional information:

Pregnancy outcome	11 x live births
Sex	10 x male 1 x female
Number of isolated malformations/MCA	10 x MCA 1 x isolated

Only in one case, the coarctation of aorta occured isolated. All other children showed additional malformations of the cardiac system and six children were affected by malformations of different organ systems. Eight children were transferred to the Deutsches Herzzentrum in Leipzig, of which two were transferred pre-birth.

Malformation combinations (MCA) or superordinated syndromes detected:

- Pierre-Robin sequence with: bilateral cleft palate and undescended testicle at full-term infant, Shone complex, VSD, tricuspid insufficiency, persistent left superior vena cava, PFO, inguinal hernia right-side, accessory rib pair, bilateral clavicular hypoplasia, craniofacial dysmorphism, laterally rising lid axes, mandibular retrognathia, hypertelorism, deep-seated dysplastic ears
- Ellis-van-Creveld syndrome with: asphyxiant thoracic dysplasia, ASD, persistent left vena cava superior
- Plagiocephaly, persistent left vena cava superior, mitral valve stenosis, bronchus stenosis left-side, tracheomalacia, laryngomalacia
- Dextro-transposition of the aorta, common ventricle, VSD, PFO at full-term infant, bronchus stenosis and plexus cyst on the left-side
- Shone complex, ASD, VSD, thrombosis of the inferior vena cava
- 2 x ASD II (1 x with bilateral inguinal hernia at full-term infant, bilateral hydrocele)
- 3 x PFO at full-term infant



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	5.1	4.0	3.5	5.7	9.5	4.0	5.7	4.7	5.3	3.5	8.7	2.3	6.1
BP	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2	5.2

Fig. 20: Development of prevalence/10,000 births with coarctation of aorta in the registration area since 2004

In 2016, one coarctation of aorta per 1,649 births was registered in Saxony-Anhalt.

12.14 Cleft Lip With or Without Cleft Palate (Q36./Q37.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Dessau-Roßlau 3 x Halle 8 x Magdeburg	12	22.6	↑
Districts: 2 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 1 x Burgenlandkreis 4 x Börde 1 x Harz 1 x Saalekreis 3 x Salzlandkreis 1 x Stendal	14	10.9	↓
Saxony-Anhalt	**26**	**14.3**	↔

Cleft Lip With or Without Cleft Palate (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	12.95	10.16 - 16.28
Districts	13.59	11.90 - 15.52
Region	13.42	11.96 - 15.04
EUROCAT	8.83	8.62 - 9.04
		3.61 S Portugal* 12.97 N Netherlands**

*/** centres with lowest resp. highest prevalence/10,000 births

In 2016, 26 births with cleft lip with or without cleft palate and a prevalence of 14.3 per 10,000 births were registered. This value is within the middle of the range of the confidence interval of the basis prevalence.

The prevalence of the indicator malformation in Saxony-Anhalt is steadily situated in the upper third of the prevalences of the European registries. The yearly prevalence as well as the basis prevalence can be rated as high.

additional information:

Pregnancy outcome	23 x live births 1 x live birth, deceased within 7 days 1 x stillbirth 1 x termination of pregnancy
Sex	19 x male 5 x female 1 x indeterminate 1 x no indication
Number of isolated malformations/MCA	8 x MCA 18 x isolated

One live birth with Potter sequence deceased on the second day of life. One child with rectal fistula was born dead in the 34th WOG. For one fetus with Patau syndrome the pregnancy was terminated in the 13th WOG.

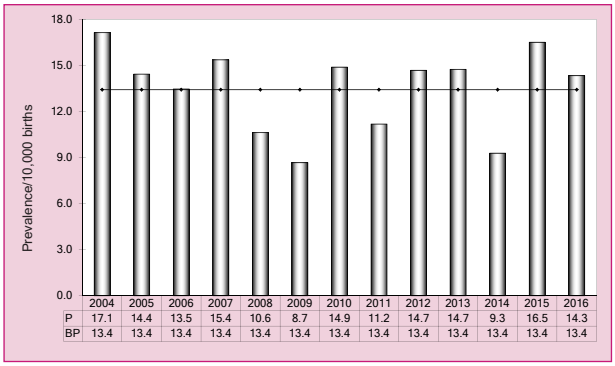
The indicator malformation cleft lip with or without cleft palate includes four malformations: The cleft lip with cleft jaw and palate appeared 18 times in 2016, the cleft upper lip five times, and the cleft lip and jaw three times. A cleft lip with cleft palate was not observed in 2016.

The cleft formation mainly occured unilateral, among these 14 times on the right side and four times on the left side (one time without an indication of the laterality). Only four times, a bilateral cleft lip with cleft jaw and palate was recorded. Three times there was no indication of the laterality.

Predominantly, the cleft lip with or without cleft palate (18 times) occured without additional malformations. In four cases. the hearing ability was bileterally impaired.

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: Omphalocele, Tetralogy of Fallot
- Potter sequence, Esophageal atresia with a fistula to the trachea, anal atresia, urinary bladder ecstrophy, indeterminate sex, penoscrotal inversion
- CATCH 22 with: CHARGE association, microcephaly, microphthalmia right-sided, coloboma of optic disc, tetralogy of Fallot, PFO and non-hemodynamically-effective PDA in the full-term infant, hypothyroidism, deep-seated ears, and dysplastic right ear
- Clubfoot right-sided, bilateral conductive hearing loss, PFO at full-term infant
- Fistula of the rectum, sacral pits, craniofacial dysmor phism, gaping cranial sutures
- Bilateral combined hearing impairment, plexus cyst and dilated brain ventricles, Hernia inguinalis left-sided
- Bilateral combined hearing impairment
- Bilateral conductive hearing loss



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	17.1	14.4	13.5	15.4	10.6	8.7	14.9	11.2	14.7	14.7	9.3	16.5	14.3
BP	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4	13.4

Fig. 21: Development of prevalence/10,000 births with cleft lip with or without cleft palate in the registration area since 2004

In 2016, one child with cleft lip with or without cleft palate per 698 births was registered in Saxony-Anhalt.

12.15 Cleft Palate (Q35.1/Q35.3/Q35.5/Q35.9)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Dessau-Roßlau 1 x Halle 3 x Magdeburg	5	9.4	↗
Districts:: 3 x Burgenlandkreis 1 x Börde 1 x Harz 2 x Saalekreis 1 x Salzlandkreis	8	6.2	↘
Saxony-Anhalt	**13**	**7.2**	↔

Cleft palate (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	6.74	4.77 - 9.25
Districts	7.72	6.47 - 9.19
Region	7.46	6.39 - 8.68
EUROCAT	6.09	5.92 - 6.27
		3.20 French West Indies (France)*
		12.84 Malta**

*/** centres with lowest resp. highest prevalence/10,000 births

A cleft palate was observed 13 times in Saxony-Anhalt in 2016. This is equal to a **prevalence** of **7.2 per 10,000 births**, which is within normal limits compared to previous years.

Compared to the prevalences indicated by EUROCAT, the stated prevalence in Saxony-Anhalt is slightly above the European total prevalance but still in the middle range of the specific European registries.

additional information:

Pregnancy outcome	10 x live births 1 x live birth, deceased within 7 days 1 x spontaneous abortion 1 x termination of pregnancy
Sex	8 x male 5 x female
Number of isolated malformations/MCA	9 x MCA 4 x isolated

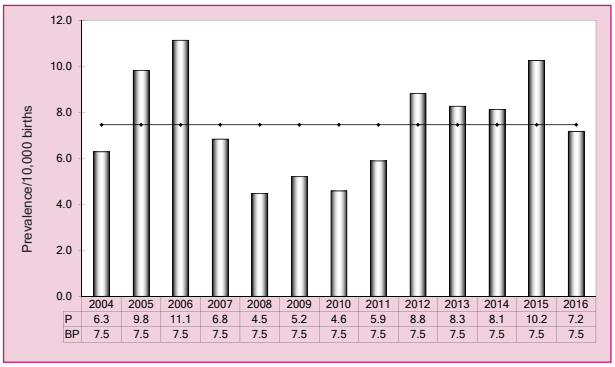


Fig. 22: Development of prevalence/10,000 births with cleft palate in the registration area since 2004

For one fetus with fibrous amniotic bands, the pregnancy terminted in the 24th WOG spontaneously. One pregnancy with a fetus with a reduction defect of limbs was terminated in the 14th WOG prior to maturity.

Malformation combinations (MCA) or superordinated syndromes detected:

- Fibrous amniotic bands between the inside of the right forearm and occipital region, craniorhachisisis with meningoencephalocele, bilateral anophthalmia, rudimentary nose, median mandibular cleft, mandibular micrognathia, peremal symbrachydactylysymbiotic of the left hand and right foot (each with aplasia of middle and end phalanx of digiti I-V), brachyphalangia of the hand and clubfoot right-sided, hypoplasia of the lungs and heart, cranio-facial dysmorphism with hypertelorism and laterally displaced palpebral fissure
- Pyruvate dehydrogenase deficiency, hydrocephaly, corpus callosum agenesis, cerebellar hypoplasia, glandular hypospadias, clubfoot right-sided, rocker bottom foot left-sided, joint contractures, bilaterally dislocated hand joints and pulmonary hypoplasia, spina bifida occulta, hepatomegaly, dorsal hooded foreskin, non-hemodynamically effective PDA at preterm infant, mandibular micrognathia and retrognathia, deep-seated ears, narrow palpebral fissure, prominent forehead
- Shone complex (preductal aortic coarctation), VSD, tricuspid insufficiency, persistent Vena cava superior left-sided, PFO, nondescensus testis at full-term infant, Hernia inguinalis right-sided, accessory rib pair, bilateral clavicular hypoplasia, craniofacial dysmorphism, laterally increasing lid axes, mandibular retrognathia, hypertelorism, deep-seated dysplastic ears
- Upper and lower limb reduction defect, thymus hypoplasia, craniofacial dysmorphism, mandibular retrognathia and micrognathia, deep-seated ears
- Stickler syndrome with: ASD II, mandibular micrognathia
- Hemivertebra, scoliosis, bilaterally missing index fingers, mandibular micrognathia
- Sensorineural hearing loss (right 30-40 dB, left 70 dB), mandibular micrognathia
- Sensorineural hearing loss (bilateral. 60 dB)
- VSD

In 2016, one child with cleft palate per 1,395 births was registered in Saxony-Anhalt.

12.16 Choanal Atresia (Q30.0)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Halle 1 x Magdeburg	2	3.8	↑
Districts: 1 x Börde 1 x Salzlandkreis	2	1.6	↗
Saxony-Anhalt	**4**	**2.2**	↑

Choanal Atresia (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	0.53	0.11 - 1.56
Districts	0.92	0.51 - 1.55
Region	0.82	0.48 - 1.31
EUROCAT	0.90	0.84 - 0.97
		0.05 S Portugal* 1.93 Saxony-Anhalt (Germany)**

*/** centres with lowest resp. highest prevalence/10,000 births

In 2016, four births with choanal atresia in Saxony-Anhalt were observed. The calculated **yearly prevalence** of **2.2 per 10,000 births** exceeds the basis prevalence of this rare malformation.
In the years from 2006 to 2009 and in 2012, no case was recorded in Saxony-Anhalt. Only two years ago, with a prevalence of 4.1 per 10,000 births (7 cases) a higher value was observed. The low numbers cause a wide range of the prevalences.

For the European registries, a prevalence of 0.9 per 10,000 births is stated. The prevalence in Saxony-Anhalt is significantly above the upper confidence limit.

additional information:

Pregnancy outcome	3 x live births 1 x termination of pregnancy
Sex	3 x male 1 x female
Number of isolated malformations/MCA	3 x MCA 1 x isolated

Twice in this year, a microdeletion was reported for the choanal atresia and once a chromosome aberration, once it occured isolated. For the fetus with Edwards syndrome and hydrops, the pregnancy was terminated in the 14th WOG, after amniocentesis was diagnosed.

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome with: dolichocephaly, mandibular retrognathia, deep-seated ears
- CATCH 22 with: microcephaly, bilateral cleft lip with cleft palate, microphthalmia right-sided, bilateral coloboma of the optic disk, tetralogy of Fallot, PFO and non-hemodynamically effective PDA at pre-term infant, hypothyroidism, deep-seated ears and dysplastic right ear
- Esophageal atresia (Vogt IIIb), ASD, bilateral conductive hearing loss (right 70 dB, left 90 dB), clubfoot left-sided and plexus cyst, hypoplasia of the penis

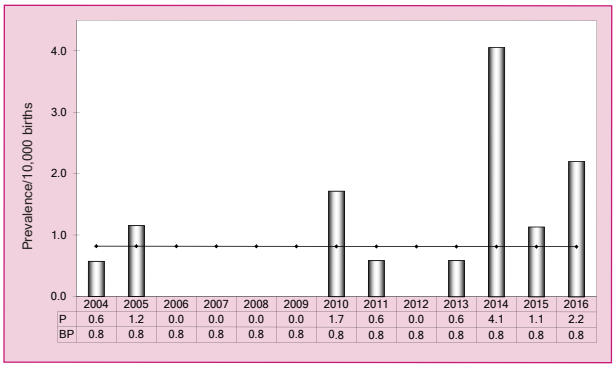


Fig. 23: Development of prevalence/10,000 births with choanal atresia in the registration area since 2004

In 2016, one child with a choanal atresia per 4,534 births was registered in Saxony-Anhalt.

12.17 Oesophageal Atresia/ Stenosis/ Fistula (Q39.0-Q39.4)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Magdeburg	1	1.9	↔
Districts: 1 x Anhalt-Bitterfeld 1 x Börde 1 x Salzlandkreis	3	2.3	↔
Saxony-Anhalt	**4**	**2.2**	↔

Oesophageal Atresia/ Stenosis/ Fistula (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	3.02	1.76 - 4.83
Districts	2.38	1.66 - 3.29
Region	2.55	1.91 - 3.33
EUROCAT (Q39.0-Q39.1)	2.45	2.34 - 2.56
		0.67 SE Ireland* 3.50 French West Indies (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

With a **prevalence** of **2.2 per 10,000 births** the indicator malformation Oesophageal Atresia/Stenosis/Fistula appeared, after two years with slightly lower prevalences, in this year within the range of the usual range of variation.

Compared to EUROCAT, the prevalence is slightly below the European average.

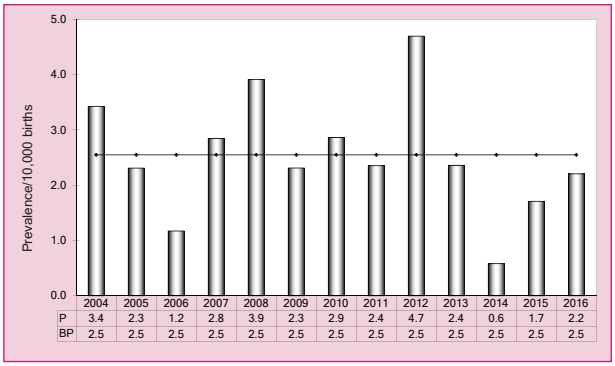
additional information:

Pregnancy outcome	3 x live births 1 x live birth, deceased within 7 days
Sex	2 x male 1 x female 1 x indeterminate
Number of isolated malformations/MCA	4 x MCA

For all four affected children, an oesophageal atresia with fistula between the trachea and the lower Speiseröhrentasche (Typ Vogt III b) was diagnosed. One child with Potter sequence deceased on the second day of life.

Malformation combinations (MCA) or superordinated syndromes detected:

- Potter sequence, analatresia, bladder ecstrophy, cleft lip with cleft palate, indeterminate sex, penoscrotic inversion
- CHARGE association with: bilateral choanalatresia, ASD, conductive hearing loss (right-side 70 dB, left-side 90 dB), clubfoot left-sided and plexus cyst, penis hypoplasia
- VATER association with: ultizystic dysplastic right kidney, dextrocardia, persistent Vena cava superior left-sided, ASD II, butterfly vertebra bone 5
- Craniosynostosis of the frontal suture, plagiocephaly



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	3.4	2.3	1.2	2.8	3.9	2.3	2.9	2.4	4.7	2.4	0.6	1.7	2.2
BP	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Fig. 24: Development of prevalence/10,000 births with oesophageal atresia/stenosis/fistula in the registration area since 2004

In 2016, one oesophageal atresia/fistula per 4,534 births was registered in Saxony-Anhalt.

12.18 Small Intestinal Atresia/Stenosis(Q41.1/Q41.2/Q41.8/Q41.9)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities:	0	0.0	↓
Districts: 1 x Burgenlandkreis 1 x Salzlandkreis 1 x Stendal	3	2.3	↔
Saxony-Anhalt	**3**	**1.7**	↔

Small Intestinal Atresia/Stenosis (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	1.06	0.39 - 2.32
Districts	1.98	1.34 - 2.83
Region	1.73	1.21 - 2.40
EUROCAT (Q41.1-Q41.8)	0.95	0.88 - 1.02
		0.29 Wielkopolska (Poland)* 1.72 Isle de la Reunion (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

The small intestinal atresia/ stenosis with a basis prevalence of 1.73 per 10,000 births belongs to the rare malformations. In 2016. there were three cases in Saxony-Anhalt with a yearly prevalence of 1.7 per 10,000 births, which is within the average range of the confidence interval.

Europe-wide, the intestinal atresia/ stenosis was observed with a prevalence of 0.95 per 10,000 births. Basis prevalence as well as yearly prevalence of Saxony-Anhalt can be catogorized as rather high, slightly below the maximum value of the registry of the Isle de la Reunion.

additional information:

Pregnancy outcome	3 x live births
Sex	2 x male 1 x female
Number of isolated malfromations/MCA	2 x MCA 1 x isolated

For three children, which were all born alive, each was diagnosed with atresia of an intestinal part, once of the jejunum and once without a precise specification of the intestinal part.

Malformation combinations (MCA) or superordinated syndromes detected:

- Cystic fibrosis, volvulus, nondescensus testis left-sided at full-term infant
- Duodenal stenosis with missing fixation on posterior abdominal wall (Apple-peel), bilateral Hernia inguinalis at preterm infant

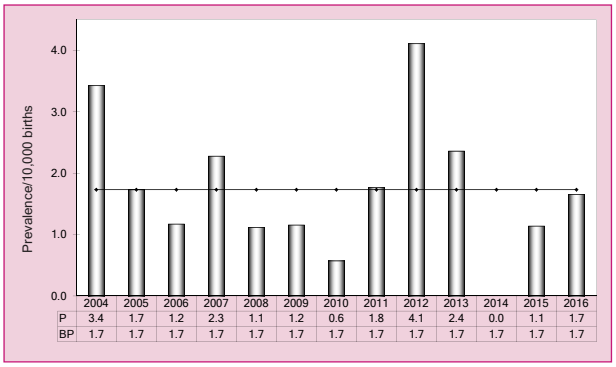


Fig. 25: Development of prevalence/10.000 births with small intestinal atresia/stenosis in the registration area since 2004

In 2016, one child with an intestinal atresia/stenosis per 6,045 births was registered in Saxony-Anhalt.

12.19 Anorectal Atresia/ Stenosis (Q42.0-Q42.3)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities:	0	0.0	↓
Districts: 1 x Anhalt-Bitterfeld 1 x Börde 1 x Saalekreis	3	2.3	↓
Saxony-Anhalt	**3**	**1.7**	↓

Anorectal Atresia/ Stenosis (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	5.86	4.03 - 8.22
Districts	5.34	4.24 - 6.64
Region	5.48	4.59 - 6.54
EUROCAT	3.15	3.03 - 3.28
		1.26 S Portugal* 6.77 Styria (Austria)**

*/** centres with lowest resp. highest prevalence/10,000 births

The indicator anorectal atresia/ stenosis, which was observed above average from 2007 to 2009, was only diagnosed three times in 2016. With a **prevalence** of **1.7 per 10,000 births** it is significantly below the basis prevalence of 5.48 per 10,000 births and the calculated confidence interval. The extreme value of the prevalence amounted to 8.4 per 10,000 births in 2008. In 2003, no case of this malformation was reported in Saxony-Anhalt.

The prevalence in Saxony-Anhalt in this year is significantly below the prevalence stated by EUROCAT of 3.15 per 10,000 births. In comparision with the basis prevalence, the opposite is shown.

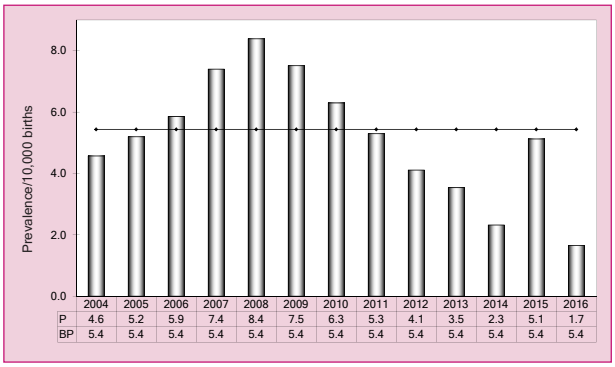
additional information:

Pregnancy outcome	1 x live birth 2 x live births, deceased within 7 days
Sex	2 x female 1 x indeterminate
Number of isolated malformations/MCA	2 x MCA 1 x isolated

Rectal and anorectal atresia/ stenosis are often only observed postnatally, since they are difficult to detect in the prenatal ultra sound. For two children, other major malformations were described prenatally.
All three children were born alive. One child was born with Potter sequence and deceased on the second day of life. In these three cases, twice a anorectal atresia without fistula and once a rectal atresia with fistula occured.

Malformation combinations (MCA) or superordinated syndromes detected:

- Potter sequence, oesophagus atresia with fistula to the trachea, bladder exstrophy, cleft lip and cleft palate, indeterminate sex, penoscrotic inversion
- McKusick-Kaufman syndrome with: persistence of the urogenital sinus, hypoplasia of the bony thorax and the lungs, multicystic dysplastic right kidney, left-sided ureteral stenosis and DUP IV, pulmonary valve stenosis, right-sided vascular ring through the anomalous subclavicular artery and myocardial hypertrophy



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	4.6	5.2	5.9	7.4	8.4	7.5	6.3	5.3	4.1	3.5	2.3	5.1	1.7
BP	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4	5.4

Fig. 26: Development of prevalence/10,000 births with anorectal atresia/-stenosis in the registration area since 2004

In 2016, one anorectal atresia/ stenosis per 6,045 births was registered in Saxony-Anhalt.

12.20 Undescended Testis (Q53.1-Q53.9)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 3 x Magdeburg	3	5.7	↓
Districts: 3 x Anhalt-Bitterfeld 1 x Burgenlandkreis 4 x Salzlandkreis 3 x Stendal	11	8.6	↑
Saxony-Anhalt	**14**	**7.7**	↔

Undescended Testis (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	13.84	10.94 - 17.27
Districts	6.00	4.84 - 7.37
Region	8.13	7.02 - 9.41
EUROCAT	no information	no information

In 2016, 14 full-term boys were affected by undescended testis in Saxony-Anhalt. The resulting **prevalence** of **7.7 per 10,000 births** (15.0 per 10,000 boys, respectively) is within the normal range of the basis prevalence of 8.13 per 10,000 births.

EUROCAT does not supply information for this indicator malformation, since the precondition for comparable predications, a consistent assessment of the malformation on the European registries and over the years, are not sufficiently existent. An under-reporting, also for our estimations, has to be presumed.

additional information:

Pregnancy outcome	14 x live births
Sex	14 x male
Number of isolated malformations/MCA	4 x MCA 10 x isolated

For the 14 boys that were all born alive, the malformation occured 10 times isolated, including four times bilaterally, five times right-sided and one time left-sided.

For two children, both testis were undescended. The other three boys with additional malformations showed on the left side a maldescensus testis.

Malformation combinations (MCA) or superordinated syndromes detected:

- Pierre-Robin sequence with: bilateral cleft palate, Shone's Complex (preductal aortic isthmus stenosis), VSD, tricuspid insufficiency, persistent Vena cava superior left-sided, PFO, Hernia inguinal right-sided, accessory rib pair, bilateral clavicular hypoplasia, craniofacial dysmorphism, laterally increasing eyelid axons, mandibular retrognathia, hypertelorism, deep-seated dysplastic ears
- Cranio-fronto-nasal syndrome with: diaphragmatic hernia left-sided, multicystic dysplastic right kidney, biliary dilatation, mandibular retrognathia, conspicuous NHS on the left, hypertelorism
- Cystic fibrosis, ileal atresia, volvulus
- PFO at full-term infant

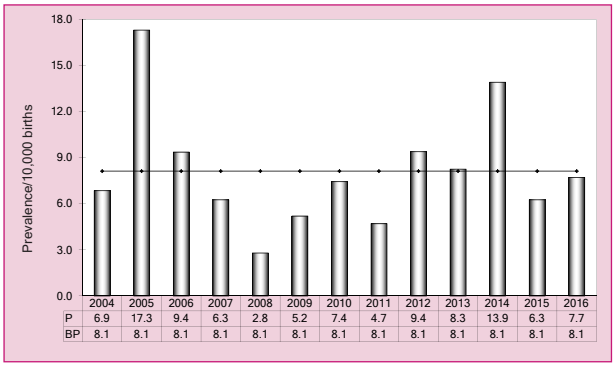


Fig. 27: Development of prevalence/10,000 births with undescended testis in the registration area since 2004

In 2016, one child with undescended testis per 1,295 births (665 boys) was registered in Saxony-Anhalt.

12.21 Hypospadias (Q54.0-Q54.3/Q54.8/Q54.9)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Dessau-Roßlau 3 x Halle 6 x Magdeburg	10	18.8	↓
Districts: 2 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 1 x Burgenlandkreis 3 x Börde 4 x Harz 3 x Mansfeld-Südharz 6 x Saalekreis 3 x Salzlandkreis	23	17.9	↘
Saxony-Anhalt	**33**	**18.2**	↓

Hypospadias (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	24.66	20.98 - 28.95
Districts	20.79	18.65 - 23.15
Region	21.84	19.95 - 23.89
EUROCAT	17.42	17.13 - 17.71
		6.28 S Portugal* 34.00 Mainz (Germany)**

*/** centres with lowest resp. highest prevalence/10,000 births

For 2016, the **yearly prevalence** amounted to **18.2 per 10,000 births** with 33 births with hypospadias.
Since 2013, the prevalences for hypospadias have been below the confidence interval of the basis prevalence of 21.84 per 10,000 births in Saxony-Anhalt. A decreasing tendency (chapter 12.37) insinuates, yet is still within the coincidence range (p=0.0802) and thus, remains to be observed. Presumably, less glandular hypospadias, i.e. the less severe formations of the indicator malformation, were reported to the Malformation Monitoring Centre in the previous years.

The prevalence is slightly above the by EUROCAT provided European prevalence of 17.42 per 10,000 births.

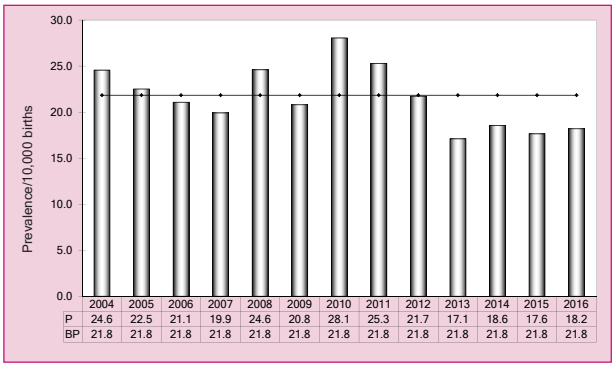
additional information:

Pregnancy Outcome	32 x live births 1 x live birth, deceased within 7 days
Sex	33 x male
Number of isolated malformations/MCA	7 x MCA 26 x isolated

All 33 boys were born alive. For 26 of them, no other malformation occured. Except for one penile hypospadias, all severe forms of hypospadias occured isolated (1 x perineal, 2 x penoscrotal, 4 x penile, 2 x coronar). A glandular hypospadias without accompanying malformaions was reported 17 times.

Malformation combinations (MCA) or superordinated syndromes detected:

- Pyruvate dehydrogenase deficiency, hydrocephaly, corpus callosum agenesis, cerebellar hypoplasia, median cleft palate, clubfoot right-sided, rocker bottom foot left-sided, joint contractures, dislocated wrists and pulmonary hypoplasia, spina bifida occulta, hepatomegaly, dorsal hooded foreskin, non-hemodynamically effective PDA at premature infant, mandibular micrognathia and retrognathia, deep-seated ears, narrow palpebral fissure, prominent forehead
- Renal agenesis left-sided, VSD, bicuspid aortic valve, aortic valve stenosis, PFO at premature infant
- Hexadactyly and membranous syndactyly (D1/D2 and D3/D4) on the left foot
- ASD
- ASD II
- Pulmonary valve stenosis
- Nesidioblastosis



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	24.6	22.5	21.1	19.9	24.6	20.8	28.1	25.3	21.7	17.1	18.6	17.6	18.2
BP	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8	21.8

Fig. 28: Development of prevalence/10,000 births with hypospadias in the registration area since 2004

In 2016, one hypospadias per 550 births (282 boys) was registered in Saxony-Anhalt.

12.22 Epispadias (Q64.0)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Halle 1 x Magdeburg	2	3.8	↑
Districts:	0	0.0	↓
Saxony-Anhalt	**2**	**1.1**	↑

Epispadias (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	0.18	0.00 - 0.99
Districts	0.26	0.07 - 0.68
Region	0.24	0.08 - 0.56
EUROCAT	no information	no information

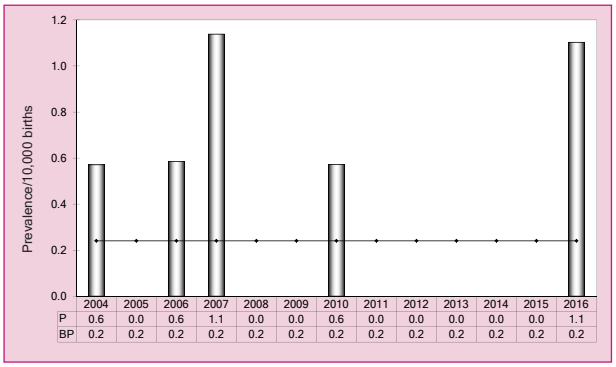
Epispadias is the indicator malformation that, with a basis prevalence of 0.24 per 10,000 births, is reported the least often. For five years, from 2011 to 2015, no case was registered.
In 2016, it occured for two children in Saxony-Anhalt. The resuling yearly prevalence of 1.1 per 10,000 births can be seen as high, however already with one affected child less, the value would be within the confidence interval of the basis prevalence calculated for the years 2004 to 2015.

European-wide reference values for the prevalence of epispadias are not provided by EUROCAT.

additional information:

Pregnancy outcome	2 x live births
Sex	2 x male
Number of isolated malformations/MCA	2 x isolated

The isolated epispadias usually, as also for the two born alive boys, are not detected during the prenatal ultrasound. Accompanying malformations were not present.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	0.6	0.0	0.6	1.1	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	1.1
BP	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

Fig. 29: Development of prevalence/10,000 births with epispadias in the registration area since 2004

In 2016, one child with epispadias per 9,068 births (4,657 boys) was registered in Saxony-Anhalt.

12.23 Indeterminate Sex (Q56.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities	0	0.0	↓
Districts: 1 x Anhalt-Bitterfeld 1 x Harz 1 x Stendal	3	2.3	↑
Saxony-Anhalt	**3**	**1.7**	↑

Indeterminate Sex (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	0.35	0.04 - 1.28
Districts	0.66	0.32 - 1.21
Region	0.58	0.30 - 1.01
EUROCAT	0.69	0.63 - 0.75
		0.28 Mainz (Germany)* 1.88 Wessex (UK)**

*/** centres with lowest resp. highest prevalence/10,000 births

The indeterminate sex is one of the very rare indicator malformations.
With three births and prevalence of 1.7 per 10,000 births, the values for 2016 are relatively high. Since 2014 and also in 2012, the yearly prevalence has been above the for Saxony-Anhalt determined basis prevalence of 0.58 per 10,000 births. Yet a tendency can not be derived from it (chapter 12.37), since in the reported period of time in almost every year less than two cases were reported and thus, a statistical evaluation is not sensible.

EUROCAT states a basis prevalence of 0.69 per 10,000 births, which is far below the prevalence of 2016 in Saxony-Anhalt. The level of the range of variation of the basis prevalence is equal though. Only due to the small numbers, the confidence interval of Saxony-Anhalt covers a wider range.

additional information:

Pregnancy outcome	2 x live births 1 x live birth, deceased within 7 days
Sex	3 x indeterminate
Number of isolated malformations/MCA	2 x MCA 1 x isolated

All three children with indeterminate sex were born alive. One child with Potter sequence deceased on the second day of life.

Malformation combinations (MCA) or superordinated syndromes detected:

- Potter sequence, oesophageal atresia with fistula to the trachea, anal atresia, exstrophy of the bladder, cleft lip with cleft palate, penoscrotal inversion
- Bladder exstrophy

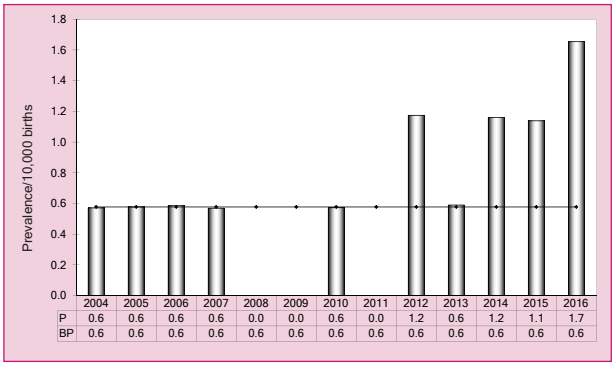


Fig. 30: Development of prevalence/10,000 births with indeterminate sex in the registration area since 2004

In 2016, one birth with indeterminate sex per 6,045 was registered in Saxony-Anhalt.

12.24 Potter Sequence (Q60.6)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities	0	0.0	↓
Districts: 1 x Anhalt-Bitterfeld 1 x Harz 1 x Jerichower Land 1 x Mansfeld-Südharz 2 x Saalekreis 2 x Salzlandkreis 1 x Stendal	9	7.0	↑
Saxony-Anhalt	**9**	**5.0**	↑

Potter Sequence (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	1.95	0.97 - 3.49
Districts	2.44	1.72 - 3.36
Region	2.31	1.70 - 3.06
EUROCAT	1.23	1.15 - 1.31
		0.51 Emilia Romagna (Italy)* 4.53 Mainz (Germany)**

*/** centres with lowest resp. highest prevalence/10,000 births

A Potter sequence was diagnosed for nine births. The **prevalence** of **5.0 per 10,000 births** results for 2016 in the highest value in the reported period of time and a value, which is significantly above the confidence interval of the basis prevalence of 2.31 per 10,000 births. The range of the prevalence of this indicator malformation is very large. In the years 2005 and 2007, the prevalence amounted to only 0.6 per 10,000 births (each only 1 case). A certain trend can not be distinguished, due to the fluctuating small numbers.

additional information:

Pregnancy outcome	1 x live birth, deceased within 7 days 8 x termination of pregnancy
Sex	3 x male 3 x female 1 x indeterminate 2 x no indication
Number of isolated malformations/MCA	6 x MCA 3 x isolated

The basis prevalence in Saxony-Anhalt is above the prevalence which is indicated for the European registries by EUROCAT. This year's value is also above the maximum basis prevalence of the other European registries.

A Potter sequence caused by medication was not registered within these cases.

Malformation combinations (MCA) or superordinated syndromes detected:

- Oesophageal atresia with a fistula to the trachea, anal atresia, urinary bladder exstrophy, cleft lip with cleft palate, indeterminate sex, penoscrotal inversion
- Meckel-Gruber syndrome with: lumbar Spina bifida, postaxial hexadactyly on the hands and feet, dysmorphia in the cranial region, mandibular micrognathia, broad nasal root, deep-seated ears
- Meckel-Gruber syndrome with: Dandy-Walker syndrome, occipital encephalocele
- Agenesis of the uterus and bladder, deep-seated ears
- VSD, club foot and talipes calcaneus, craniofacial dysmorphism, deep-seated ears, enlarged adrenal abnormality, hypertelorism
- Hypoplastic adrenal glands, clubfoot, bilateral joint contractures, epicanthus internus and hypertelorism, mandibular micrognathia, deep-seated ears

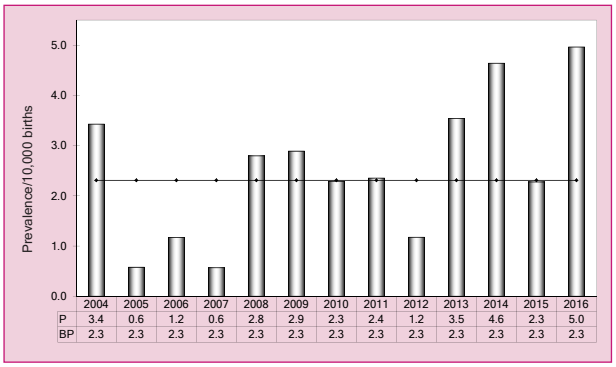


Fig. 31: Development of prevalence/10,000 births with Potter sequence in the registration area since 2004

In 2016, one Potter sequence per 2,015 births was registered in Saxony-Anhalt.

Please note:

What are ACE inhibitors and what is Sartan fetopathie?

The group of pharmaceuticals "sartans" were developed from ACE inhibitors. Mainly used in the antihypertensive therapy, they have a teratogenic effect in case of maternal intake during second and third trimenon of pregnancy. The suspected pathomechanism of both substances results in a reduced perfusion of the foetal organs, in particular of the kidneys. That means both substances interrupt the renin-angiotensin system at different points. The result of such a foetal damage is an intrauterine oliguria. Since amniotic fluid production depends from the second trimenon on mainly from foetal urine production, an oligohydramnios can occur which might be diagnosed by prenatal ultrasound screening. This leads into **occurrence of a potter sequence** with lung and thorax hypoplasia, distorsion of limbs, characteristic face and further consequential problems. Affected infants often suffer postnatal from a renal failure which is in most cases not reversible. Additionally, a hypoplasia/dysplasia of the cranial bone can occur at insufficient cranial ossification (it is also possible that only gaping cranial sutures are present).
German speaking people can get further information about this topic by visiting the website of the pharmacovigilance and advisery centre for embryonic toxicology (www.embyotox.de

12.25 Renal Agenesis, Unilateral (Q60.0/Q60.2)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Magdeburg	1	1.9	↓
Districts: 2 x Anhalt-Bitterfeld 1 x Harz	3	2.3	↓
Saxony-Anhalt	**4**	**2.2**	↓

Renal agenesis, unilateral (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	7.63	5.52 - 10.27
Districts	6.27	5.07 - 7.66
Region	6.64	5.64 - 7.80
EUROCAT	no information	no information

An unilateral renal agenesis affected four children in 2016. This is equal to a **prevalence** of **2.2 per 10,000 births**. Since the 1990s, no lower number has been registered with the Malformation Monitoring Centre. Thus, the yearly prevalence is significantly below the confidence interval of the years 2004 to 2015 of 6.64 per 10,000 births.

EUROCAT does not provide data for the unilateral renal agenesis.

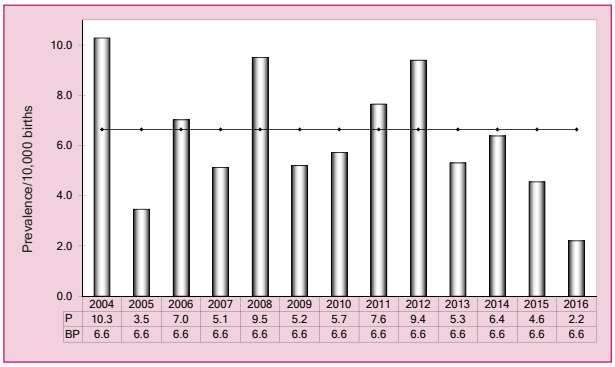
additional information:

Pregnancy outcome	4 x live births
Sex	3 x male 1 x female
Number of isolated malformations/MCA	1 x MCA 3 x isolated

For three of the four children that were born alive no other malformation was diagnosed despite the unilateral renal agenesis. Three times, the left kidney was affected, one time the right kidney.

Malformation combinations (MCA) or superordinated syndromes detected:

- Penile hypospadias, VSD, bicuspid aortic valve, aortic valve stenosis, PFO in premature infant



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	10.3	3.5	7.0	5.1	9.5	5.2	5.7	7.6	9.4	5.3	6.4	4.6	2.2
BP	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6	6.6

Fig. 32: Development of prevalence/10,000 births with unilateral renal agenesis in the registration area since 2004

In 2016, one renal agenesis, unilateral per 4,534 births was registered in Saxony-Anhalt.

12.26 Cystic Kidney (Q61.1-Q61.9)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 4 x Magdeburg	4	7.5	↔
Districts: 2 x Börde 1 x Jerichower Land 2 x Salzlandkreis 2 x Stendal	7	5.5	↓
Saxony-Anhalt	**11**	**6.1**	↓

Cystic Kidney (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	9.23	6.89 - 12.10
Districts	7.26	6.05 - 8.69
Region	7.79	6.71 - 9.04
EUROCAT	no information	no information

Eleven children were diagnosed with cystic kidneys in 2016. The **prevalence** in this year is **6.1 per 10,000 births**. This value can be seen as significantly low in comparison to the basis prevalence of 7.79 per 10,000 births. The calculation of a trend for the total period from 2004 to 2015 (chapter 12.37) resulted in a decreasing trend for cystic kidneys with a percentage change of -4.22 (CI -7.89 % to -0.22%).

Europäische Vergleichswerte für die Prävalenz der Zystennieren sind von EUROCAT nicht verfügbar.

additional information:

Pregnancy outcome	10 x live births 1 x live birth. deceased within 7 days
Sex	7 x male 4 x female
Number of isolated malformations/MCA	6 x MCA 5 x isolated

Two children were affected by a cystic kidney degeneration of both kidneys. The finding occured 9 times only unileteral, amoung which two times left-sided and seven times right-sided.

One child with additional major malformations deceased after surgery on the second day of life.

Malformation combinations (MCA) or superordinated syndromes detected:

- McKusick-Kaufman syndrome with: Persistence of the urogenital sinus, anal atresia, hypoplasia of the osseous thorax and lungs, ureteral stenosis left-sided and DUP grade IV, pulmonary valve stenosis, right vascular ring through the anomalous subclavicular artery and myocardial hypertrophy
- Cranio-fronto-nasal syndrome with: diaphragmatic hernia and nondescensus testis left-sided, biliary dilatation, mandibular retrognathia, conspicuous NHS on the left side, hypertelorism
- VATER association with: oesophageal atresia (Vogt IIIb), dextrocardia, persistent Vena cava superior left-sided, ASD II, butterfly vertebra bone 5
- Ureteropelvic junction obstruction and DUP degree IV left-sided, DUP degree III right-sided , ventricular asymmetry, cavum septum pellucidum, umbilical herniae
- bilateral DUP degree III, ureteropelvic junction stenosis and megaureter right-sided, ureteropelvic junction obstruction left-sided
- PFO at full-term infant, hyperplastic left kidney

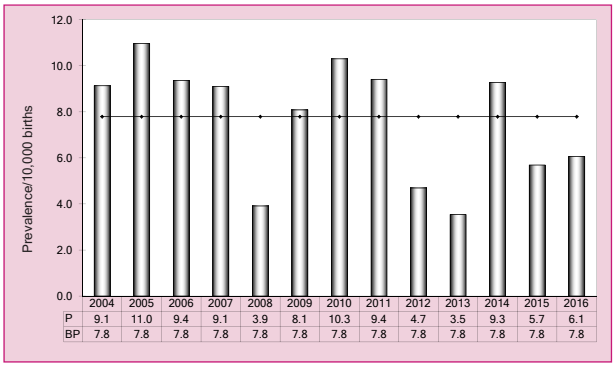


Fig. 33: Development of prevalence/10,000 births with cystic kidneys in the registration area since 2004

In 2016, one cystic kidney per 1,649 births was registered in Saxony-Anhalt.

12.27 Bladder Exstrophy (Q64.1)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities	0	0.0	↔
Districts: 1 x Anhalt-Bitterfeld 1 x Stendal	2	1.6	↑
Saxony-Anhalt	**2**	**1.1**	↑

Bladder Exstrophy (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	0.00	0.00 - 0.53
Districts	0.40	0.15 - 0.86
Region	0.29	0.11 - 0.63
EUROCAT	no information	no information

The bladder exstrophy is one of the very rare malformations, which was, in the 12 reported years, only observed in four of the years and in each of these years only occured one or two times. In 2016, this malformation was observed twice with a prevalence of 1.1 per 10,000 births. Thus, the yearly prevalence is above the calculated confidence interval of the basis prevalence of 0.29 per 10,000 births. However, the yearly prevalence would be within the range of variation if only one case instead of two occured.

EUROCAT does not provide any data on bladder extrophy for comparision.

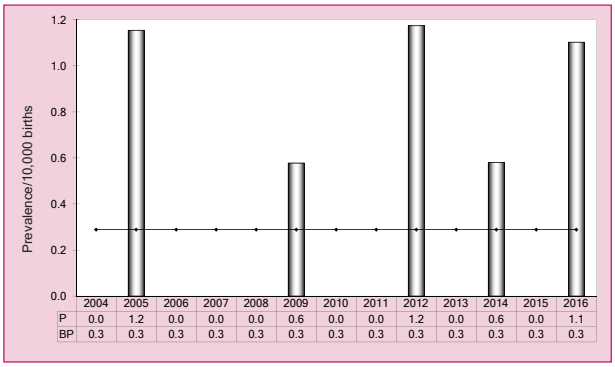
additional information:

Pregnancy outcome	1 x live birth 1 x live birth, deceased within 7 days
Sex	2 x indeterminate
Number of isolated malformations/MCA	2 x MCA

One child with Potter sequence that was born alive deceased on the second day of life.

Malformation combinations (MCA) or superordinated syndromes detected:

- Potter sequence, oesophagus atresia with fistula to the trachea, anal atresia, cleft lip with cleft palate, indeterminate sex, penoscrotal inversion
- indeterminate sex



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	0.0	1.2	0.0	0.0	0.0	0.6	0.0	0.0	1.2	0.0	0.6	0.0	1.1
BP	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Fig. 34: Development of prevalence/10,000 births with bladder exstropy in the registration area since 2004

In 2016, one birth with a bladder exstrophy per 9,068 births was registered in Saxony-Anhalt.

12.28 Preaxial Polydactyly (Q69.1/Q69.2)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Halle	1	1.9	↓
Districts: 1 x Altmarkkreis Salzwedel 1 x Börde 1 x Mansfeld-Südharz	3	2.3	↓
Saxony-Anhalt	**4**	**2.2**	↓

Preaxial Polydactyly (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	4.08	2.59 - 6.12
Districts	3.83	2.91 - 4.95
Region	3.90	3.09 - 4.84
EUROCAT	no information	no information

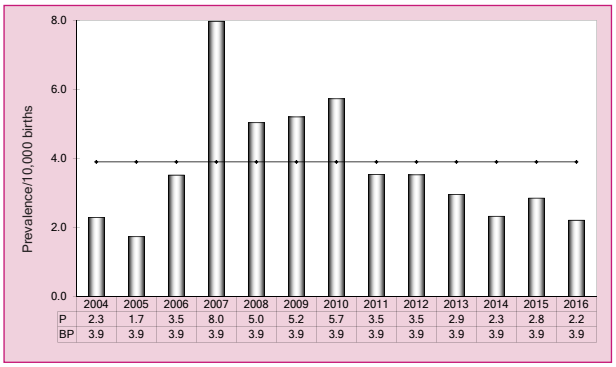
Less frequently as usually, a preaxial polydactyly was diagnosed for four children in 2016. The calculated **yearly prevalence** of **2.2 per 10,000 births** is below the basis prevalence of 2004 to 2015.
Polydactylies were in the reported time period approximately to one-third preaxial and to two-thirds postaxial located. In 2016, the postaxial polodactylies were diagnosed 17 times with their usual frequency.

European data for comparision of the prevalence of the preaxial polydactyly is not availabe through EUROCAT.

additional information:

Pregnancy outome	4 x live births
Sex	4 x male
Number of isolated malformations/MCA	4 x isolated

Four born alive children were each unilaterally affected, twice the right thumb and twice the left thumb. Accompanying malformations were not diagnosed for these children.



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	2.3	1.7	3.5	8.0	5.0	5.2	5.7	3.5	3.5	2.9	2.3	2.8	2.2
BP	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9

Fig. 35: Development of prevalence/10,000 births with preaxial polydactyly in the registration area since 2004

In 2016, one preaxial polydactyly per 4,534 births was registered in Saxony-Anhalt.

12.29 Limb Reduction Defects of both Upper and Lower Limbs (Q71./Q72./Q73.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 4 x Halle 3 x Magdeburg	7	13.2	↑
Districts: 1 x Burgenlandkreis 2 x Börde 1 x Harz 1 x Saalekreis	5	3.9	↓
Saxony-Anhalt	**12**	**6.6**	↓

Limb Reduction Defects of both Upper and Lower Limbs (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	8.34	6.13 - 11.09
Districts	8.58	7.26 - 10.12
Region	8.51	7.37 - 9.82
EUROCAT	5.64	5.47 - 5.81
		2.21 S Portugal* 9.23 Auvergne (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

In 2016, 12 children were affected by a limb reduction defect. The prevalence in 2016 of 6.6 per 10,000 births is within the range of variation of the prevalences of the pas 12 years. of 8.51 per 10,000 births and slightly above the basis prevalence of the European malformation registries (5.64 per 10,000 births).

In most cases (8 x) only the upper limbs were affected, three times the upper and lower limbs and one time only the lower limbs. Predominently (7 x), the reduction defects occured on boths sides, twice only on the right side and three times only on the left side. Only three times, with missing phalanges, lobster-claw hand and brachydactyly type C, no additional malformations were diagnosed.

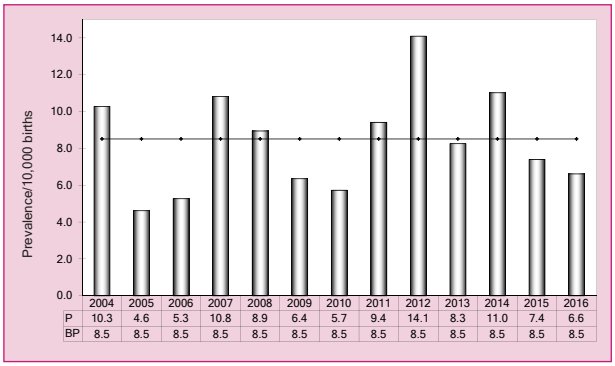
additional information:

Pregnancy outcome	8 x live births 1 x spontaneous abortion 3 x termination of pregnancy
Sex	9 x male 3 x female
Number of isolated malformations/MCA	9 x MCA 3 x isolated

The pregnancy of one fetus with amniotic cords terminated spontaneously in the 24th WOG. Due to medical indication, three pregnancies were terminated at the beginning of the second trimenon, in the 13th and 14th WOG, respectively.

Malformation combinations (MCA) or superordinated syndromes detected:

- Fibrous amniotic cord between the inner side of the right forearm and the occipital region, craniorhachischisis with meningoencephalocele, bilateral anophthalmia, rudimentary nose, median cleft palate and mandibular cleft, mandibular micrognathia, right clubfoot, hypoplasia of the lungs and heart, craniofacial dysmorphism with hypertelorism and laterally displaced palpebral fissure
- Edwards syndrome with: holoprosencephaly, omphalocele, horseshoe kidney, craniofacial dysmorphism, deep-seated ears
- Prune-belly sequence with: urethral atresia, ossification defects on the skull, clubfoot left-sided
- Median cleft of the soft palate, thymus hypoplasia, craniofacial dysmorphism, mandibular retrognathia and micrognathia, deep-seated ears
- Pierre-Robin sequence with: hemivertebra, scoliosis, mandibular micrognathia
- Nagel-Patella syndrome with: missing thumb-nails, bilaterally missing patella, bending of tibia and fibula and retarded hip maturity
- Turricephaly, mandibular retrognathia, simian fold on the right side
- osseous syndactyly on the right hand (Digiti 2-4)
- ASD II, syndactylia at the right foot (Toes II./III.)



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	10.3	4.6	5.3	10.8	8.9	6.4	5.7	9.4	14.1	8.3	11.0	7.4	6.6
BP	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5

Fig. 36: Development of prevalence/10,000 births with limb reduction defects in the registration area since 2004

In 2016, one limb reduction defect per 1,511 births was registered in Saxony-Anhalt.

12.30 Diaphragmatic Hernia (Q79.0/Q79.1)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities	0	0.0	↓
Districts: 1 x Stendal	1	0.8	↓
Saxony-Anhalt	**1**	**0.6**	↓

Diaphragmatic Hernia (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	4.44	2.87 - 6.55
Districts	1.85	1.23 - 2.67
Region	2.55	1.91 - 3.33
EUROCAT (Q79.0)	2.84	2.73 - 2.97
		1.26 S Portugal* 5.76 Malta**

*/** centres with lowest resp. highest prevalence/10,000 births

With a basis prevalence of 2.6 per 10,000 births, the diaphragmatic hernia is a malformation with an expected frequency of three to 8 cases per year in Saxony-Anhalt. In 2016, the diaphragmatic hernia was only diasgnosed once. The resulting **yearly prevalence** of **0.6 per 10,000 births** is only a fraction of the basis prevalence. Such low prevalences were observed for the last time in the middle of the 1990s. This development hints at a decreasing trend (chapter 12.37), which is just within the coincidence range (p=0.0733) and is observed accordingly.

The total prevalence of the European registries is similar to the basis prevalence in Saxony-Anhalt, yet covers a smaller range of variation. Likewise, the range of variation significantly falls below in 2016.

additional information:

Pregnancy outcome	1 x live birth
Sex	1 x male
Number of isolated malformations/MCA	1 x MCA

One born alive child was affected by an extensive left-sided diaphragmatic hernia with a complete relocation of the heart and the lungs to the right side.

Malformation combinations (MCA) or superordinated syndromes detected:

- Cranio-fronto-nasal syndrome with: multicystic dysplastic kidney right-sided, nondescensus testis at full-term infant, biliary dilatation, mandibular retrognathia, abnormal NHS on the left side, hypertelorism

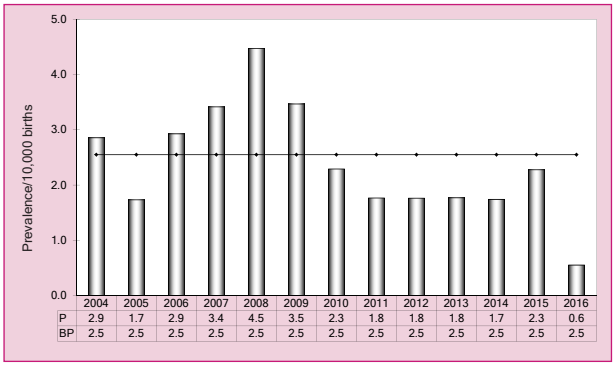


Fig. 37: Development of prevalence/10,000 births with diaphragmatic hernia in the registration area since 2004

In 2016, one diaphragmatic hernia per 18,135 births was registered in Saxony-Anhalt.

12.31 Omphalocele (Q79.2)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 4 x Halle	4	7.5	↑
Districts: 3 x Börde 1 x Saalekreis 1 x Salzlandkreis	5	3.9	↔
Saxony-Anhalt	**9**	**5.0**	↑

Omphalocele (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	3.55	2.17 - 5.48
Districts	3.17	2.34 - 4.20
Region	3.27	2.54 - 4.15
EUROCAT	3.21	3.09 - 3.34
		0.63 S Portugal* 6.55 French West Indies (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

The prevalence of the indicator malformation omphalocele amounts to **5.0 per 10,000 births** in 2016 and thus, results in a value above the limits of the confidence interval of the basis prevalence in Saxony-Anhalt.

Compared to the overall European prevalences, the value of the basis prevalence is relatively similar. The yearly prevalence in Saxony-Anhalt is located within the upper third of the European registries.

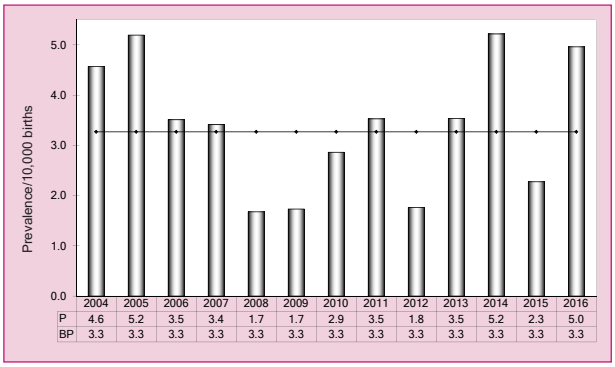
additional information:

Pregnancy outcome	1 x live birth 1 x spontaneous abortion 7 x termination of pregnancy
Sex	4 x male 3 x female 2 x no indication
Number of isolated malformations/MCA	7 x MCA 2 x isolated

In 2016, four times the omphalocele was diagnosed as a symptom of a trisomy and one time as a symptom of a Cantrell pentalogy. The pregnancies were terminated in the 12th and 13th WOG, respectively. The other terminations of pregnancy (1 x in combination with anencephaly und 1 x isolated omphalocele) took place in the 19th and 18th WOG, respectively. Two pregnancies of fetuses with isolated omphalocele terminated spontaneously in the 14th and 22th WOG, respectively.

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: tetralogy of Fallot, cleft lip with cleft palate
- Edwards syndrome with: holoprosencephaly, horseshoe kidney, club hands, craniofacial dysmorphism, deep-seated ears
- Edwards syndrome with: holoprosencephaly, VSD
- Down syndrome with: AVSD
- Anencephaly, deap-seated ears
- Cantrell pentalogy, diverticulum of the left-sided ventricle
- Wiedemann-Beckwith syndrome



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	4.6	5.2	3.5	3.4	1.7	1.7	2.9	3.5	1.8	3.5	5.2	2.3	5.0
BP	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3	3.3

Fig. 38: Development of prevalence/10,000 births with omphalocele in the registration area since 2004

In 2016, one omphalocele per 2,015 births was registered in Saxony-Anhalt.

12.32 Gastroschisis (Q79.3)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Dessau-Roßlau 2 x Magdeburg	3	5.7	↔
Districts: 1 x Burgenlandkreis 1 x Saalekreis	2	1.6	↓
Saxony-Anhalt	**5**	**2.8**	↓

Gastroschisis (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	4.97	3.30 - 7.18
Districts	4.29	3.11 - 5.47
Region	4.47	3.61 - 5.48
EUROCAT	2.99	2.87 - 3.11
		1.04 Emilia Romagna (Italy)* 5.53 Northern England (UK)**

*/** centres with lowest resp. highest prevalence/10,000 births

A gastroschisis occured five times in Saxony-Anhalt in 2016. The prevalence of 2.8 per 10,000 births is below the confidence interval of the prevalence of the years 2004 to 2015. In 2004, the maximum value of 8.6 per 10,000 births was reached. In the following years, the prevalence fluctuated between 2.3 and 5.2 per 10,000 births, within which range also this year's prevalence is located.

The yearly prevalence is slightly below the confidence interval of the European overall prevalence and is in 2016 within the lower third of the reference values given by the EUROCAT centers.

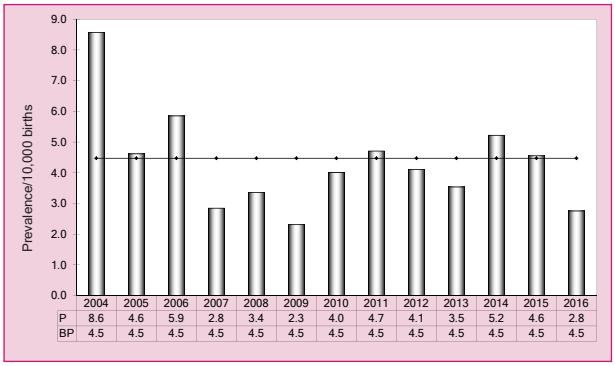
additional information:

Pregnancy outcome	4 x live births 1 x termination of pregnancy
Sex	4 x male 1 x female
Number of isolated malformations/MCA	1 x MCA 4 x isolated

All cases with gastroschisis were already characterised prenatally. The four live births were delivered via sectio in the 33rd and 35th WOG. Only one child was diagnosed with addtitional malformations of the heart. One twin pregnancy was terminated in the 11th WOG, due to feto-fetal transfusion.

Malformation combinations (MCA) or superordinated syndromes detected:

- ASDII, hemodynamically ineffective PDA at premature infant



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	8.6	4.6	5.9	2.8	3.4	2.3	4.0	4.7	4.1	3.5	5.2	4.6	2.8
BP	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5	4.5

Fig. 39: Development of prevalence/10,000 births with gastroschisis in the registration area since 2004

In 2016, one gastroschisis per 3,627 births was registered in Saxony-Anhalt.

12.33 Prune-belly-Sequence (Q79.4)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 1 x Magdeburg	1	1.9	↔
Districts	0	0.0	↓
Saxony-Anhalt	**1**	**0.6**	↔

Prune-belly-Sequence (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	1,24	0.50 - 2.56
Districts	0,73	0.36 - 1.30
Region	0,87	0.51 - 1.37
EUROCAT	no information	no information

The Prune-belly-Sequence is a rare malformation, which only occured once this year and hence, is with a **prevalence** of **0.6 per 10,000 births** within the coincidence range. The over the years 2004 to 2015 calculated basis prevalence amounts to 0.87 per 10,000 births.

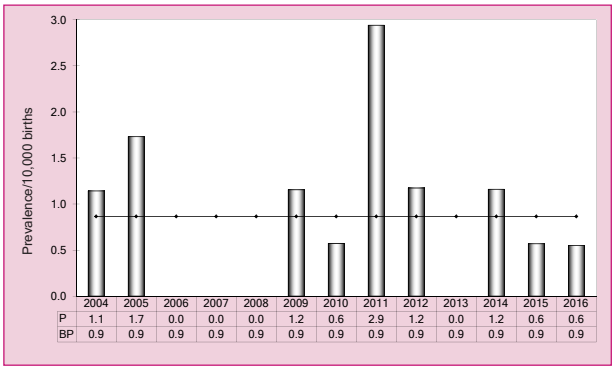
A European overall prevalence for comparison is not available.

additional information:

Pregnancy outcome	1 x termination of pregnancy
Sex	1 x female
Number of isolated malformations/MCA	1 x MCA

Malformation combinations (MCA):

- Diastrophic dysplasia with: micromelia of the arms and legs, urethral atresia, skull ossification defects, clubfoot left-sided



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	1.1	1.7	0.0	0.0	0.0	1.2	0.6	2.9	1.2	0.0	1.2	0.6	0.6
BP	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9

Abb. 40: Development of the prevalence/10,000 births with Prune-belly-Sequence in the registration area since 2004

In 2016, one Prune-belly-Sequence per 18,135 births was registered in Saxony-Anhalt.

12.34 Down's Syndrome - Trisomy 21 (Q90.)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 3 x Halle 2 x Magdeburg	5	9.4	↓
Districts: 1 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 2 x Burgenlandkreis 3 x Börde 4 x Harz 2 x Mansfeld-Südharz 1 x Saalekreis 2 x Salzlandkreis 3 x Stendal	19	14.8	↔
Saxony-Anhalt	**24**	**13.2**	↓

Down's Syndrome (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	22.36	18.86 - 26.45
Districts	16.50	14.61 - 18.61
Region	18.08	16.38 - 19.96
EUROCAT	22.98	22.65 - 23.32
		9.26 S Portugal* 42.51 Paris (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

In 2013, the highest prevalence was reported for Down's Syndrome since the 1980s with 25.4 per 10,000 births. Since then, the calculated prevalence values have been decreasing. The minimum value in the reported period of time was observed in the year 2005 12,1 per 10,000 births. With 24 cases and thus, a **prevalence** of **13.2 per 10,000 births**, the prevalence for 2016 is below the confidence interval of the basis prevalence.

Likewise in the European comparison, this year's prevalence is relatively low. The prevalence is within the lower third of the European registries.

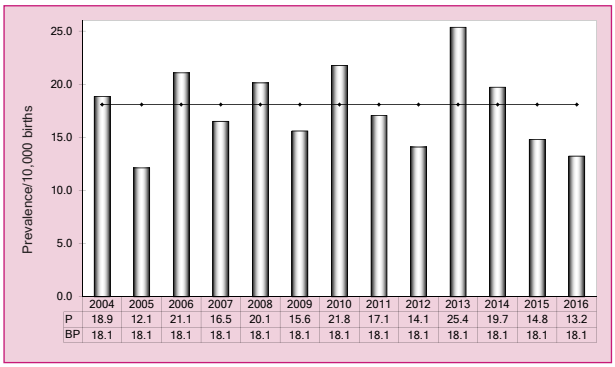
additional information:

Pregnancy outcome	9 x live births 15 x termination of pregnancy
Sex	8 x male 15 x female 1 x no indication
Number of isolated malformations/MCA	8 x MCA 16 x isolated

For 15 fetuses with Down's syndrome, the pregnancy was terminated with an average of 16.2 weeks of gestation, at the earliest in the 12th WOG and at the latest in the 19th WOG.

Malformation combinations (MCA):

- Omphalocele, AVSD
- Tetralogy of Fallot, haemodynamically effective PDA at premature infant, microcephaly, conductive hearing loss left-sided 30-55 dB and right-sided 20-65 dB
- Tetralogy of Fallot
- Canalis common atrioventricularis, mitral valve insufficiency, dilated brain ventricles
- AVSD
- ASD II, pulmonary valve insufficiency, PDA at premature infant, retarded hip maturity right-sided
- ASD II, Pulmonary hypoplasia, bilaterally abnormal NHS, non-hemodynamically effective PDA at premature infant
- Triphalangeal thumb, clinodactyly of the left-sided 5th finger



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	18.9	12.1	21.1	16.5	20.1	15.6	21.8	17.1	14.1	25.4	19.7	14.8	13.2
BP	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1	18.1

Fig. 41: Development of prevalence/10,000 births with Down syndrome in the registration area since 2002

In 2016, one child with Down's syndrome (trisomy 21) per 756 births was registered in Saxony-Anhalt.

12.35 Patau Syndrome - Trisomy 13 (Q91.4-Q91.7)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities	0	0.0	↓
Districts: 1 x Börde 1 x Harz	2	1.6	↗
Saxony-Anhalt	**2**	**1.1**	↔

Patau Syndrome (2004 to 2015)		
	Basis prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	1.42	0.61 - 2.80
Districts	0.86	0.46 - 1.47
Region	1.01	0.63 - 1.54
EUROCAT	2.09	1.99 - 2.19
		0.59 S Portugal* 4.04 Paris (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

The third most frequent trisomy, the Patau Syndrome, was verified in the birth year 2016 for two fetuses by use of amniocentesis and the pregnancies were then terminated in the 13th and 17th WOG, respectively.

With two cases, the **prevalence** in 2016 amounts to **1.1 per 10,000 births**. This is almost exactly equal to the over the past 12 years calculated basis prevalence of 1.01 per 10,000 births.

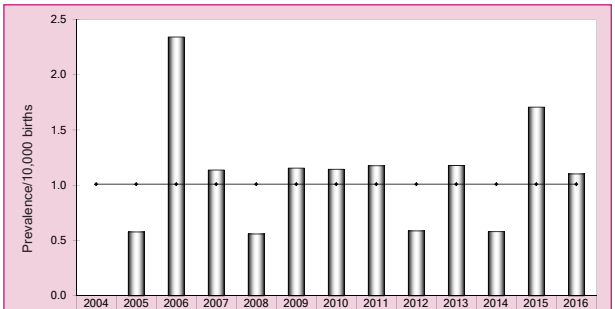
EUROCAT shows for the Patau Syndrome a prevalence of 2.09 per 10,000 births. The prevalence in Saxony-Anhalt is below the confidence interval, yet in the regional comparison within the lower third of the other registries.

additional information:

Pregnancy outcome	2 x termination of pregnancy
Sex	1 x female 1 x no indication
Number of isolated malformations/MCA	1 x MCA 1 x isolated

Malformation combinations (MCA):

- Tetralogy of Fallot, omphalocele, cleft lip with cleft palate



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	0.0	0.6	2.3	1.1	0.6	1.2	1.1	1.2	0.6	1.2	0.6	1.7	1.1
BP	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Fig. 42: Development of prevalence/10,000 births with a Patau syndrome in the registration area since 2004

In 2016, one Patau syndrome (trisomy 13) per 9,068 births was registered in Saxony-Anhalt.

12.36 Edwards Syndrome - Trisomie 18 (Q91.0-Q91.3)

	Number	Prevalence /10,000 births	Trend in comp. to basis prevalence
Major cities: 3 x Halle	3	5.7	↔
Districts: 1 x Burgenlandkreis 1 x Harz 1 x Mansfeld-Südharz 1 x Saalekreis 1 x Salzlandkreis	5	3.9	↔
Saxony-Anhalt	**8**	**4.4**	↔

Edwards Syndrome (2004 to 2015)		
	Basis prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	4.79	3.16 - 6.97
Districts	3.56	2.68 - 4.65
Region	3.90	3.09 - 4.84
EUROCAT	5.46	5.30 - 5.63
		1.31 S Portugal* 13.69 Paris (France)**

*/** centres with lowest resp. highest prevalence/10,000 births

In the birth year 2016, an Edwards Syndrome was diagnosed 8 times. The **prevalence** of **4.4 per 10,000 births** complies with the upper range of the confidence interval of the basis prevalence of 3.90 per 10,000 births.

In comparison to European data, the determined yearly prevalence in Saxony-Anhalt is below the overall prevalence. The minimum and maximum values of the EUROCAT centers, however, are widely spread. The prevalence in Saxony-Anhalt can be ranged in the lower third.

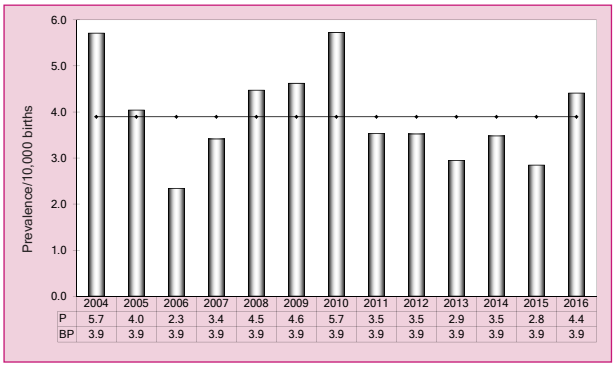
additional information:

Pregnancy outcome	8 x termination of pregnancy
Sex	6 x male 1 x female 1 x no indication
Number of isolated malformations/MCA	5 x MCA 3 x isolated

In all 8 cases, major malformations were observed in the prenatal ultrasound. The pregnancies were terminated between the 12th and 21st WOG. Three times we did not receive the postnatal reports of the accompanying malformations. For the evaluation, these diagnoses are not considered, since they are postnatally not confirmed.

Malformation combinations (MCA):

- Holoprosencephaly, omphalocele, horseshoe kidney, clubhands
- Holoprosencephaly, omphalocele, VSD
- Dolichocephaly, bilateral choanal atresia
- Hydrocephaly, VSD, atypical location of the coronary vessels
- Urinary bladder obstruction, megacystis



	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	5.7	4.0	2.3	3.4	4.5	4.6	5.7	3.5	3.5	2.9	3.5	2.8	4.4
BP	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9	3.9

Fig. 43: Development of prevalence/10,000 births with Edwards syndrome in the registration area since 2004

In 2016, one child with Edwards syndrome (trisomy 18) per 2,267 births was registered in Saxony-Anhalt.

12.37 Indicator Malformations, In Total

The chapters 12.1 to 12.36 show an overview of the occurence of 36 indicator malformtions (chapter 12.0) that are world-wide clearly defined by the ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research). The monitoring of these malformations in Saxony-Anhalt meets the requirements for an evaluation on a temporal and regional level and therefore, faciliates the identification of noticeable accumulations (cluster).

In 2016, of the 239 born children with an indicator malformation, 177 were born alive (74.1 %). From 2004 to 2015, the percentage of live births was at 76.6 % in Saxony-Anhalt. In 2014, the smallest percentage was registered (72.9 %). In 2016, only two stillbirths and two spontaneous abortions as from the 16th WOG were detected with indicator malformation(s). Their percentage (2016 jointly: 1.7 %) is decreasing and is significantly below the expected value. On the contrary, the amount of terminations of pregnancy is increasing. In 2016, the percentage of terminations of pregnancy can be evaluated as high (24.3 %, 58 terminations of pregnancy). Between 2004 and 2015, the pregnancy was prematurely terminated on average for about 1/5 of the fetuses with an indicator malformation (20.8 %)

In total, 309 indicator malformations were diagnosed for 239 births. 129 born children were affected by an isolated indicator malformation, 110 children showed additional malformations. 21 born children had two and 10 children more than two indicator malformations.

	Number	Prevalence in %	Trend in comp. to basis prevalence
Major cities	76	1.43	↓
Districts	163	1.27	↓
Saxony-Anhalt	239	1.32	↓

Indicator malformations, in total (2004 to 2015)		
	Basis prevalence in %	Confidence Interval (CI of 95%)
Cities	1.63	1.54 - 1.75
Districts	1.36	1.31 - 1.43
Region	1.44	1.39 - 1.49

The prevalence of all born children with indicator malformation is, as in the previos year (2016: 1.32; 2015: 1.33 per 10,000 births) below the confidence interval of the for the years 2004 to 2015 calculated basis prevalence (1.44 per 10,000 births, CI 1.39-1.49).

As usually, the seperately observed prevalences of districts and major cities (fig. 44) result in lower values for the districts (2016: 1.27 vs. 1.43 per 10,000 births). A comparison of the current prevalences with the respective basis prevalence shows individually as well as jointly a significantly lower rate than expected.

A trend analysis aims to depict the long-term tendencies regarding the occurence of malformations.

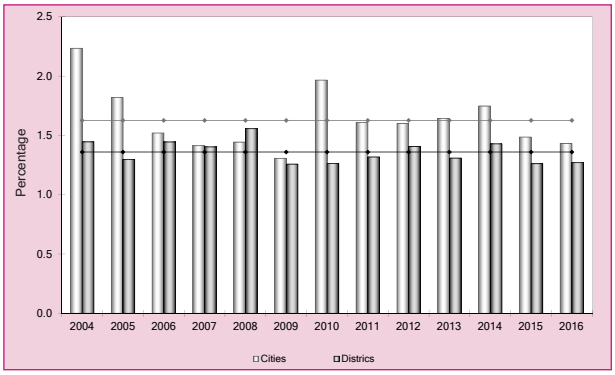


Fig. 44: Indicator malformations in total (2004 to 2016), comparison of frequency (in %) in the major cities and districts

In the current report, the magnitude and orientation of the change in indicator malformation prevalences in the time period from 2004 to 2016 is analyzed.

The trend estimation is only conducted for indicator malformations which have at least an expected value of five and if the observation value of each included year is at least two. hence, figure 45 on page 65 only shows the estimated average percentage changes of yearly prevalences of indicator malformations which meet the requirements. The mathematical foundation of the analysis is a binary-logistic regression on the basis of the maximum likelihood estimation.

The measure for the magnitude and orientation of the yearly percentage change is the regression coefficient B. A significantly increasing trend, which is characterized by a positive regression coefficient, is displayed in the diagram including the CI of 95 % on the right side from the y-axis. A decreasing trend is depicted by a regression coefficient on the left side from the y-axis (in the negative domain). A depicted trend is significant if the confidence interval does not overlap the zero value.

The temporal change is examined with regard to the heterogeneity of the trend component as well as the non-linear component by using a chi-square test. For a probability value of $p > 0.05$ for the linear ratio and $p < 0.05$ for the non-linear ratio determinative, i.e. the trend has to be categorized as **non-linear**. This can be observed for neural tube defects, Spina bifida, and undescended testis.

A probability value of $p < 0.05$ for the linear ratio and $p > 0.01$ for the non-linear ratio indicates that the linear ratio is dominant and the non-linear ratio is insignificant. The observed trend is, according to the regression coefficient B, significant. A **significantly increasing trend** can be observed in the reported period of time for microcephaly (+10.17 %, CI 4.04 % to 17.79 %). A **significantly decreasing trend**, according to a negative regression coefficient B and a non-effective non-linear ratio, can be seen for anorectal atresia/ -stenosis and cystic kidneys.

For the diaphragmatic hernia, this results for the linear ratio in a probability value, which is just still within the coincidence range (p = 0.073), while the non-linear ratio has almost no impact.
For all other depicted indicator malformations, the trend can neither be evaluated as significantly positive nor negative.

If the chi-square test results for the linear as well as the non-linear component each in probability values of p > 0.05, there can be no decision made regarding a aignificant increase or decrease, even if the non-linear ratio is not crucial for the evaluation of the trends.

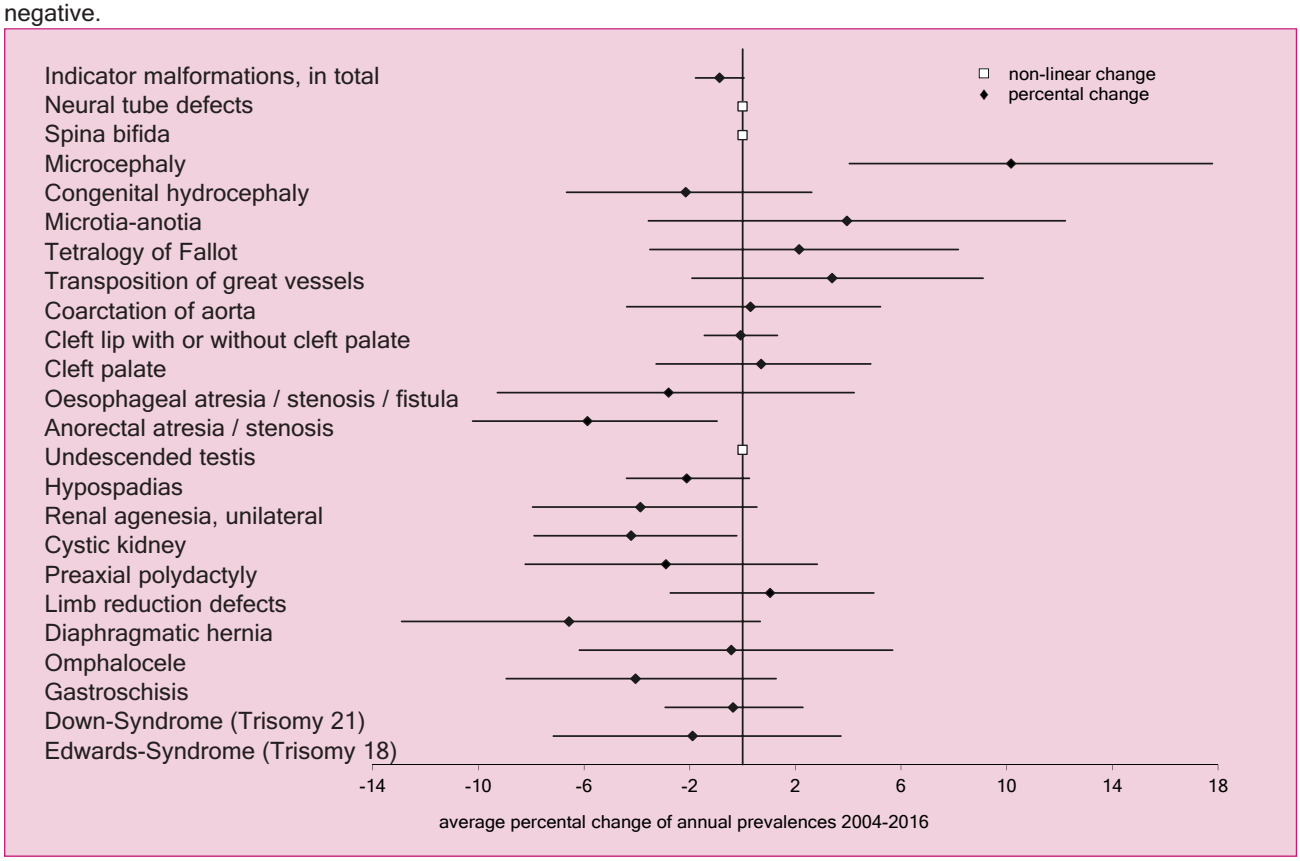


Fig. 45: Trend analysis 2004-2016 with average percental change of prevalence per year (95% confidence interval)

	Regression coefficient B in %	Confidence interval (CI of 95%)
Indicator malformations, in total	-0.87 %	-1.78 % to 0.05 %
Microcephaly	10.17 %	4.04 % to 17.79 %
Congenital hydrocephaly	-2.15 %	-6.66 % to 2.62 %
Microtia/Anotia	3.95 %	-3.57 % to 12.22 %
Tetralogy of Fallot	2.14 %	-3.50 % to 8.16 %
Transposition of great vessels	3.39 %	-1.91 % to 9.10 %
Coarctation of aorta	0.30 %	-4.38 % to 5.22 %
Cleft lip with or without cleft palate	-0.07 %	-1.45 % to 1.32 %
Cleft palate	0.70 %	-3.27 % to 4.85 %
Oesophageal atresia/stenosis/fistula	-2.80 %	-9.28 % to 4.23 %
Anorectal atresia/ -stenosis	-5.88 %	-10.22 % to -0.97 %
Hypospadias	-2.12 %	-4.39 % to 0.26 %
Renal agenesia, unilateral	-3.87 %	-7.95 % to 0.54 %
Cystic kidney	-4.22 %	-7.89 % to -0.22 %
Preaxial polydactyly	-2.90 %	-8.23 % to 2.82 %
Limb reduction defects	1.04 %	-2.73 % to 4.97 %
Diaphragmatic hernia	-6.57 %	-12.90 % to 0.67 %
Omphalocele	-0.42 %	-6.17 % to 5.68 %
Gastroschisis	-4.06 %	-8.94 % to 1.26 %
Down's Syndrome (Trisomy 21)	-0.36 %	-2.93 % to 2.28 %
Edward's Syndrome (Trisomy 18)	-1.89 %	-7.16 % to 3.72 %

15 Summary

The annual report 2016 about the prevalence of congenital malformations and anomalies as well as genetically caused diseases is based on the data that has been transmitted to the Centre of Malformation Monitoring Saxony-Anhalt from 2004 to 2016.The statistical analysis of data is population-based by use of the nationwide malformation data and according to the official birth rate of the fedderal state. To better classify the calculated indicator malformation prevalences, we indicate, if available, European-wide registered values calculated by EUROCAT.

For the third time in a row, an increase in the yearly birth rate can be seen in Saxony-Anhalt. For 2016 extrapolated, **17,964 children were born alive** in Saxony-Anhalt. Between January and November, the Statistical offices indicates 16,591 live births. This number shows that 3.12 % more children were born alive than in the period of time from January to November 2015 (16,089).

There were no information available regarding stillbirths by the Statistical office for 2016. Therefore, for the report the expected number of 66 stillbirths was used.

In 2016, approximately 785,600 children were born alive in Germany (according to the Federal Statistical Office between January and November 722,224). Compared to numbers from the previous years (2015: 737,575), a slightly increasing trend can be noticed nationwide for the past five years. From Saxony-Anhalt are about 2.3 % of all newborns in Germany.

The prevalence calculations in 2016 are based on a **total number of 18,135 births** (chapter 2). Besides data on live- and stillbirths, the analysis in the report also includes data on **terminations of pregnancy (2016: 81)** und **spontaneous abortions from the 16th WOG on (2016: 24)**.

673 born children (3.71 % of all births) were affected by a **major malformation** in 2016. The malformation rate is above the rate of the past 12 years (3.48 %, CI 3.40 % to 3.56 %) (chapter 8). 86.8 % of the born children with major malformations were born alive in 2016. Only 8 children (1.4 % of the live births with major malformations) deceased within the first year of life. In the reported period of time, the minimum value occured in 2017 with 1.3%. The amount of terminations of pregnancy is with 11.3 % of the births with major malformations in the upper range of the past years.

The steadily **most frequent single diagnosis**, ASD, was detected in 2016 with more than 1.1 % of the born children and more often than usually. The third most frequent malformation, the uropathy grade II-IV, was observed slightly more often. The number of 42 congenital hearing defects (4th place) is within the expected range of the since the introduction of the NHS in Saxony-Anhalt in 2007 observed high number of affected persons. The Down's Syndrome again occured less frequently in this year than it was expected (chapter 11).

One of the exactly defined **indicator malformations** (chapter 12) was in 2016 detected for 1.32 % of all born children. With regard to the respective basis prevalences, **higher prevalences** were registered for anencephaly, encephalocele, microcephaly, arhincephaly/holoprosencephaly, anophthalmia/microphthalmia, tetralogy of Fallot, transposition of the great vessels, choanalatresia, epispadias, indeterminate sex, Potter sequence, exstrophy of the urinary bladder und omphalocele. In contrast, for hydrocephaly, anorectal atresia/-stenosis, hypospadias, unilateral renal agenesia, cystic kidney, preaxial polydactyly, limb reduction defects, diaphragmatic hernia, gastroschisis und Down's Syndrome **lower prevalences** were registered.

In 2016, **79 terminations of pregnancy with malformations** were reported to the Malformation Monitoring Centre. In chapter 14 (in German version), these are grouped by malformations of the CNS (25.0 %), chromosomal aberrations (39.5 %), and multiple anomalies and other malformations (35.5 %). The median of the maternal age for CNS malformations is 28 years, for chromosomal aberrations 36 years, and for multiple anomalies and other malformations 29 years.

A **genetically caused disease** was diagnosed in 2016 for 50 born children. A sequence, association of complex was described for 19 born children. Affected of a fetopathy or the consequences of a congenital infection were 19 children. For more then half of the 45 born children with a **chromosomal aberration**, a Down's Syndrome (24) was diagnosed.

Limb reduction defects, as one of the most common subgroups of the skeletal malformations, are in the focus of this year's annual report (chapter 16). Besides giving information about classification and etiology, we present prevalences of Saxony-Anhalt from 2000 to 2016. In the course of this, the reduction defect of the lower limbs, exemplarily, is discussed in detail as a rare major malformation.

The Malformation Monitoring Centre received for the birth year 2016 2,339 reports about 2,055 births. Of these **673 children/ fetuses** from Saxony-Anhalt showed at least one **major malformation** and another **379 children/ fetuses** showed **only minor malformations and anomalies** (chapter 6-8 (partly in German version)).

The Malformation Monitoring Centre Saxony-Anhalt registers and evaluates data of children and fetuses with congenital malformations and anomalies as well as genetically caused diseases. The analysis of risks with statistical methods is only possible through the comparison with data of children without malformations.

Due to the long-term cooperation with many commited colleagues from different medical institutions, who voluntarily and selfless report congenital malformations to the Malformation Monitoring Centre Saxony-Anhalt, a substantial data base could be established, on the basis of which, also in 2016, the annual report was composed. **We would like to thank all "senders" and hope that this excellent cooperation will continue!**

16 Skeletal malformations

The skeletal malformations involve a very heterogeneous group of congenital structural anomalies, defects and/ or deformations that can affect the whole bone system.

Due to the different pathogeneses, a differentiation into the categories limb reduction and vertebrae malformations, cranial malformations (ossification disorder: craniosynostosis), and the skeletal dysplasias medically sensible. Malformations of the limbs and of the vertebral column, which more or less affect one part of the body, are rarely due to a genetic cause, but rather normally are caused by disruptive endogenous or exogenous influences, which impact the embryo or fetus during the important phases of development of the skeletal sytem (infection, hypoxia, toxin/teratogen,lower perfusion). Special emphasis is on the group of the constricting bands complex.

Additionally to the possible described defects for congenital systemic diseases of the skeleton (skeletal dysplasias), a diffuse disruption of the bone structur and development of the body size (microsomia) in combination with other organ and metabolic diseases can appear. These are often due to genetic cuases (autosomal dominant new mutationen, rarely autosomal recessive).
Thereby, the spectrum of disease reaches from a major, normally lethal skeletal dysplasia (synonym thanatophoric microsomia), which manifests prenatally, to poly- or syndactyly with a very good prognosis. (Charakteristic symptoms of the thanatophoric dysplasia are: Micromelia, macrocephaly, small thorax and distinct facial features.)

With almost 80 %, the limb reduction defects constitute for the largest proportion of the skeletal malformations (Fig. 48) and will be further examined in the the following section.

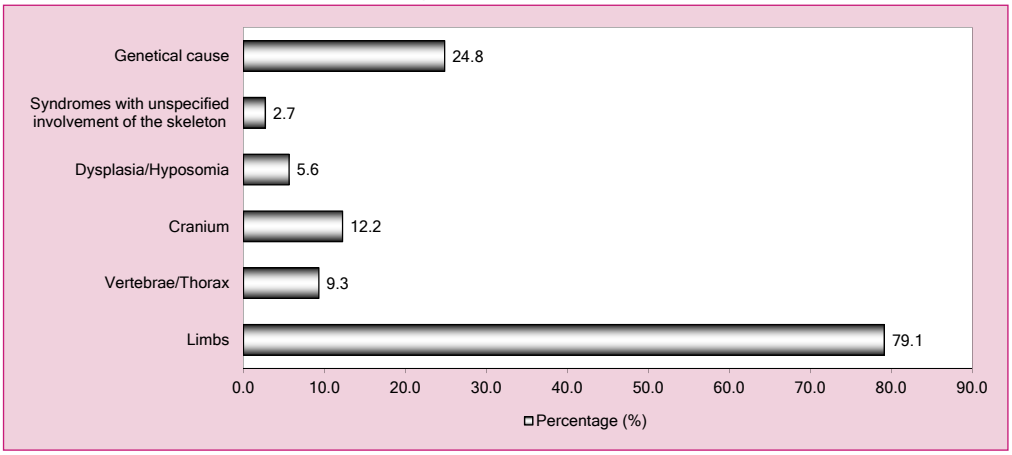


Fig. 48: Skeletal malformations in subgroups (multiple mentions possible)
Evaluation of data of all cases with skeletal malformations (n= 1.332) in the time period from 2000 to 2016

Limb reduction defects

A worldwide consistent nomenclature makes it possible to exactly verify congenital malformations in the anatomical area of limbs also enhances the verification across national borders and disciplinary boundaries. After several attempts of describing the technical terms in a common way, a compromise was initiated among experts that is based on recommendations of the International Society for Prothetics and Orthotics (ISPO) (www.ispoint.org).

A distinction is made between transversal and longitudinal reduction defects of the limbs. This described classification is idealized and can only be made use of in clinical praxis when adapted to the respective patient.

The aim of this classification is to replace the hitherto confusin of technical terms in the international language usage by clear terminologies.

- **Amelia** = transversal malformation:
  complete absence of a whole limb
- **Peromelia** = transversal malformation:
  amputation-like absence of longer and shorter parts of limbs
- **Ectromelia** = longitudinal malformation:
  absence of one bone of limbs with two bones, e.g. forearm, lower leg
- **Hemimelia** = transversal malformation:
  amputation-like complete or partial absence of limb(s)
- **Meromelia** = longitudinal malformation:
  same meaning as Ectromelia
- **Phocomelia** = longitudinal malformation:
  seal arms/ feet: absence of a whole limb that is not at the end of a body part

Examples for the terms quoted from Matussek et al. [1] and translated

„Amputation-like“ structure anomalies are equal to transversal malformations and include all terminal transversal deficits. Compared with this, longitudinal malformations describe all non-transversal deficits with the subcategories proximal longitudinal, distal longitudinal and combined longitudinal deficits.

For the classification of transversal malformations the proportion of the only just formed part of the limb is used.

For the longitudinal malformations, the amount of absent bony parts is depicted. Moreover, the precise observation on whether the bones are completely missing or hypo- or hyperplastic inherent are taken into account for the classification. Furthermore, reduced or insufficiently inherent bony areas, with regard to this bone proximally or distally located from the limb, are classified as longitudinal malformations [1].

For the phalanx distalis, these are more detailed classifications, under consideration of the soft tissue formation. Most commonly, the literature refers to modifications by Swanson et al., though also integrates for the hand modifications assmptions of Oberg and colleagues [2, 3].

One classification, which covers besides the skeletal malformations also modifications, especially soft tissue formation disorders, is the by Swanson made division into seven categories:

I Absence of the formation of parts:
- transversal defects
- longitudinal defects

II missing differentiation of parts :
- Syndactyly
- Camptodactyly
- Thumb-in-palm deformity
- Clinodactyly
- Synostoses
- Symphalangy

III Duplicate formation:
- Ulnar polydactyly
- Polydactyly

IV Hypergenesis:
- Macrodactyly

V Hypogenesis:
- Brachydactyly

VI Amniotic band syndrome

VII generalized skeletal deformations

modified in accordance with Matussek et al. [1] und Swanson et al. [3]

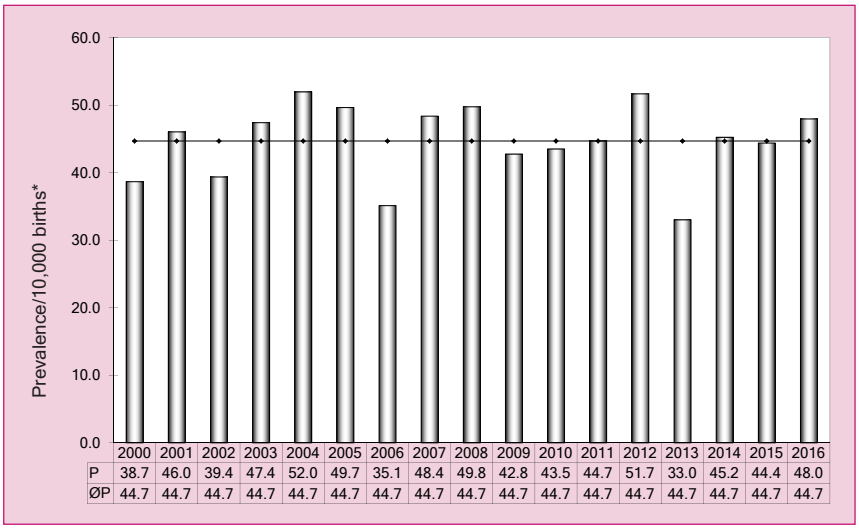
The development of limbs from undifferentiated mesenchyme and ectodermal cells starts between the 26th day after conception in the area of the upper limbs and on the 28th day after conception in the area of the lower limbs. Over the course of four weeks, the process of differentiation takes place from proximal to distal. Complex interactions between signaling pathways initiate the differentiation.

Even with increasing technical possibilities to depict differentiated processes, it is still not finally understood how the sprouting of limbs in the correct positions takes place. How an exact temporal disposition interconnects the processes and how the cell differentiation in the process of embryogenesis is initiated, is not certainly explainable. The formation direction of the limbs seemsto run from the polarization zone, in the first step preaxial-postaxial (radial-ulnar) triggered. In the next step, the development of the limbs runs in dorsal-volar direction (initiated from the apical ectodermal border zone) [2, 4].

With this complexity and the thereby possible probability of error, it is not surprising that congenital malformations belong to the most frequent malformations.

An evaluation of the data from the **Malformation Monitoring** in **the period of time** from **2000 to 2016** revealed that **44.7 per 10,000 births** show a **major malformation of the skeletal system**. The respective numbers for each year from 2000 on are depicted in figure 49.

In the category of the **skeletal malformations**, the **European registries for comparison (EUROCAT)** stated in the **time period** from **2011 to 2015** the **Limb reduction defects** with **43.2 per 10,000 births** (95% CI: 42.4 - 43.9) (http://www.eurocat-network.eu/accessprevalencedata/prevalencetables).



	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
P	38.7	46.0	39.4	47.4	52.0	49.7	35.1	48.4	49.8	42.8	43.5	44.7	51.7	33.0	45.2	44.4	48.0
ØP	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7	44.7

Fig. 49: Prevalence of skeletal malformtions
Data evaluation (Period of time from 2000 to 2016) based on 298,024 births

* births =
live births + stillbirths + termination of pregnancys after prenatal diagnosis of a malformation + spontaneous abortions from the 16th WOG

P = yearly prevalence
ØP = Prevalence 2000-2016

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For more than 120 congenital skeletal malformations and their phenotypes 8,404 characterizations (Human Genes and Genetic Disorders) can be found in the Online Mendelian Inheritance in Man (OMIM) database (www.omim.org). Only about 40% of all skeletal malformations are clarified on the molecular level [5].

As **cause for congenital limb reduction defetcs**, the teratogenic impact of Thalidomid (Contergan©) was only discovered in the 1960s and resulted in the understanding that exogenous noxae can have adverse health effects on the unborn life.
For isolated limb reduction defects, genetic causes are less relevant. Rather exogenous and endogenous noxae play a role in the etiology.
Valproic acid during the pregnancy can influence especially the growth of the radius. Smoking (likewise passive smoking) of the pregnant woman leads to, in the same way as a fetal hypoxia, increasingly to logitudinal limb reduction defects, occasionally also to preaxial reduction defects of the lower limbs [5].
Vascular modifications, as by fetal hypoxia developed ruptured limb vessels, induce also a malformation of the distally located structures [6].
Pyrexia during the pregnancy is associated with oromandibular- and limb-hypoplasia, in combination with a Musculus pectoralis-hypoplasia (Poland-Hypoplasia) with underdevelopment of the ipsilateral upper limbs. Likewise, a congenital varicella infection can result in an underdevelopment of the limbs [5].

Transversal limb reduction defects, the most frequent within the limb reduction defects, originate very often from the amniotic band syndrome (ADAM complex). Thus, amputations occur (missing forearm or lower leg, concerning whole limbs), as well as ring-shaped strangulation with hypoplasia of the distally located part, lymphedema behind the strangulation, distal syndactylies and innumerable additional, also other body areas affecting, defects. Moreover, the lower limbs are more frequently and more severely affected.

Distal structures of the limbs are more often affected by amniotic bands than proximal parts. The limbs are arbitrarily, mostly unsymmetrically affected. An important differential diagnosis is the Eine wichtige Differentialdiagnose ist das Goltz-Gorlin syndrome (focal dermal hypoplasia), which can have the effect of an amniotic band sequence. As iatrogenic cause for the formation of limb and finger malformations is the chorionic villus biopsy known, if it is performed before the 10th week after conception. [5, 7].

Longitudinal limb reduction defects can occur unilateral or bilateral and show different severities among both sides. Not only intraindividually is the spectrum large, also intrafamilially, especially for autosomal dominant inheritances subtle malformations appear. Most of the major longitudinal malformations have an autosomal dominat inheritence and occur de novo [5].

Regarding the **medical care** of children with rare limb reduction defects, medical practitioners of different specialist fields have been consulted. On the occasion of the annual conference of the Saxon-Thuringo association for child and adolescent medicine and pediatric surgery in April 2017 a poster about the topic „Reduction defects of the lower limps“ was compiled (see page 77). With regard to its contents, challenges and possibilities of coping for the affected families are outlined and answers from questions to experts are presented.

Little and Cornwall describe psychological stress for patients and by limb reduction effects affected families, also for only slight functional impairments. The reconstruction of a limb or, respectively, the surgical correction is the most wanted aim of the families. Cultural aspects with regard to how the situation is handled and how the patient is cared for, should be incorperated into the decision making process for surgical care [2].

Check list of sociopaediatric aspects

- Diagnosis: Presentation of the patient at the Human Genetics Institute and if a syndromal disease is present, planning of council in the respective pediatric fields
- Presentation of the patient to expert teams (pediatric surgery, orthopedics) for surgery planning, starting to think about rehabilitation programs
- Assessment of the general and motoric developmental stage
- Encouragement: prescription of especially everyday life relevant therapies (physiotherapy, ergotherapy) which lead to autonomy
- Psychotherapeutic support in stressful situations, e.g. in the prepubertyt
- Clarification of the current social integration of the patient/ support for the everyday life through family/ nursing service
- Counselling of the families with regard to social law, e.g. on the possibility of applying for a disabled person's pass and the care degree
- For the children nursing facility: Examination of special needs (early support vs. integrative kindergarten place) according to ntional laws
- For the integration into a regular kindergarten, application for an „integration assistent“
- Sorting out of educational perspectives before school enrollment, initiation of a special educational review procedure for the integration into a regular school everday life with a priority on physical development (inclusion) poss. with support of an integration assistent vs. schooling for children with distinct physical impairment at a special-needs school for physical development (protected frame)
- Accommodation for disadvantages (allow for more working time, tolerance for discrepancies in geometry or the like, more oral examinations) and permission for non-participation in sports lessons if special needs priority is omitted
- For integration in school, testing of therapeutic appliances in the ergo- or physiotherapy or in a sanatorium (Arthwriter hand aid, special pens, usage f digital media, special workplaces, walking aids, active wheelchair, ortheses)

18 Newborn Hearing Screening 2016

Introduction

Every newborn is entitled to receive a general newborn hearing screening which belongs as from 01-01-2009 to the recommended early detection examinations after birth of a child.
The **aim** of the newborn hearing screening (NHS) is to detect **congenital hearing disorders at an early stage (up to the 3rd month of life)** and to **initiate the corresponding therapies (up to the 6th month of life)**.

The **basis** for this early detection examination is "Enclosure 6 - early detection examination of hearing disorders at newborns (newborn hearing screening)" of the **Children Directive issued by the Federal Joint Committee (G-BA)** on 19-06-2008.

The Children Directive determines the **process of the newborn hearing screening** in the following way:
- measurement of each ear by TEOAE or AABR up to the 3rd day of life (outside of hospital by no later than early detection examination 2 (U2))
- AABR examination is mandatory for children with increased risk for a hearing disorder
- examinations of premature infants by no later than calculated date of delivery and examinations of not healthy newborns by no later than 3rd month of life
- at suspicious first screening, repetition of examination on both ears by AABR preferably on the same day, but by no later than early detection examination 2 (U2)
- at suspicious finding of the follow-up AABR examination a comprehensive confirmation diagnostics is necessary up to the 12th week of life

According to the Children Directive **performance and results of the newborn hearing screening as well as a possible confirmation diagnostics** have to be **recorded** in the **"yellow book of examination" of every child**. The responsible paediatrist resp. ENT physician can evaluate by reading this information if the required diagnostics resp. therapy in case of a hearing disorder was initiated.

The **Malformation Monitoring Centre Saxony-Anhalt** cooperates with the Centre for Newborn Hearing Screening Saxony-Anhalt since 2006 as **tracking centre for the newborn hearing screening** (Federal State dependent screening centre).

The Newborn Hearing Screening Directive stipulates that the hearing screening should be performed via AABR at **children with an increased risk for congenital hearing disorders.** The following overview outlines in extracts possible **indications for the performance of an AABR examination** due to an increased risk of hearing disorders (modified according to JCIH 2007*):
- positive family history regarding hearing disorders
- clinical suspicion of hearing disorder/ deafness
- premature birth, birth weight under 1500 g
- neonatal intensive care
- hyperbilirubinemia (exchange transfusion)
- pre-, peri- or postnatal hypoxia (pH < 7.20)
- peri- and postnatal cerebral hemorrhage, oedema
- intrauterine infections
- culture positive postnatal infections associated with increased risk of hearing loss
- craniofacial anomalies
- distinctive diseases with hearing loss
- neurodegenerative diseases or sensomotoric neuropathies
- outer characteristics, which point to a distinctive disease that appears in combination with a hearing disorder (e.g. white strand of hair)
- APGAR-values of 0-4 in the first minute and/or 0-6 after 5 minutes

** References:*
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Participating institutions

25 maternity clinics took part in Saxony-Anhalt in 2016. All these clinics offer a newborn hearing screening already for several years by TEOAE or AABR. All 25 maternity clinics participated 2014 in the newborn hearing screening.
A screening-ID is assigned to each child - if there is no denial of this examination and /or data transmission by the parents/guardians - and the hearing screening results will be forwarded to the tracking centre of newborn hearing screening Saxony-Anhaltt.

The screening ID, which has to be assigned to each infant as condition to participate in the hearing screening trakking is also used by several midwifes. In this way also infants who are exclusively under care of a midwife (e.g. home births) can participate in the newborn hearing screening.

The following table on page 81 gives an overview about the single maternity clinics and number of births with a screening ID.

Maternity clinics in Saxony-Anhalt and participation in the Newborn Hearing Screening Tracking (ordered by location)

Maternity Clinic	Tracking period 2016	Live births* with screening ID in this period*
Ameos Klinikum Aschersleben	01-01 to 31-12-2016	589
Gesundheitszentrum Bitterfeld/Wolfen	01-01 to 31-12-2016	445
Helios Klinik Jerichower Land	01-01 to 31-12-2016	400
Städtisches Klinikum Dessau	01-01 to 31-12-2016	868
Altmark-Klinikum Krankenhaus Gardelegen	01-01 to 31-12-2016	382
Ameos Klinikum Halberstadt	01-01 to 31-12-2016	586
Ameos Klinikum Haldensleben	01.01. - 23.02.2016	26
Krankenhaus St. Elisabeth und St. Barbara Halle	01-01 to 31-12-2016	2,157
Universitätsklinikum Halle (Saale)	01-01 to 31-12-2016	1,143
Helios Klinik Köthen	01-01 to 31-12-2016	445
Krankenhaus St. Marienstift Magdeburg	01-01 to 31-12-2016	1,082
Klinikum Magdeburg	01-01 to 31-12-2016	1,483
Universitätsklinikum Magdeburg A.ö.R.	01-01 to 31-12-2016	1,328
Carl-von-Basedow-Klinikum Saalekreis Merseburg	01-01 to 31-12-2016	759
Saale-Unstrut Klinikum Naumburg	01-01 to 31-12-2016	359
Harzklinikum Dorothea Christiane Erxleben, Klinikum Quedlinburg	01-01 to 31-12-2016	529
Altmark-Klinikum Krankenhaus Salzwedel	01-01 to 31-12-2016	462
Helios Klinik Sangerhausen	01-01 to 31-12-2016	762
Ameos Klinikum Schönebeck	01-01 to 31-12-2016	570
Johanniter-Krankenhaus Genthin-Stendal	01-01 to 31-12-2016	842
Asklepios Klinik Weißenfels	01-01 to 31-12-2016	521
Harzklinikum Dorothea Christiane Erxleben, Klinikum Wernigerode	01-01 to 31-12-2016	725
Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg	01-01 to 31-12-2016	710
Georgius-Agricola Klinikum Zeitz	01-01 to 31-12-2016	409
Helios Klinik Zerbst/Anhalt	01-01 to 31-12-2016	213
Total number of live births* with screening-ID in clinics in Saxony-Anhalt		**17,795**

additional live births with screening ID e.g. home births/ births in a birthing centre, and live births outside of Saxony-Anhalt, repectively	01-01 to 31-12-2016	**138**

Tracked newborns in total	**17,933**

* births + multiple births, in case that no own birth register number was assigned, number of stillbirths is deducted

In total, **17,795 births** received a screening ID in their maternity clinic in Saxony-Anhalt in 2014. Therefore, these infants could participate in the hearing screening tracking.

Furthermore, **138 data records of infants** which were delivered at home or born in a birthing centre are included in our analyses. These infants received also a screening ID after birth, e.g. by their corresponding midwife.

Tracking Effort

Tracking of the newborn hearing screening requires an ample organising and personnel effort. It starts with recording the results of the hearing test in the maternity clinic and forwarding them by mail or fax to the Monitoring of Congenital Malformations. The results are entered here in a special tracking database. In total, we received results of **110 senders** in 2016.

The following table shows how many newborns received a screening ID per month and and how many results were forwarded to the Monitoring of Congenital Malformations per month. On average, **1,900 results** were registered per month, however in some cases we received multiple reports for one child (e.g. from the maternity clinic, paediatric clinic, ENT clinic, ENT physician, paediatrist and from the parents).

Newborns with screening ID and number of incoming results

2016	Infants with screening ID	Number of reports
January	1,405	1,820
February	1,438	1,879
March	1,492	1,952
April	1,337	1,774
May	1,355	1,788
June	1,496	1,919
July	1,712	2,164
August	1,584	2,043
September	1,668	2,157
October	1,559	2,013
November	1,413	1,971
December	1,474	1,911
total	**17,933**	**23,391**

To carry out the tracking thoroughly, **2,734 letters and faxes,** resp., were forwarded in 2016 (one up to seven letters per infant). With reference to all infants with screening ID this corresponds to an average of 0.15 letters per infant.

Additionally, the parents and attending physicians of the infants born in 2016 were contacted by telephone. In total **253 calls** were made in connection with the hearing screening tracking (one up to four calls per infant).

Results (as of October 2017)

For the evaluation of the newborn hearing screening in 2016 all reports are taken into account that were sent to the hearing screening tracking centre with results of children that were born in 2016.

14,800 infants out of **17,933 infants** with screening ID obtained a **'pass' result** in the **newborn hearing screening**. In **3,133 cases, the first hearing test had to be followed-up** or no newborn hearing screening took place in the maternity clinic, resp. (these cases are regarded also as follow-up cases). There are numerous reasons why a hearing test did not take place, e.g. ambulant delivery, early discharge from maternity clinic, transfer of the child to another clinic or a defective hearing screening device.

The **follow-up examination** of the 3,133 infants showed in **2,381 cases** a **'pass' result**. The remaining **752 infants** had again a **'fail' result**.
279 of these 752 infants received a **complete paediatric audiological confirmation diagnostics**. According to our knowledge, **219 infants** did **not receive a confirmation diagnostics** and therefore, are considered as **lost to follow-up**.

222 infants did **not participate in the screening** (no reaction of parents to reminder letters or refusal of examination) and in **one case** the **status** is **still pending**, i.e. the examinations were not finished in October 2016 or the tracking process still requires more time, respectively.

In **31 cases,** the **tracking** was stopped from our side **without any result** because we could not get into contact with the parents.

In total, the **follow up-examinations** of **289 infants** who were born in 2016 could be completed **(confirmations diagnostics)**. Among 279 infants with a 'fail' result, 10 infants had a 'pass' result in the first screening. Maybe these 10 infants received a follow-up-examination due to existing risk factors.
Within the follow-up examination, a **hearing disorder** could be **ruled out** in **235 cases**. In **44 cases**, a **hearing disorder was diagnosed** (33 x bilateral and 11 x unilateral) and the corresponding therapy was initiated. For instance, **23 infants** received a **hearing aid** (18 times hearing aids bilateral, 10 times hearing aid unilateral).

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according to §13 to §42, incl. exhibits, of the valid Children Directive of the Federal Joint Committee on the Early Diagnosis of Diseases for Children up to the Completion of their 6th Year of Life

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Kompetenznetz Neugeborenen-Screening

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Introduction

The newborn screening is a medical prevention measure which has the aim of a complete and early detection of endocrine and metabolic diseases and a high quality therapy for all infants with a treatable type of these diseases. The details of the newborn hearing screening (NHS) and the screening on mucoviscidosis (CF) are stipulated in the enclosures 14 to 42 of the Directives on the early diagnosisn of diseases for children up to the completion of their 6th year of life ("Children Directive").

The German Society of Newborn Screening (DGNS) compiles annually a national screening report in cooperation with the German screening laboratories. The screening data is analysed on the basis of several quality criteria for the realization of NHS and CF screening in Germany which are defined by the Directive. The report only refers to congenital metabolic and endocrinologic diseases which are defined as "target" diseases by the Directive. Furthermore, it gives a complete statistical compilation of related screening figures, recall rates and confirmed diagnoses for the current year. Additionally, data about process quality for whole Germany is presented.
The screening samples from the particular Federal States are distributed by the laboratories as it is presented in figure 1. It shows that the screening laboratory Magdeburg completely handles all screening samples from Saxony-Anhalt.

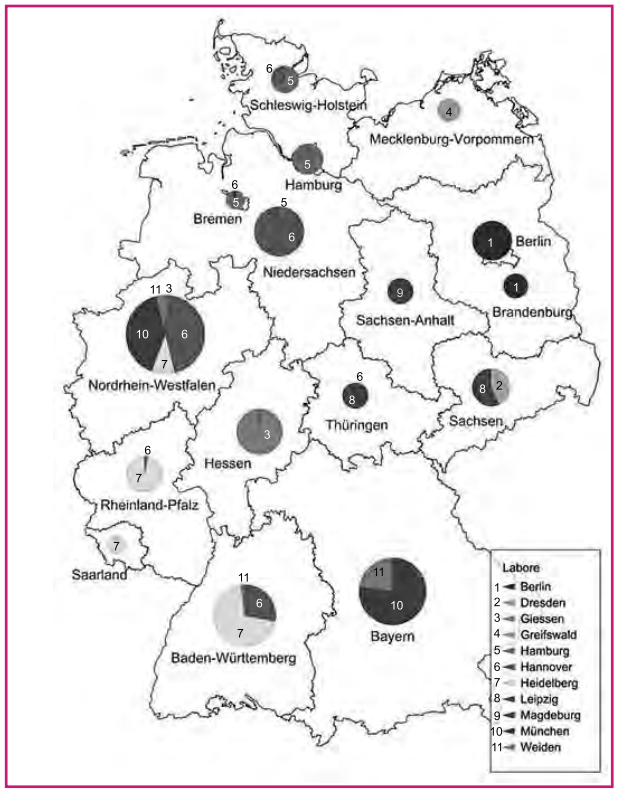

Fig. 1: Sample distribution of the Screening centres in Germany[1]

Table 1 shows the corresponding frequencies in 2016 of the diseases for which screening takes place in Germany[1] for a total number of 714,927 births.

Tab. 1: Frequency of diseases in Germany, detected during screening[1]

Disease	Confirmed cases	Prevalence
Hypothyroidism	235	1 : 3,139
Congenital adrenal hypoplasia (CAH)	36	1 : 20,488
Biotinidase deficiency (incl. partial defects)	12	1 : 61,465
Galactosemia (classical)	7	1 : 105,368
Phenylketonuria (PKU) n=65 / Hyperphenylalaninemia (HPA) n=83 / Cofactor deficiency n=1	149	1 : 4,950
Maple syrup urine disease (MSUD)	0	
Medium-Chain-Acyl-CoA-Dehydrogenase (MCAD) deficiency	72	1 : 10,244
Long-Chain-3-OH-Acyl-CoA-Dehydrogenase (LCHAD) deficiency	6	1 : 122,929
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase (VLCAD) deficiency	7	1 : 105,368
Carnitin-Palmitoyl-CoA-Transferase I (CPTI) deficiency	0	
Carnitin-Palmitoyl-CoA-Transferase II (CPTII) deficiency	0	
Carnitin-Acylcarnitin-Translocase (CACT) deficiency	0	
Glutaric aciduria type I (GA I)	5	1 : 147,515
Isovaleric acidaemia (IVA)	10	1 : 73,758
Total	**539**	**1 : 1,368**

In the following, the data from the screening in Saxony-Anhalt in 2016 are outlined:

Process quality

The process quality describes the process itself and its evaluation on a basis of given indicators by expert committees.
Indicators for the newborn screening are:

- complete coverage of target population
  - coverage method and rate
  - blank card systems
- completeness of control (recall)- and follow up examinations
- registration of examination parameter and cut-offs
- according to disease, laboratory and age/ gestational age stratified recall rates, positive predictive values, prevalences
- specificity and sensitivity of test methods
- process times (only in the preanalytic and laboratory-field: age at blood sampling, time between blood sampling, arriving at laboratory and result transmission
- individual screening results of newborns, which have to be examined further on
- confirmation diagnostics
  - diagnostics type
  - diagnostics period of time
- final diagnosis
- start of therapy

Registration rates

Since every newborn is entitled to take part in the extended newborn screening and cystic fibrosis screening according to §15 and §31 of the Children Directive, a trakking for completeness is necessary. This can be realized for children, which are delivered in obstetric clinics by control of the respective consecutive number in the birth register and by means of a so called blank card system. According to the Childrens Directive the obstetric clinics have to document on a blank test card the total refusal of screening, the refusal of an early blood sample taking within the screening, the transfer to specialised institutions or death of the newborn. This test card is send to the responsible laboratory; however it differs between the single Federal States how successful this method is.

We collected the following registration rates in Saxony-Anhalt in 2016:
According to the provisional information of the Federal Statistical Office, 18,093 children were born alive in Saxony-Anhalt (according to the maternal residence).

Tab. 2: First examinations according to maternal residence

	Number
First screening in Magdeburg	17,865
Non-resident in Saxony-Anhalt	840
Screening of children living in Saxony-Anhalt	**17,024**

The discrepancy between the number of live births in Saxony-Anhalt and the number of screened children amounts to 1,069.

The basis of the data provided by the Statistical Office are the total number of births (sorted according to maternal residence) from the maternity clinics and which are reported to the register office. However, the number of mothers with residence in Saxony-Anhalt but who delivered their infant in another Federal State can not be recorded in our screening statistics if the screening of the infant also took place in another Federal State.

Tab. 3: Registration by blank cards

Blank cards in total	**367**
Blank card: child deceased/ stillbirtht	66
Blank card: refusal of earlyt	231
Blank card: transfer to another clinic	54
Blank card: screening refused by parents	15
Screening took place	277
Screening did not take place - tracking without result	9

Due to the tracking (telephone calls, letters to the parents), only for 2.5% of the received blank cards a result could not be achieved. For all other live births the newborn screening and the CF screening could be conducted successfully in our screening laboratory or at a nearby screening laboratory.

Furthermore, the tracking of missing screening tests successfully takes place due to the in table 4 listed reasons.

Tab. 4: Completeness of controll (recall) and follow-up examinations

Reason of second screening:	'Fail' in first screening	First screening < 36 hrs.	First screening < 32 WOG
Requested	55	375	181
Received at own laboratory	55	347	171
Deceased before control examination	-	4	9
Received at other laboratory	-	9	1

WOG = Weeks of Gestation

Examination Numbers, Recall Rates and Assured Cases

Table 5 shows recall rates of the single parameters and assured cases.

In total, 195 control examinations had to be done in 2016.

Tab. 5: Recall rates 2016 and diagnosed patients with a metabolic disease based on 17,864 screening tests, prevalence 1992-2016

'Target' disease including all variations of the disease	Number of recalls* 2016	assured cases 2016	Prevalence in Saxony-Anhalt 1992-2016
Hypothyroidism (CH)	54	4	1 : 3,969
Phenylketonuria (PKU/HPA)	4	3	1 : 5,379
Galactosemia	3	0	1 : 136,265
Biotinidase deficiency	5	1	1 : 143,274
Congenital adrenal hypoplasia (CAH)	57	0	1 : 17,258#
Medium-Chain-Acyl-CoA-dehydrogenase (MCAD) deficiency	2	2	1 : 12,459##
Long-Chain-3-OH-Acyl-CoA-dehydrogenase (LCHAD) deficiency	0	0	1 : 95,516
(Very-)Long-Chain-Acyl-CoA-dehydrogenase (VLCAD) deficiency	2	0	1 : 286,548
Maple syrup urine disease (MSUD)	0	0	
Carnitin-Palmitoyl-CoA-Transferase I and II (CPTI/CPTII) deficiency	0	0	
Carnitin-Acylcarnitin-Translocase (CACT) deficiency	0	0	
Glutaric aciduria type I (GA I)	0	0	1 : 286,548
Isovaleric acidaemia (IVA)	1	0	
Cystic fibrosis (CF)	9	0	
Others	67	0	

* Recall: Request of a second blood sample for abnormal findings in the first screening test. The presented numbers include early blood sampling at full-term infants (< 36 hrs.) and premature infants (< 32th WOG)

\# Screening for congenital adrenal hypoplasia (CAH) since 1997 in Saxony-Anhalt

\## Extended screening (TMS) since May 2001 in Saxony-Anhalt

Process Times

Time of Taking Blood Samples

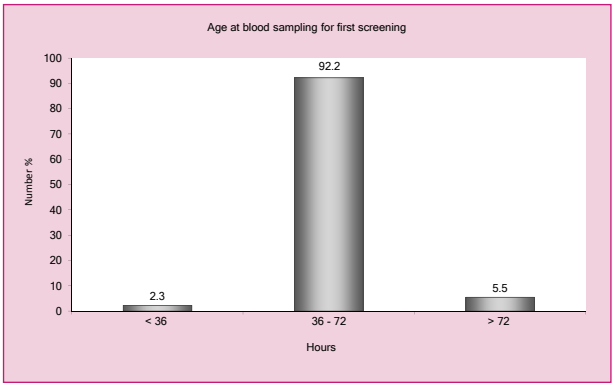

Fig. 2: Age at time of blood sampling for first screening

The optimal time for taking blood samples for the newborn screening (36 -72 hours of life, §20 Children Directive) took place within the required period of time in 92.2% of all cases (2015: 92.4%). For a total number of 5.5%, the sampling of blood took not place within the required period of time (2015: 5.5%). This trend remaines unchanged in comparison to previous years.

Note: Data of newborn infants was only registered when all required information was given (date of birth and time as well as date of blood taking and time).

Transit Times

As per §21 of the Children Directive, the sender date of the blood samples should be equal to the date of blood sampling. By this way it is ensured that the transit by mail does not exceed 72 hours. Figure 3 shows that 15.4% (2015: 16.9%) of all submissions only reached the laboratory after 3 days. On average, the samples from the 24 clinics reached the laboraty within the required time frame, although there are to some extent large differences in transit times (Table 6).

Similar to previous years, there were delays in the transit by mail. Some blood samples only reached the laboratory after 10 days of transit. Since every delayed blood sampling or delayed transit by mail could mean a (life) risk for the affected child, the laboratory tries to improve transit times by providing training (yearly sender conference). The following information must be observed: Blood samples should be sent on the day of the sampling, if possible by Deutsche Post to the screening PO Box, not to the

Tracking Centre for the hearing screening.

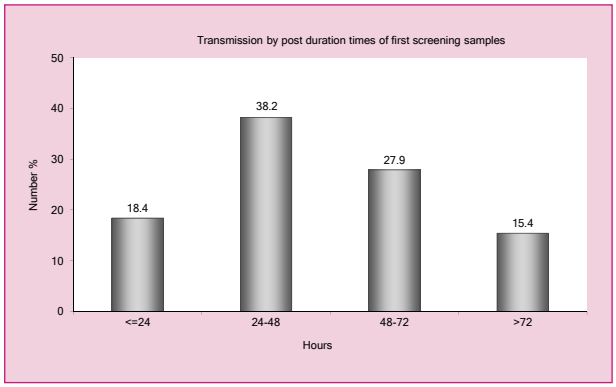

Fig. 3: Post-sending time frames of the blood sample cards (first screening), time from the sampling until the receipt at the laboratory

Tab. 6: Post-sending times of the blood sample cards per sending clinic (Mittelwert aller Stationen einer Klinik)

Maternity hospital/ pediatric ward	Average transit times (h)
Magdeburg St. Marienstift*	13.7
Magdeburg Klinikum*	26.1
Magdeburg Universitätsklinikum*	**28.2**
Gardelegen	37.8
Halle St. Elisabeth und St. Barbara	40.4
Quedlinburg	40.8
Schönebeck	42.2
Stendal	45.1
Naumburg	45.4
Dessau-Roßlau	46.5
Aschersleben	48.5
Burg	49.6
Zeitz	49.6
Salzwedel	49.8
Halle Universitätsklinikum	50.2
Köthen	50.9
Merseburg	51.8
Wernigerode	53.5
Bitterfeld-Wolfen	53.5
Sangerhausen	55.2
Lutherstadt Wittenberg	58.6
Weißenfels	66.2
Halberstadt	68.2
Zerbst	72.9

* Clinic with a sample courier

Transmission of Results

Fig. 4 shows the duration of time that is needed to process the diagnostics of all first screening tests in the laboratory. The completion of results after more than 36 hours is caused by internal repetitions. The 5.2% (2015 3.7%) of all results, which were only completed after 48 hours, reflect for the most part disturbences in the laboratory procedure (device maintenances, -repairs etc.).

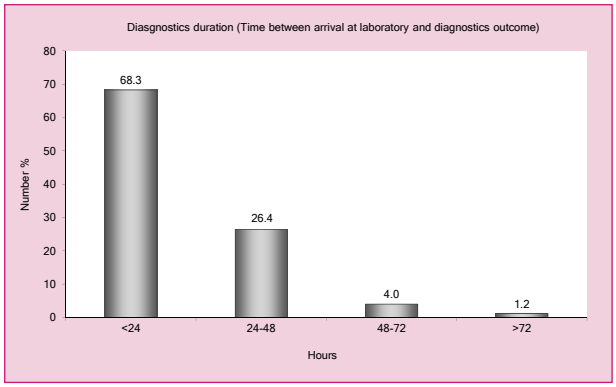

Fig. 4: Duration of diagnostics (date of result - arrival date)

The following figure shows the time from oral transmission of 195 pathological results up to the arrival of a control sample. Generally, pathological results are immediately transmitted orally and faxed as partial result after they were confirmed internally by the laboratory. All these activities are documented.

The cases with a response time of more than 5 days all concerned premature infants. In these cases, the blood sampling of the control sample was postponed to a gestational age of 32 weeks (timely second blood sampling).These children spent the whole time in the intensive care of a premature children ward.

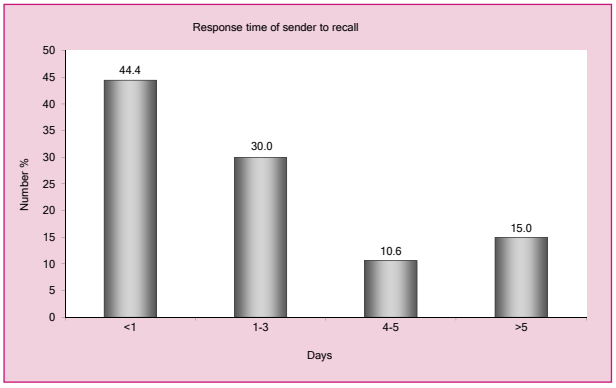

Fig. 5: Response time of sender to recall

Confirmation Diagnostics and Therapy of Patients with Positive Screening

14 suspected cases (on the basis of their screening result) were confirmed through confirmation diagnostics, of which 9 patients needed to start a therapy:

Tab. 7: Diagnosis, confirmation diagnostics and therapy start

Diagnosis	Confirmation diagnostics	Age at start of therapy
3 x Galactosemia, Duarte variant	Analysis of total galactose, mutation analytics	no need for therapy
1 x Biotinidase deficiency	Biotinidase activity in serum	14 days
4 x Hypothyroidism	Serum-TSH, fT3, fT4, sonography	5-12 days
2 x Phenylketonuria	Serum-Phe, BH4-Test	11/21 days (the parents of one patient initially refused the diagnostics/ therapy)
2 x Hyperphenylalaninämie	Serum-Phe	no need for therapy
2 x MCAD-Mangel	Organic acids in the urine, mutation analytics	6/8 days

Summary

In 2016, there was a change in regulation of the Federal Joint Committee (G-BA). On September 1, 2016, an new version of the Children Directive became effective. The screening for mucoviscidosis was added as a new screening disease to the paragraphs 29 to 42. Hence, new consent forms were created and the layout of the blood sample cards was adapted. Parents have the opportunity to decide on whether they want to have the mucoviscidosis screening conducted independently from the extended newborn screening. This is possible up to the completion of the 4th week of life of the newborn. Both screenings can be conducted from the same blood sampling if enogh blood was drawn.
The Gene Diagnostics Law is also in place for mucoviscidosis screening and is the superordinated law with criminal law section.

The newborn screening and metabolic laboratory belong to the Institute for Clinical Chemistry and Pathobiochemistry since October 2015 (Central laboratory of the University Clinic Magdeburg A.ö.R.). Nevertheless, an intensive cooperation with the medical specialists for pediatrics remains in place and is firmly encouraged.

The process quality of the newborn screening in Saxony-Anhalt is, similarly to the previous years, excellent and above the nationwide average of all screening laboratories (National Screening Report of the German Association for Newborn Screening).

As always, we were able to follow up on all patients with a positive result in the first screening and confirm the diagnosis or rule it out, respectively.
The confirmation of a positive screening result through the treating institution could be obtained in all cases. We thank all inpatient/ outpatient clinics which provided us with the needed information.

For 2016, an incidence of 1/1,762 can be calculated for all target diseases of the newborn screening in Saxony-Anhalt.

The Metabolism Centre Magdeburg is available on the Internet at:

www.stwz.ovgu.de

Senders and parents, as well as interested parties can access and download information/ forms for the newborn screening and for special metabolism diagnostics on this website.

The national screening report of the DGNS[1] is available on the website of the association (http://screening-dgns.de) 2 years after the end of the respecting time period.

[1] Source: Deutsche Gesellschaft für Neugeborenenscreening e.V. (DGNS): Nationaler Screeningreport Deutschland 2015 http://www.screening-dgns.de/Pdf/Screeningreports/DGNS-Screeningreport-d_2015.pdf