Annual Report 2012

GESCHLECHTSDIFFERENZIERUNGSSTÖRUNGEN

Intersex

Zwitter

Intersexualität

Androgen-
resistenz

Gonaden-
dysgenesie

weiblicher
Hermaphroditismus

männlicher
Hermaphroditismus

Disorders of Sex Differentiation
(DSD)

indifferentes Geschlecht

Störungen der Geschlechtsentwicklung

Malformation Monitoring Centre Saxony-Anhalt

Medical Faculty

Otto-von-Guericke-University Magdeburg

SACHSEN-ANHALT
Ministerium für
Arbeit und Soziales

Annual Report 2012
On Congenital Malformations
And Chromosomal Anomalies
Saxony-Anhalt, Germany

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Introduction

Dear reader,

Parents are expecting a child - this is something special and always a singular event. In other words we are facing a miracle every time when a new baby is born. However, there is always the concern that the baby may not be healthy. When the baby finally is born, a new stage of life starts for the parents. This stage of life brings a lot of joy and excitement but at the same time there is always the fear to do something wrong. In this situation parents need support. The medical staff like doctors and midwifes but also experienced parents and grandparents can give advice here, before and after the birth of the child.

In 2012 the number of 16,888 children (2011: 16,835) were born in the Federal State of Saxony-Anhalt; in Germany 673,544 children were born. The Monitoring of Congenital Malformations Saxony-Anhalt collects and analyses all congenital malformations and anomalies of live births, stillbirths and terminations of pregnancy after prenatal diagnosis of fetal anomaly from our Federal State. The population-based malformation surveillance of Saxony-Anhalt is singular in Germany. Furthermore, the steady and high quality registration and elaboration of the Annual Report is only possible due to the continuous and extensive work of the team of Dr. med. Anke Rißmann. The present Annual Report 2012 focuses on disorders of sexual differentiation which can be detected already perinatal.

Why did the Monitoring of congenital malformations choose the topic "Disorders of sexual differentiation"? It might be the case that the birth of a child with a genital malformation represents a challenge not only for the parents and later for the affected child itself but in some cases also for the doctor in charge during the delivery. Usually, we are confronted with a normal delivery, however an exceptional case is present when a congenital adrenal hyperplasia (CAH) with salt loosing syndrome is detected during delivery and needs to be treated adequately. To avoid any harm on the child, additionally a test for CAH is part of the newborn screening in Germany since 2002. In this way the necessary diagnostics and decision finding about gender assignment can be made calmly and help can be provided in an endocrinological centre by an interdisciplinary team.

Currently, concerned people debate on the above mentioned topic, which shows how controversial this issue is. The medical or social assignment of a person to one or none of both genders is not like in case of a neutral diagnosis (like for example an elbow fracture). Here, the self-perception and identity of a person are concerned. A conflict is created when a person with intersexual phenotype receives a gender which he or she cannot or does not want to accept. Another conflict can arise when the person is classified as intersexual because of the physical characteristics, but he or she feels belonging to one gender and does not ascribe importance to the physical variation.

The topic was raised at the same time by a statement of the German Ethics Council in February 2012. It resumes that it is absolutely necessary to train doctors and midwifes in this medical field in order that affected cases can be identified as early as possible and a qualified interdisciplinary competence centre can interfere.

Most of the children born in Saxony-Anhalt are healthy. However, statistically one of thousand newborns is endangered by a genetically caused metabolic disease or organ disorders. If the disease is not detected on time mental or physical damage can result. In the worst case a child dies consequentially.
Children are our greatest asset and our future. Every step to improve diagnostics and medical care for every single child increases the life expectancy of these children. We altogether support this aim.

Yours sincerely

Norbert Bischoff
Federal Minister of Labour and Social Affairs
Saxony-Anhalt

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Abbreviations

AABR	automated auditory brainstem response (Hirnstammaudiometrie)
ASD	atrial septal defect
bil	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
EUROCAT	European Surveillance of Congenital Anomalies
ENT	ears, nose, throat
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
P	prevalence
PDA	persistent ductus arteriosus
PFO	persistent foramen ovale
SA	spontaneous abortion
SB	stillbirths
s.o.	suspicion of
TEOAE	transistory evoked otoacoustic emissions
TOP	termination of pregnancy
VSD	ventricular septal defect
WOG	weeks of gestation

Figures

1 Saxony-Anhalt - Registration Area

2 Birth Rate 2012

	Live births*	Stillbirths*	Spontaneous Abortions (> 16 WOG)	Terminations of Pregnancy	Total
Altmarkkreis Salzwedel	621	3	1	1	**626**
Anhalt-Bitterfeld	1,141	5	1	6	**1,153**
Börde	1,383	5	3	3	**1,394**
Burgenlandkreis	1,306	5	1	1	**1,313**
Dessau-Roßlau	587	3	-	1	**591**
Halle	2,106	11	-	11	**2,128**
Harz	1,587	9	3	5	**1,604**
Jerichower Land	648	1	2	2	**653**
Magdeburg	2,137	4	5	5	**2,151**
Mansfeld-Südharz	957	2	2	4	**965**
Saalekreis	1,357	3	-	5	**1,365**
Salzlandkreis	1,370	5	1	5	**1,381**
Stendal	824	3	-	2	**829**
Wittenberg	864	4	1	1	**870**
Major cities: Dessau-Roßlau, Halle, Magdeburg	4,830	18	5	17	**4,870**
Districts, in total	12,058	45	15	35	**12,153**
Saxony-Anhalt	**16,888**	**63**	**20**	**52**	**17,023**

* Federal Statistical Office Saxony-Anhalt 2013

3 Participating Institutions of the Region 2012

3.1 Maternity units / paediatric units (ordered by location)

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

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

- AMEOS Klinikum Aschersleben, Pränatale Ultraschalldiagnostik: CA Dr. Hasslbauer
- Dipl. Heilpädagogin Grimm, Glindenberg/Magdeburg
- AMEOS Klinikum St. Salvator Halberstadt, Pränatale Ultraschalldiagnostik: CA Dr. Schmidt
- Dres. Perlitz, Fachärzte 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 / OA Dr. Seliger
- Universitätsklinikum Halle (Saale), Pränatale Ultraschalldiagnostik:
  CA Prof. Dr. Tchirikov / OA Dr. Thäle / OÄ Dr. Scheler
- Dr. Altus, Fachärztin für Humangenetik, Magdeburg
- Dr. Karstedt, Facharzt für Kinder- und Jugendmedizin, Kinderkardiologie, Magdeburg
- Dr. Karsten, Facharzt für Frauenheilkunde und Geburtshilfe, Magdeburg
- Universitätsklinkum Magdeburg A.ö.R., Institut für Humangenetik
- Universitätsklinkum Magdeburg A.ö.R., Universitätsfrauenklinik, Pränatale Ultraschalldiagnostik: OÄ Dr. Gerloff
- Universitätsklinkum Magdeburg A.ö.R., Universitätskinderklinik, Screeninglabor
- Trackingstelle Neugeborenenhörscreening Sachsen-Anhalt, Magdeburg
- Dipl.-Med. Fiedler und Giesecke, Fachärzte für Orthopädie, Merseburg
- Johanniter-Krankenhaus Genthin-Stendal GmbH, Pränatale Ultraschalldiagnostik: CA Dr. Müller / CA Dr. Neumann
- Harz-Klinikum Wernigerode-Blankenburg GmbH, Pränatale Ultraschalldiagnostik: OÄ Dr. Schulze

3.3 Pathological-anatomical instituts (ordered by location)

- Institut für Pathologie Dr. Taege und Dr. Bilkenroth, Eisleben
- Universitätsklinikum Halle (Saale), Institut für Rechtsmedizin
- Klinikum Magdeburg gGmbH, Institut für Pathologie
- Universitätsklinikum Magdeburg A.ö.R., Institut für Pathologie

4 Malformation Registration in Saxony-Anhalt

4.1 General Information

The present Annual Report 2012 outlines in the established form epidemiological data regarding congenial malformations in Saxony-Anhalt. In this year we want to place first our thanks for the thorough and dedicated work of our senders. Without their collaboration the data collection of the monitoring of congenital malformations Saxony-Anhalt would not be possible!

The special topic in chapter 16 deals with the disorders of sexual differentiation and genital defects in the current year. As basis serves a statement of the German Ethics Council from February 2012 which outlined in detail the ethical, social and legal difficulties of the intersexual phenotype. The Council as independent institution illustrated how opinions about this topic changed during the last years. Medical treatment improved significantly and early performed gender assigning surgeries are more and more obsolete. The disorders of sexual differentiation (DSD) summarise as term a lot of specific symptoms which comply all with the European criterion of rare diseases (Rare disease: not more than 5 out of 10,000 persons are affected). In this connection the congenital adrenal hyperplasia (adrenogenital syndrome, AGS) is the most frequently registered rare disease on www.orpha.net with 1 per 10,000 affected persons.

Since 1992 the Monitoring of congenital malformations Saxony-Anhalt is a member of EUROCAT (European Surveillance of Congenital Anomalies). EUROCAT is the European Association of 38 malformation registration centres from 21 countries which monitor together 31% of the European population in regard to congenital malformations (more than 1.7 million births). All these registration centres consider themselves also as epidemiological monitoring stations. The so gained knowledge serves to improve the primary prevention of congenital malformations. Until now the fields of drug safety, eating, lifestyle and environmental pollution inclusive the work area are examined in this connection (www.eurocat-network.eu).

Furthermore, the Monitoring of Congenital Malformations Saxony-Anhalt represents Germany with its collected data at the ICBDSR since 2001 (International Clearinghouse for Birth Defects Surveillance and Research), which is the International Association of 42 malformation registers from 38 countries of the world (www.icbdsr.com).

Saxony-Anhalt is the only Federal State in Germany with a region wide population-based malformation registration. This steady and high quality work 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 Mrs. Dipl.-Wirtsch. V. Rätzel, 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 diagnosis of fetal anomaly (all weeks of gest.)
- 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. 2012 is considered the year of birth although some terminations of pregnancy after prenatal diagnostics took place at the end of 2011. 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.

All data transmitted to the Monitoring of Congenital Malformations is medically controlled upon receipt and the diagnoses are encoded according to ICD-10.
Details about the intake of medication during pregnancy are registered by using the internationally recommended ATC codes.

The percentage indications and prevalences are rounded values.
The present report outlines the total number of infants with major malformations as well as the geographical distribution of appearance in the big cities and districts in chapter 7 and 8. 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 2012.

As we did in the previous years we analysed the reported pathological prenatal screening results separately in Chapter 10.

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 2012 in comparison to the last 12 years (2000-2011). Here, a total number of 211,097 births forms basis for the basic prevalence calculation 2000 to 2011.

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 percental change of an indicator malformation prevalence is illustrated as well during the publishing time of the Annual Report.

This report outlines in chapter 13 data regarding genetically caused diseases, chromosomal disorders, sequences, associations, complexes and embryopathies. Chapter 14 contains an analysis of malformation caused terminations of pregnancy.

Chapter 16 is dedicated once more to a “special” topic and deals with disorders of sexual differentiations in this year.

As in the previous years the Newborn hearing screening forms part of the Report of the Monitoring of Congenital Malformations 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 database of the Monitoring of Congenital Malformations Saxony-Anhalt includes data about newborns and foetuses with congenital malformations as well as births without any malformation, which form a control group. In the year 2012 we received information about 2059 births (12.1% of all births). Fortunately, the decreasing number of reportings stopped and we noticed an increasing trend again (2007: 13.9%, 2011: 11.9%).

We received a total number of 2,288 reportings in 2012 from the maternity and paediatric units resp. from institutions of pre- and postnatal diagnostics which are mentioned in chapter 5.2. In 9.4% of all cases we received information from two or more institutions. By receiving these double-reportings it was often possible to classify complex malformations exactly or to reconfirm a diagnosis. A correct and preferably detailed diagnosis description forms a basis for a steady high data quality and consequently convincing statistics.

Since the Annual Report 2011 was published the number of births and corresponding data records for 2011 increased from 1,901 to 2,022. The later registered births are now included into the analyses of the current report and are taken into account in any future analyses.

The completeness of many data records which is important for evaluating risks and characteristics remained also in 2012 on a high level. However, some single information was not reported in exceptional cases. The gestational age at births was indicated in 98.6% and the births weight in 97.4% of all cases in 2012. Thanks to the excellent work of all senders a lot of indications like gender of the child (99.2%) and maternal age (99.3%) were registered. We received information about the month of births, pregnancy outcome and administrative district in 100% of the cases.

We kindly ask again all reporting institutions in Saxony-Anhalt to describe every diagnosed malformation as detailed as possible when completing the documentation sheet. Unfortunately, in 21 of all registered cases of terminations of pregnancy, spontaneous abortions and stillbirths only a chromosomal disorder was reported, however in one third of the cases a prenatal ultrasound screening result is present which shows additional major malformations (like omphalocele, cardiac and cerebral malformations). As we cannot assume that these diagnoses were confirmed it is not possible to include them into our statistics.

The significance of the Annual Report mainly depends on complete and correct data records. We receive two thirds of malformation registrations and indications of control cases by means of the "green documentation sheets", which we make available to the reporting institutions free of charge. Documentation sheets may be ordered at any time by phone +49 391-6714174 or e-mail to monz@med.ovgu.de. The documentation sheet is also available for download on our homepage www.angeborene-fehlbildungen.com (subitem Fehlbildungsmonitoring - Infos für Einsender).

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 history and an exact description of the malformation and corresponding symptoms are important here. This documentation sheet is also available for download on our homepage.

Mostly, we receive the reports by mail on our documentation form sheets. In many institutions fax reports have become the preferred method of transmission. Our fax number is: +49 391-6714176. Since the beginning of last year it is also possible to enter data online and send it via secure internet connection. Please contact us if you are interested in reporting your data online.

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 of Saxony-Anhalt according to the information of the Statistical Office Halle

male	8,630	live births and stillbirths
female	8,321	live births and stillbirths
total	16,951	live births and stillbirths

Sex ratio m : f = 1.04

The Statistical Office Halle registered in 2012 a total number of 16,951 births which can be split up into 16,888 live births and 63 stillbirths. Compared to the previous year (16,906 life births and stillbirths) the total number of births in Saxony-Anhalt increased about 0.3%.

The sex ratio of all live births and stillbirths shows with 1.04 again a light androtropism (2011: 1.06, 2010: 1.04). Similar to the previous years infants with major malformations show an androtropism with a value of 1.30 (2011: 1.31; 2010: 1.24).

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

male	332	births
female	255	births
unclear	1	birth
unknown	9	births
total	597	births

Sex ratio m : f = 1.30

Sex ratio of all births with only minor malformations and anomalies

male	137	births
female	119	births
total	256	births

Sex ratio m : f = 1.15

11 Organ System Involvement in Infants and Foetuses with Major Malformations

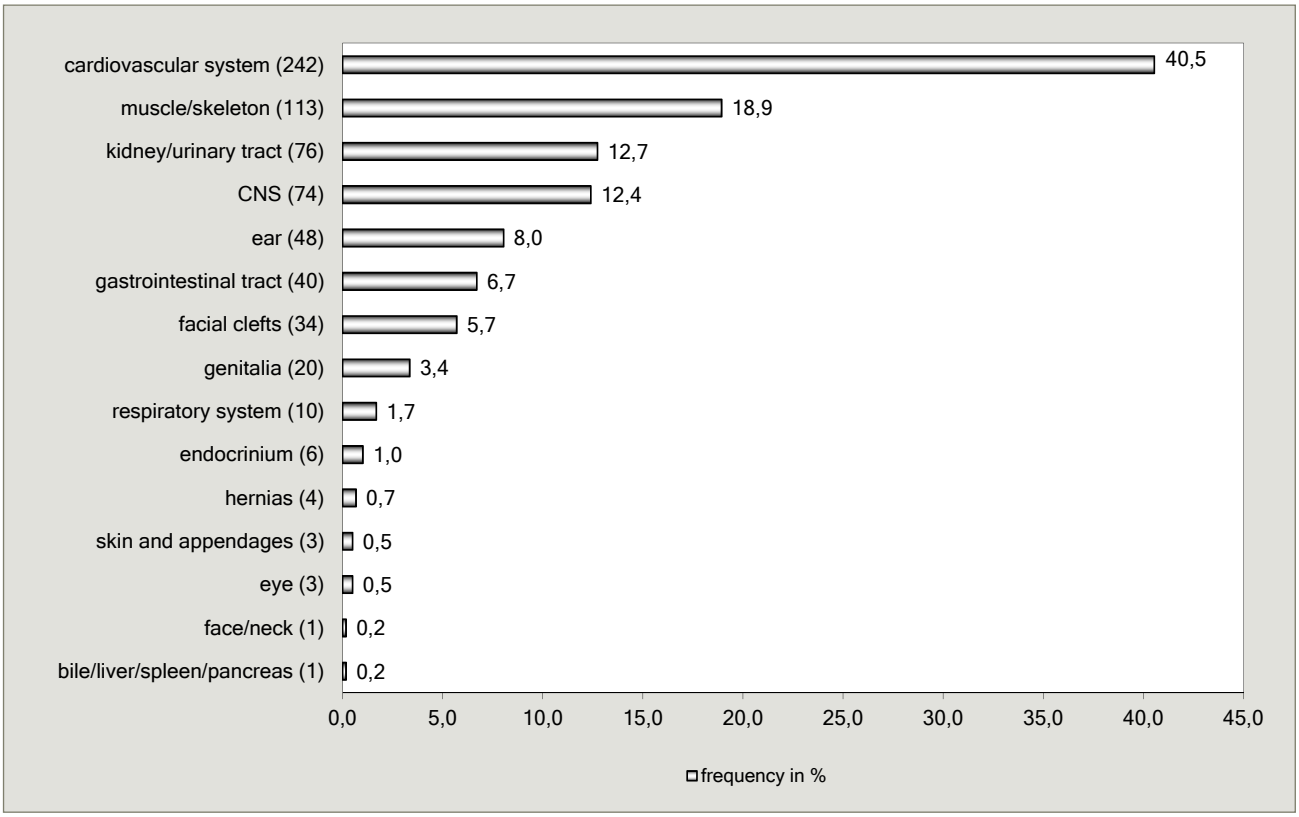


Fig. 5: Organ system involvement in major malformations (absolute figures and percentages of reported malformations)

Chapter 11 shows the findings of 597 infants/foetuses with major malformations born in 2012 ordered by organ system involvement. Infants/foetuses with malformations of different organ systems are mentioned multiply within the above shown diagram. Births with multiple malformations which cannot be assigned to one organ system like chromosomal disorders, infections and metabolic diseases are not included in the figure.

Malformations of the cardiovascular system form also in 2012 with 40.5% (242 births) the biggest part among births with major malformations. Compared to 2011 less births with this malformations were registered on a percentage basis (2011: 43.5%). During the last years the percentage remained always on a similar level (2000-2011: 38.4% of infants/foetuses with major malformations).
The second place of the ranking is occupied by malformations of the musculoskeletal system with a percentage of 18.9%. On the third place we can find in 2012 malformations of the kidney and urinary tract (12.7%). Position four is occupied by the CNS malformations with a value of 12.4%. In comparison to the year 2011 (8.2%) the number of registered cases increased. However, when considering the last years there have always been fluctuations of the registered values (2000-2011: 10.3% of infants/foetuses with major malformations).
Malformations concerning the organ system ear were registered more frequently in 2012 compared to other malformations (2010: 5.8%; 2011: 5.1%; 2012: 8.0%).

In 2011 the percentage of malformations of the gastrointestinal tract increased to 7.5%. In 2012 the value decreased to 6.7% and is again similar to the years before (2009: 6.7%; 2010: 6.1%).
Malformations of the genitalia were also registered very frequently in 2011 with a value of 5.1%. However, in 2012 we registered a percentage of 3.4% which corresponds to the values we registered in the years before 2011 (2000-2011: 3.6%). Also the cases of facial clefts fluctuate during the last years. In 2012 the percentage of these malformations (5.7%) lies significantly above the value of 2011 (3.8%).

The most frequent single diagnoses 2012 (only major malformations)

	ICD 10	Diagnosis	Infants/Foetuses 2012		Infants/Foetuses 2000-2011 Prevalence /10.000
			Number	Prevalence /10.000	
1.	Q21.1	Atrial septal defect (inclusive persistent foramen ovale/PFO)	134	78.7	70.5
2.	Q21.0	Ventricular septal defect	81	47.6	44.2
3.	H90.	Conductive and sensorineural hearing loss	48	28.2	7.4 (15.5*)
4.	Q02.	Microcephaly	35	20.6	11.5
5.	Q62.3	other obstructive defects of renal pelvis and ureter (dilated uropathy grade II-IV/ureterocele)	31	18.2	19.4
6.	Q66.0	Talipes equinovarus (clubfoot)	26	15.3	17.6
7.	Q69.	Polydactyly (pre- und postaxial)	25	14.7	11.8
8.	Q90.	Down's Syndrome (Trisomy 21)	24	14.1	16.7
9.	Q37.	Cleft hard and soft palate with unilateral/bilateral cleft lip	23	13.5	11.0
10.	Q25.0	Persistant Ductus Botalli (hemodynamically effective)	22	12.9	7.8
11.	Q65.3 Q65.4 Q65.5	Congenital subluxation of hip (unilateral/bilateral/laterality unspecified)	18	10.6	17.1
12.	Q60.0	Renal agenesia (unilateral)	16	9.4	6.9
13.	Q62.2	Congenital megaureter	15	8.8	7.0
	Q63.0	Accessory kidney	15	8.8	6.1
14.	Q23.3	Congenital mitral insufficiency	12	7.0	3.6
15.	Q04.0	Congenital malformations of corpus callosum	11	6.5	4.7
16.	Q22.1	Pulmonary valve stenosis	10	5.9	6.0
	Q05.	Spina bifida	10	5.9	5.9
17.	Q25.1	Coarctation of aorta	9	5.3	4.7
	Q71.3	Congenital absence of unspecified hand and finger	9	5.3	2.8
18.	Q54.1 Q54.2 Q54.3 Q54.8 Q54.9	Hypospadias (without coronal/glandular)	8	4.7	7.3
	Q25.6	Stenosis of pulmonary artery (peripheral pulmonary valve stenosis)	8	4.7	2.0
	Q03.0 Q03.1 Q03.8 Q03.9	Congenital hydrocephalus without neural tube defect	8	4.7	6,1

* 2007-2011 (since 2007 data synchronization with newborn hearing screening tracking centre)

The overleaf shown table presents the most frequently registered single diagnosis, ordered by frequency of appearance in 2012. For comparison the right column shows the average prevalences of the diagnoses during the whole reporting period. Basis for these prevalences is a total number of 211,097 infants/foetuses registered in the years 2000-2011.

As expected the atrial septum defect (78.7 per 10,000 births) and the ventricle septum defect (47.6 per 10,000 births) are in 2012 at the top of the table, whereby the atrial septal defect appeared less frequently than in the years 2000-2011 (70.5 per 10,000 births, CI 67.0 to 74.2). From a statistical point of view every 93th infant/foetus suffered from at least one of these two cardiac malformations in 2012 (107.5 per 10,000 births).

On the third place we registered in 2012 the hearing loss/deafness. Initially the registration of this malformation by the newborn hearing screening centre started in 2007. Since this year they provide regionwide verified data regarding this malformation. Therefore the time period before 2007 cannot be used to evaluate the actual prevalence. However, the prevalence of 2012 of 28.2 per 10,000 births exceeds highly the value of 2007-2011 (15.5 per 10,000 births, CI 13.1 to 18.3).

We observed more frequently the diagnosis microcephaly (2012: 20.6 per 10,000 births, 2000-2011: 11.5 per 10,000 births, CI 10.1 to 13.0) which is to find on rank four on our table. The frequency of the prevalences of microcephaly varies very much: between 4.4 per 10,000 births in 2001 (probably not all cases were registered here) and 19.9 per 10,000 births in 2006.

Rank five and six are occupied by dilated uropathy (18.2 per 10,000 births) and clubfoot (15.3 per 10,000 births). These prevalences are within the registered average values.

In 2012 polydactyly (2012: 14.7 per 10,0000 births) was registered more frequently as expected in reference to the years 2000-2011 (11.8 per 10,000 births, CI 10.4 to 13.3). Since 2007 its prevalence always remained on a similar level. In approximately 45% a polydactyly with exact diagnosis information appears preaxial (chapter 12.28). However, the preaxial polydactylies do not show a linear trend of appearance within the reporting period (chapter 12.37). On the other hand, an increase of postaxial polydactylies can be observed as well.

The prevalence of the most frequently appearing chromosomal aberration Down`s syndrome (14.1 per 10,000 births) falls below the values of the previous years (chapter 12.34) and occupies rank eight in 2012.

The single diagnosis cleft palate with cleft lip (13.5 per 10,000 births) forms the major part of the indicator malformations cleft lip and cleft palate with cleft lip (2000-2011: 11.0 per 10,000 births, CI: 9.7 to 12.5). In the European comparison Saxony-Anhalt has one of the highest prevalences of this malformation. After a period of ups and downs we registered again a very high value in 2012.

Also PDA was registered very frequently in 2012 with a value of 12.9 per 10,000 births. The lowest average prevalence of 2000-2011 (7.8 per 10,000 births, CI 6.7 to 9.0) might originate from an underreporting of cardiac malformations in the years before 2012. Since 2010 we receive reports from the cardiac centre Leipzig about affected infants/foetuses from Saxony-Anhalt.

The subluxation of hip occupies in 2012 rank 11 with a prevalence of 10.6 per 10,000 births. It was registered more frequently than in 2011, but clearly less frequently than during the period 2000-2010 (17.1 per 10,000 births, CI 15.5 to 19.0). An ultrasonography of the babies hip forms further a part of the early examination U3. Not all maternity clinics perform this examination already within the early examination U2 before mother and child go home. This might be the reason for an apparent decrease of registered cases.

We registered in 2012 for the unilateral renal agenesia (9.4 per 10,000 births) a higher prevalence than the calculated average value (6.9 per 10,000 births CI 5.9 to 8.1). The malformation is to find on rank 12. Only in 2004 we registered more cases with 10.3 per 10,000 births. We registered the two following renal malformations on rank 13 (each 8.8 per 10,000 births), megaureter and the accessory kidney, more frequently than the average prevalence indicates (7.0 per 10,000 births, CI 5.9 to 8.2) resp. (6.1 per 10,000 births, CI 5.2 to 7.2).

Similar to PDA the mitral valve insufficiency was reported more frequently in 2012 than in the previous years (2012: 7.0 per 10,000 births, 2000-2011: 3.6 per 10,000 births, CI 2.9 to 4.6). It can be found now on rank 14. The same increase was registered for stenosis of pulmonary artery (2012: 4.7 per 10,000 births, 2000-2011: 2.0 per 10,000 births, CI 1.4 to 2.7). During the last years this malformation occupied often rank 39, this year it climbed up to rank 18.

Hypoplasia or corpus callosum agenesia also appeared more often in 2012 than in the years before. (2012: 6.5 per 10,000 births, 2000-2011: 4.7 per 10,000 births, CI 3.8 to 5.7).

The prevalences which we calculated 2012 for the malformations pulmonary valve stenosis, spina bifida, coarctation of aorta and congenital absence of unspecified hand and finger are within the average prevalences of the years 2000-2011. These malformations occupy rank 16 and 17.

The single diagnoses hypospadias and hydrocephalus were registered less frequently in 2012 (each 4.7 per 10,000 births). In contrast to the identically named indicator malformation hypospadias, the major malformation does not include light clandular and coronar forms which are the most frequently appearing ones. The frequency of the light forms was as high as expected in 2012 (11.2 per 10,000 births), but significantly less frequent was the registration of severe forms (2000-2011: 7.3 per 10,000 births, CI 6.2 to 8.5) The single diagnosis hydrocephalus corresponds totally to the indicator malformation (chapter 12.6). For 2000-2011 we calculated a prevalence of 6.1 per 10,000 births (CI 5.1 to 7.2).

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

12.0 Definitions

1. Neural tube defects (NTO): 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. The three most common types of neural tube defects: Spina bifida, anencephaly, encephalocele.

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. Including infants with craniorachischisis, 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 meges 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), two standard deviations below the age and sex appropriate distribution curves. 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 sydrome: a cardiac defect with a hypoplastic left ventricle, associated with aortic and/or mitral valve atresia, with or without other cardiac defects.

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/stenosis: 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 multiple areas of the jejunum or ileum. Exclusive duodenal atresia.

19. Anorectal atresia/stenosia: 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 neighboring organs. Exclusive mild stenosis which does not need correction, and ectopic anus.

20. Undescended testis: bilateral undescended testis 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) and hypoplasia of abdominal muscles (skin covered 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 testis, clubfoot and limb deficiencies.

34. Down's 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. Edward's 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 birth with malformations born in a certain population with reference to the total number of birth in this population. Since 2000 the prevalence calculations are only referring to children whose mothers have their residence in Saxony-Anhalt. Between 1997 and 1999 the registration area of the Monitoring of Congenital Malformations did not cover the entire area of Saxony-Anhalt. (1997: 14, 1998: 15, 1999: 16 out of 21 administrative districts). The calculation of the basis prevalences (2000-2011) is based on a total number of 211,097 births.

The analysis of the indicator malformations is made with regard to the diagnoses. It is possible that one child has more than one indicator malformation. Therefore the number 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 basic prevalence
Major cities 1 x Dessau-Roßlau 4 x Halle	5	10.3	↔
Districts: 1 x Anhalt-Bitterfeld 1 x Burgenlandkreis 1 x Jerichower Land 1 x Saalekreis 3 x Salzlandkreis 1 x Stendal	8	6.6	↓
Saxony-Anhalt	**13**	**7.6**	↘

Neural tube defects (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	9.55	7.11 - 12.55
Districts	9.20	7.85 - 10.76
Region	9.28	8.10 - 10.63
EUROCAT	9.73	9.54 - 9.93
		4.48 S Portugal* 18.46 Isle de la Reunion (France)**

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

In 2012 we registered 13 neural tube defects in Saxony-Anhalt which are twice as much cases as in 2011.
Within the neural tube defects no anencephaly was registered in 2012. Therefore the number is composed of 10 infants/foetuses with spina bifida and three with encephalocele. The resulting prevalence increased to 7.6 per 10,000 births. This annual prevalence is again lower than the basis prevalence of the registration period starting in 2000. This trend can be clearly observed in the districts.

Compared with EUROCAT the annual prevalence and the basis prevalence of Saxony-Anhalt are lower than the European values.

additional information:

Pregnancy outcome	3 x live birth 10 x termination of pregnancy
Sex	9 x male 4 x female
Number of isolated malformations/MCA	10 x MCA 3 x isolated

The sex ratio of births with NTDs shows that mainly male infants were affected which is a similar trend to the previous years.
Most cases of Neural tube defects appeared within a multiple congenital anomalie, only in three cases the defect appeared isolated.

23.1% of affected cases were live births. This is a low value in comparison to the previous years. One child was born after 34 weeks of gestation. In this case multiple malformations were detected already during prenatal ultrasound screening and the parents decided to continue the pregnancy. Two live births presented an encephalocele.

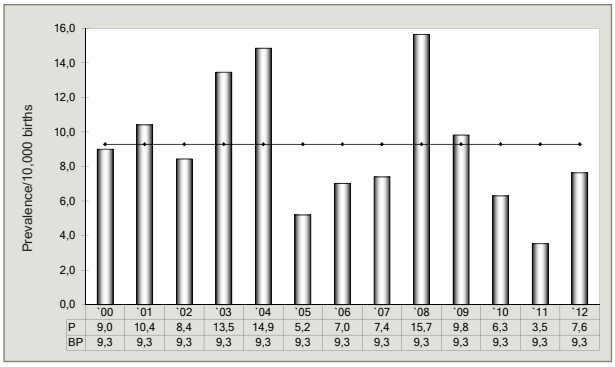


Fig. 6: Development of prevalence/10,000 births with neural tube defects in the registration area since 2000

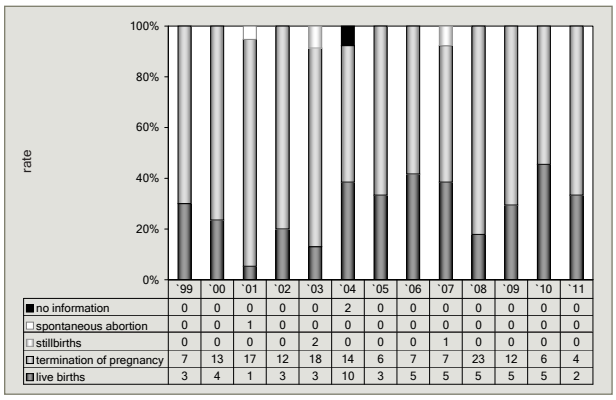


Fig. 7: Pregnancy outcomes of neural tube defects in the registration area since 2000

In 2012 one neural tube defect per 1,309 births was registered in Saxony-Anhalt.

12.2 Anencephalie (Q00.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↓
Districts	0	0.0	↓
Saxony-Anhalt	**0**	**0.0**	↓

Anencephalie (2000-2011)			
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births	
Cities	1.12	0.41 - 2.44	
Districts	2.60	1.87 - 3.53	
Region	2.23	1.64 - 2.96	
EUROCAT	3.66	3.54 - 3.78	
		1.48	Wielkopolska (Poland)*
		7.18	Isle de la Reunion (France)**

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

No infant/foetus with anencephaly was registered in 2012. Since the beginning of malformation registration in 1980 only in 1991 no case of anencephaly was registered. During the last four years the congenital malformation anencephaly presents a prevalence below the basis prevalence.

A long-term observation shows singular annual accumulations of the malformation e.g. in 2003 and 2008. Therefore we are interested how the future trend of anencephaly continues.

In the European comparison annual prevalence and basis prevalence of Saxony-Anhalt are lower than the European reference values.

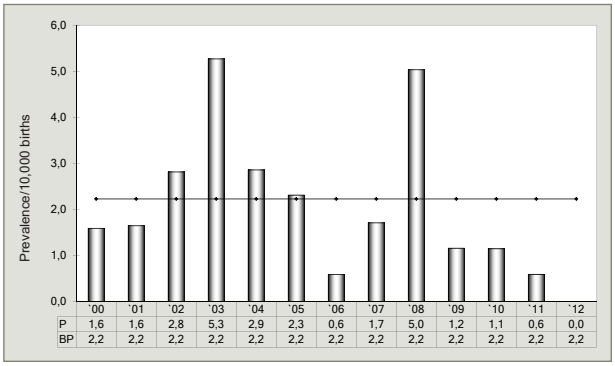


Fig. 8: Development of prevalence/10,000 births with anencephaly in the registration area since 2000

In 2012 no anencephaly was registered in Saxony-Anhalt.

12.3 Spina bifida (Q05.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities 4 x Halle	4	8.2	↔
Districts: 1 x Burgenlandkreis 1 x Jerichower Land 1 x Saalekreis 2 x Salzlandkreis 1 x Stendal	6	4.9	↔
Saxony-Anhalt	**10**	**5.9**	↔

Spina bifida (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	6.37	4.41 - 8.89
Districts	5.71	4.59 - 7.01
Region	5.87	4.95 - 6.96
EUROCAT	4.96	4.82 - 5.11
		1.89 Zagreb (Croatia)* 10.03 Mainz (Germany)**

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

Ten births with spina bifida were registered in Saxony-Anhalt in 2012.
The prevalence of 5.9 per 10,000 births is within the middle range of the basis prevalence. In this way the prevalence we calculated in the previous year of 1.2 per 10,000 births is equalised again. We registered four infants/foetuses with spina bifida in the city Halle and six in the districts.

Compared to European data records our prevalence of 2012 is higher than the European basis prevalence of 5.0 per 10,000 births. However, other registration centres like for example Mainz have clearly higher values than our prevalences calculated in Saxony-Anhalt.

additional information:

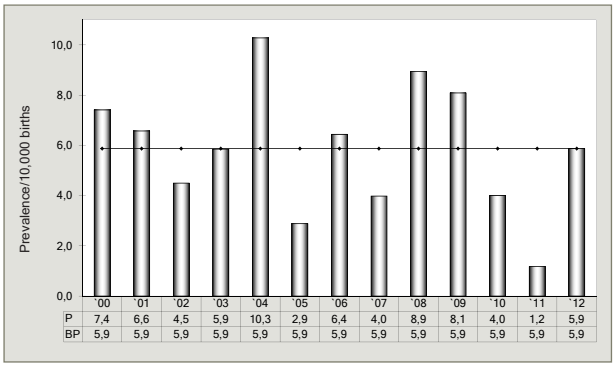
Pregnancy outcome	1 x live birth 9 x termination of pregnancy
Sex	8 x male 2 x female
Number of isolated malformations/MCA	9 x MCA 1 x isolated

The sex ratio shows that mainly male infants/foetuses were affected.

Compared to the previous years the number of live births is very low in 2012. Eight affected pregnancies were terminated between 17 and 22 weeks of gestation. One foetus suffered from Arnold-Chairi malformation and lumbosacral spina bifida with hydrocephalus: This pregnancy was terminated after 28 weeks of gestation. In total, four foetuses had an Arnold-Chairi malformation, in one case a potter sequence and in one case a Catch 22 was diagnosed. One child was delivered after 34 weeks of gestation. Some of the malformations were already known prenatally.

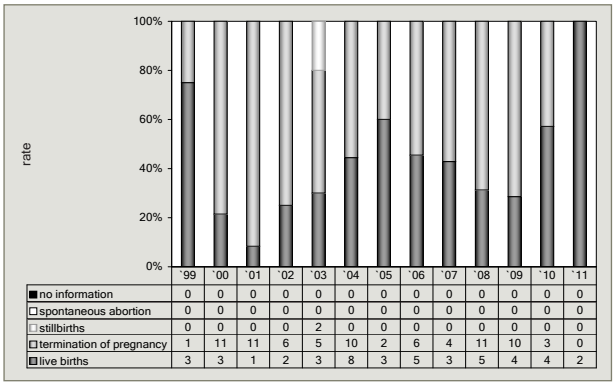
Malformation combinations (MCA) or superordinated syndromes detected:

- Anal atresia with fistula, persistence of sinus urogenitalis (at male gender), malformed os sacrum, cloacal extrophy, lipoma above tailbone, micropenis, hypospadias
- Potter sequence (bilateral renal agenesia)
- CATCH 22 with: microcephaly, truncus ateriosus communis
- Arnold-Chairi-syndrome with: scoliosis of the lower thoracic spine and lumbar column by fuson of the III. and IV. rib
- Arnold-Chairi-syndrome with: Tethered cord syndrome
- Arnold-Chairi-syndrome with: hydrocephalus
- Arnold-Chairi-syndrome
- Hydrocephalus, hygroma colli cysticum
- joint contracture



	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	7,4	6,6	4,5	5,9	10,3	2,9	6,4	4,0	8,9	8,1	4,0	1,2	5,9
BP	5,9	5,9	5,9	5,9	5,9	5,9	5,9	5,9	5,9	5,9	5,9	5,9	5,9

Fig. 9: Development of prevalence/10,000 births with spina bifida in the registration area since 2000



	`99	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11
no information	0	0	0	0	0	0	0	0	0	0	0	0	0
spontaneous abortion	0	0	0	0	0	0	0	0	0	0	0	0	0
stillbirths	0	0	0	0	2	0	0	0	0	0	0	0	0
termination of pregnancy	1	11	11	6	5	10	2	6	4	11	10	3	0
live births	3	3	1	2	3	8	3	5	3	5	4	4	2

Fig. 10: Pregnancy outcomes of spina bifida in the registration area since 2000

In 2012 one spina bifida per 1,702 births was registered in Saxony-Anhalt.

12.4 Encephalocele (Q01.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Dessau-Roßlau	1	2.1	↔
Districts: 1 x Anhalt-Bitterfeld 1 x Salzlandkreis	2	1.6	↗
Saxony-Anhalt	**3**	**1.8**	↗

Encephalocele (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	2.06	1.03 - 3.68
Districts	0.89	0.49 - 1.49
Region	1.18	0.77 - 1.75
EUROCAT	1.12	1.05 - 1.19
		0.24 SE Ireland* 3.17 Mainz (Germany)**

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

Three infants/foetuses with encephalocele were registered in 2012. Therefore the prevalence calculated 2012 in Saxony-Anhalt is 1.8 per 10,000 births.
The observation period 2000-2011 shows similar values and the prevalence of 2012 corresponds to the trend of the previous years. In the districts we observed a slightly increasing trend.

In comparison to EUROCAT our result lies above the confidence interval.

additional information:

Pregnancy outcome	2 x live birth 1 x termination of pregnancy
Sex	1 x male 2 x female
Number of isolated malformations/MCA	1 x MCA 2 x isolated

In two cases the infants were live births, one infant presented an occipital encephalocele. One infant had an atrophic parietal encephalocele; the size of the calvarial defect was 3.5 mm. We have no information about prenatal diagnostics in this case.
One pregnancy was terminated after 21 weeks of gestation. In this case the female foetus suffered from additional anomalies like the amniotic band syndrome.

Malformation combinations (MCA) or superordinated syndromes detected:

- amniotic band syndrome at left hand and right leg, missing phalanges at left hand, amelia of left leg, clubfoot right, blt. cleft lip with cleft palate, missing cranial bone, missing right eyelid, lateral descending left eyelid

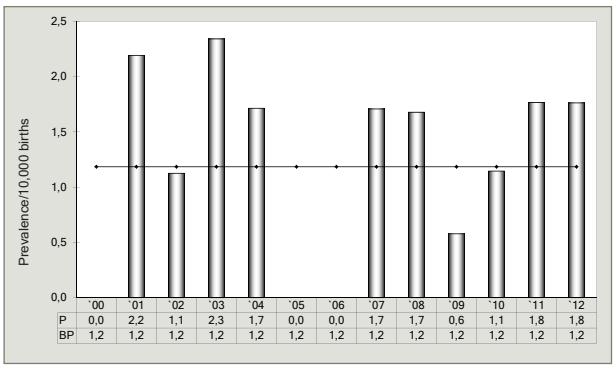


Fig 11: Development of prevalence/10,000 births with encephalocele in the registration area since 2000

In 2012 one encephalocele per 5,674 births was registered in Saxony-Anhalt.

12.5 Microcephaly (Q02.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Dessau-Roßlau 4 x Halle 9 x Magdeburg	14	28.7	↑
Districts: 4 x Anhalt-Bitterfeld 2 x Burgenlandkreis 4 x Börde 2 x Harz 1 x Mansfeld-Südharz 1 x Saalekreis 7 x Salzlandkreis	21	17.3	↑
Saxony-Anhalt	**35**	**20.6**	↑

Microcephaly (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	14.23	11.21 - 17.80
Districts	10.53	9.08 -12.20
Region	11.46	10.14 - 12.96
EUROCAT	2.40	2.30 - 2.50
		0.46 Norway* 11.46 Saxony-Anhalt (Germany)**

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

35 births with microcephaly were registered in 2012 as they had a head circumference below the 3rd percentile in regard to the gestational age or a corresponding head circumference at birth. This number clearly exceeds the number of cases we registered in 2011. We assumed that the malformation microcephaly was underreported in the previous year. In 2012 we have no indication for such an assumption.

The prevalence of 20.3 per 10,000 births is therefore higher than the basis prevalence of the years 2000-2011.
In comparison with other European registration centres the prevalences of Saxony-Anhalt are very high. It is therefore important to observe how the trend of the next years continues.

additional information:

Pregnancy outcome	33 x live birth 1 x spontaneous abortion 1 x termination of pregnancy
Sex	20 x male 15 x female
Number of isolated malformations/MCA	19 x MCA 16 x isolated

In regard to the pregnancy outcome only two pregnancies ended by spontaneous abortion and termination of pregnancy.

The births with microcephaly already presented intrauterine problems in many cases. That means there were risk factors present like maternal medication intake, consume of nicotine and drugs and placental insufficiency. Often the births were preterm infants and children born SGA. In total 19 affected births suffered from additional malformations.

Malformation combinations (MCA) or superordinated syndromes detected:

- Down's syndrome with: canalis atrioventricularis communis, lateral ascending lid axis, transverse palmar crease left, sandal`s gap
- Down's syndrome (Robertsonian translocation) with: canalis atrioventricularis communis
- Holoprosencephaly, median cleft lip with cleft palate, corpus callosum agenesis, cerebellar hypoplasia, hypophysis hypofuction, duplex right and hypoplastic left kidney, ASD II, haemodynamic not relevant PDA at preterm birth
- CATCH 22 with: lumbal spina bifida, truncus arteriosus communis
- cleft lip with left palate right, mandibular retrognathia
- acessory left thumb
- glandular hypospadias,
- phenylalanine embryopathy with: VSD, PFO at preterm birth, hypotelorism, epicanthus inversus, shortened palpebral fissure, sacral dimple
- transposition of great vessels, VSD, PFO at preterm birth
- transposition of great vessels, PFO at preterm birth
- ASD II, VSD
- ASD II, combined sound conduction and perception disorder right (left 60 dB, right 40 dB)
- ASD II, haemodynamic relevant PDA and PFO at preterm birth, umbilical hernia
- ASD II, PDA and PFO at fullterm birth
- VSD, PFO at preterm birth
- VSD
- atresia of duodenum, colon anomaly (rectal prolapse)
- Sacrococcygeal teratoma

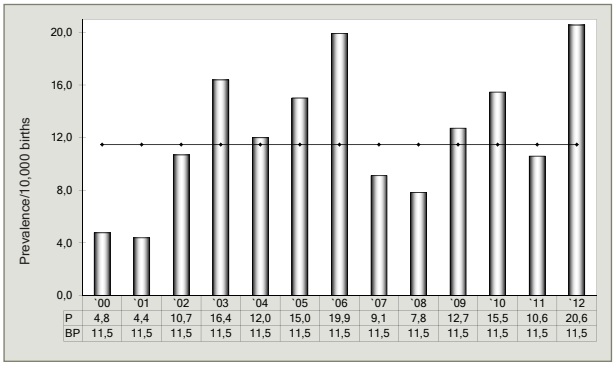


Fig. 12: Development of prevalence/10,000 births with hydrocephaly in the registration area since 2000

In 2012 one microcephaly per 486 births was registered in Saxony-Anhalt.

12.6 Congenital Hydrocephaly (Q03.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↓
Districts: 2 x Anhalt-Bitterfeld 1 x Börde 2 x Harz 1 x Mansfeld-Südharz 1 x Saalekreis 1 x Salzlandkreis	8	6.6	↔
Saxony-Anhalt	**8**	**4.7**	↓

Congenital Hydrocephalus (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	7.11	5.04 - 9.76
Districts	5.71	4.59 - 7.01
Region	6.06	5.12 - 7.17
EUROCAT	5.65	5.50 - 5.80
		1.72 S Portugal* 13.09 Paris (France)**

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

Eight births with congenital hydrocephalus were registered in 2012 whereby no case was reported from the major cities. Please note that the hydrocephalus which occurred in combination with spina bifida resp. encephalocele is not regarded here. Also the hydrocephalus that appeared postnatal is not included in this analysis.

The prevalence lies at 4.7 per 10,000 births and ranges under the basis prevalence of 2000-2011. Compared to the European data the frequency registered in Saxony-Anhalt is within the lower range.

additional information:

Pregnancy outcome	4 x live birth 2 x spontaneous abortion 2 x termination of pregnancy
Sex	2 x male 6 x female
Number of isolated malformations/MCA	4 x MCA 4 x isolated

The sex ratio shows that mainly female infants/foetuses were affected.

Two pregnancies were terminated intentionally and spontaneously at presence of a foetus with congenital hydrocephaly. Another spontaneous abortion occurred as one foetus suffered from congenital cytomegalic infection. The congenital malformation appeared in four cases isolated. MCA were seen in four cases.

Malformation combinations (MCA) or superordinated syndromes detected:

- Trisomy 9 with: diaphragmatic hernia left, hermaphroditism (ovotestis), shortened left lower leg, missing distal phalanx of the II. finger of both hands, corpus callosum agenesis, misjunction of pulmonary veins, membranous syndactyly of toes II to V at the right foot
- cytomegaly, missing sternum, horseshoe kidney, hydrops fetalis
- cerebellar agenesis
- haemodynamic relevant PDA at full term infant

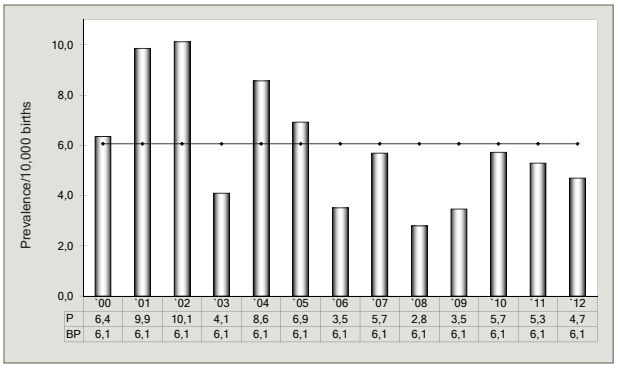


Fig. 13: Development of prevalence/10,000 births with congenital hydrocephalus in the registration area since 2000

In 2012 one congenital hydrocephalus per 2,128 births was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↓
Districts: 1 x Anhalt-Bitterfeld 1 x Mansfeld-Südharz 1 x Salzlandkreis	3	2.5	↑
Saxony-Anhalt	**3**	**1.8**	↔

Arhinencephaly/Holoprosencephaly (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	2.43	1.30 - 4.16
Districts	1.27	0.77 - 1.96
Region	1.56	1.08 - 2.20
EUROCAT	1.29	1.22 - 1.36
		0.35 Wielkopolska (Poland)*
		2.87 Isle de la Reunion (France)**

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

In 2012 one live birth with holoprosencephaly and further congenital malformations was registered. Furthermore, a termination of pregnancy was registered at one birth with arhinencaphaly and Potter sequence and at another birth with isolated holoprosencephaly. Both diagnoses are summarized within the description of this indicator malformation. We received the reporting only from the districts. The prevalence of the current year is higher than the average value.

This corresponds to a prevalence of 1.8 per 10,000 births in Saxony-Anhalt and lies within the range of the basis prevalence 2000-2011.

Compared to EUROCAT the Saxony-Anhalt prevalence lies above the confidence interval. However, other European centres have similar high values.

additional information:

Pregnancy outcome	1 x live birth 2 x termination of pregnancy
Sex	1 x male 2 x female
Number of isolated malformations/MCA	2 x MCA 1 x isolated

In all cases the diagnosis was already known prenatally. One live birth was delivered after 33 weeks of gestation, the diagnosis was also confirmed prenatally. The parents decided to continue the pregnancy. Additionally, the births suffered from cardiac malformations and one facial cleft. After confirmation of the prenatal diagnosis two pregnancies were terminated after 19 and 21 weeks of gestation.

Malformation combinations (MCA) or superordinated syndromes detected:

- blt. cleft lip with cleft palate and polycystic kidney, megaureter left, corpus callosum agenesis, uncompletely lobed right lung, agenesis of nose, hypotelorism
- microcephaly, median cleft lip with cleft palate, corpus callosum agenesis, cerebellar hypoplasia, hypofuction of hypophysis, duplex kidney right, hypoplastic left kidney, ASD II, haemodynamic not relevant PDA at preterm birth

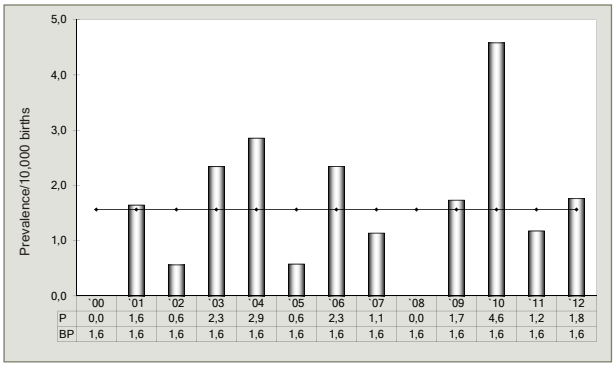


Fig. 14: Development of prevalence/10,000 births with arhinencephalie/holoprosencephalie in the registration area since 2000

In 2012 one case of arhinencephalie/holoprosencephalie per 5,674 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 basic prevalence
Major cities	0	0.0	↓
Districts	0	0.0	↓
Saxony-Anhalt	**0**	**0.0**	↓

Anophthalmos/Microphthalmos (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	1.50	0.65 - 2.95
Districts	0.57	0.26 - 1.08
Region	0.81	0.47 - 1.29
EUROCAT	0.99	0.93 - 1.06
		0.13 Zagreb (Croatia)*
		3.00 Odense (Denmark)**

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

No birth with anophthalmos was registered in 2012. The malformation was neither registered in combination with another malformation nor as superordinated syndrome nor as isolated malformation.

Overall the malformation is to be classified as very rarely appearing malformation. Also in comparison with other European centres the rarity of appearance can be confirmed.

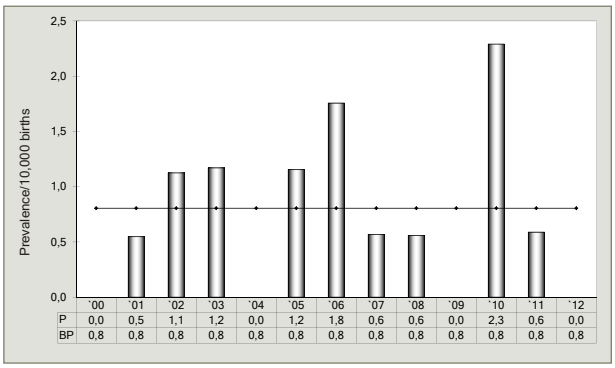


Fig. 15: Development of prevalence/10,000 births with anophthalmos/microphthalmos in the registration area since 2000

In 2012 no child/foetus with anophthalmos/ microphthalmos was registered in Saxony- Anhalt.

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

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

Microtia/Anotia (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%) /10,000 births**
Cities	1.69	0.77 - 3.20
Districts	1.33	0.82 - 2.04
Region	1.42	0.96 - 2.03
EUROCAT	no informationn	no informationn

In 2012 we registered one female birth with unilateral anotia and missing acoustic meatus in the district Altmarkkreis, Salzwedel.

We calculated a basis prevalence of 0.6 per 10,000 births. The current prevalence is similar to the previous year: In 2011 we registered also one affected child from the districts.

additional information:

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

This rarely appearing malformation is not analysed by EUROCAT.

Malformation combinations (MCA) or superordinated syndromes detected:

- combined sound conduction and perception disorder (right 70 dB) and missing right acoustic meatus

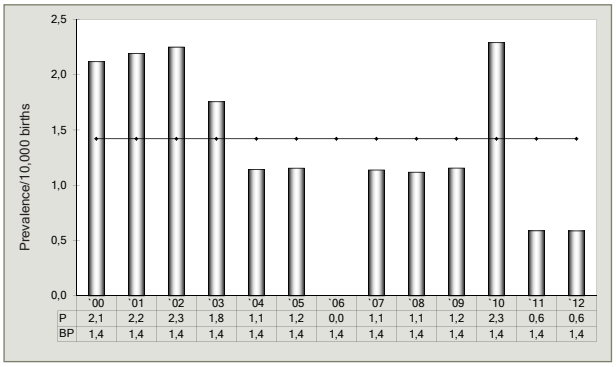


Fig. 16: Development of prevalence/10,000 births with microtia/anotia in the registration area since 2000

In 2012 one child with microtia/anotia per 17,023 was registered in Saxony-Anhalt.

12.10 Tetralogy of Fallot (Q21.3)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 3 x Halle	3	6.2	↑
Districts: 1 x Altmarkkreis Salzwedel 1 x Börde 2 x Mansfeld-Südharz	4	3.3	↔
Saxony-Anhalt	**7**	**4.1**	↗

Tetralogy of Fallot (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	2.81	1.57 - 4.63
Districts	3.11	2.30 - 4.11
Region	3.03	2.33 - 4.87
EUROCAT	3.14	3.03 - 3.26
		2.10 S Portugal* 5.28 Mainz (Germany)**

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

Seven cases of tetralogy of fallot were reported in 2012. We registered the malformation less frequently in 2011 but we now have again a similar value to the value we registered in 2005, 2006 and 2008-2010.
The prevalence of 4.1 per 10,000 births increased slightly in the current year. The increasing trend can be observed especially in the major cities (current prevalence of 6.2 per 10,000 births).

In comparison with European data, the value from Saxony-Anhalt occupies a position above the confidence interval.

additional information:

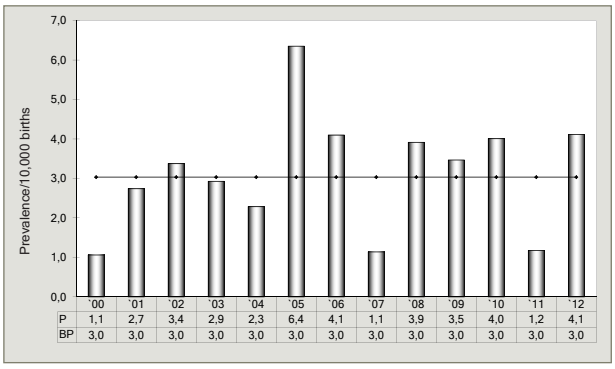
Pregnancy outcome	7 x live birth
Sex	4 x male 3 x female
Number of isolated malformations/MCA	3 x MCA 4 x isolated

The sex ratio is nearly balanced.

In all cases the infants were live births between 35 and 41 weeks of gestation. On our documentation sheets we also ask for information about prenatal diagnostics. Especially the diagnostics of congenital cardiac defects is sometimes difficult. Therefore we are very interested in a complete and detailed description of prenatal results.
We received prenatally information about one white spot and one missing arteria umbilicalis. In other five registered cases of Fallot tetralogy we received no information about prenatal diagnostics. Unfortunately, it was also not indicated if the Fallot tetralogy was already known prenatally.

Malformation combinations (MCA) or superordinated syndromes detected:

- renal agenesis right, accessory thumb
- plagiocephaly, stenosis of left canaliculus lacrimalis
- ASD, haemodynamic relevant PDA at fullterm birth



	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	1,1	2,7	3,4	2,9	2,3	6,4	4,1	1,1	3,9	3,5	4,0	1,2	4,1
BP	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0	3,0

Fig. 17: Development of prevalence/10,000 births with tetralogy of fallot in the registration area since 2000

In 2012 one tetralogy of fallot per 2,432 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 basic prevalence
Major cities: 2 x Halle	2	4.1	↔
Districts: 1 x Anhalt-Bitterfeld 2 x Burgenlandkreis 1 x Stendal 2 x Wittenberg	6	4.9	↔
Saxony-Anhalt	**8**	**4.7**	↔

Transposition of Great Vessels (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	5.43	3.64 - 7.80
Districts	4.00	3.07 - 5.11
Region	4.36	3.51 - 5.34
EUROCAT	3.35	3.23 - 3.47
		1.14 S Portugal* 5.28 Barcelona (Spain)**

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

We registered eight births with TGV in Saxony-Anhalt in 2012. The ratio between districts and major cities is balanced.
The prevalence of 4.7 per 10,000 births ranges above the prevalence we registered in the previous years and shows a value which is similar to the previous year and at the same time within the average of the basis prevalence for the period 2000-2011.

In comparison with European centres the value from Saxony-Anhalt lies above the confidence interval. EUROCAT indicates a basis prevalence of 3.35 per 10,000 births.

additional information:

Pregnancy outcome	7 x live birth 1 x live birth, deceased after 7 days
Sex	6 x male 2 x female
Number of isolated malformations/MCA	8 x MCA

The sex ratio shows also in 2012 a clear androtropism as six male infants and two female infants suffered from TGV.

All infants with TGV were live births between 36 and 41 weeks of gestation. One infant with situs inversus deceased postnatal.

We received a report of prenatal diagnoses TGV in five cases, in four cases the pre- and postnatal diagnosis corresponded to each other. The examiner saw in one case only a misjunction of pulmonary veins; additionally a situs inversus, a mitral atresia, a right aortic arch and a levo-transposition were present. This infant deceased postnatal.

In two cases TGV appeared in combination with other malformations or superordinated syndromes.

Malformation combinations (MCA) or superordinated syndromes detected:

- Microcephaly, VSD, PFO at full term infant
- Microcephaly, PFO at full term infant
- Situs inversus, misjunction of pulmonary veins, mitral atresia, right aortic arch, levo-transposition, splenic asplenia
- VSD, persistence of the left vena cava superior, PFO at preterm infant
- VSD, pulmonary valve stenosis
- VSD, PFO at full term infant,
- VSD, blt. retarded hip
- ASD II

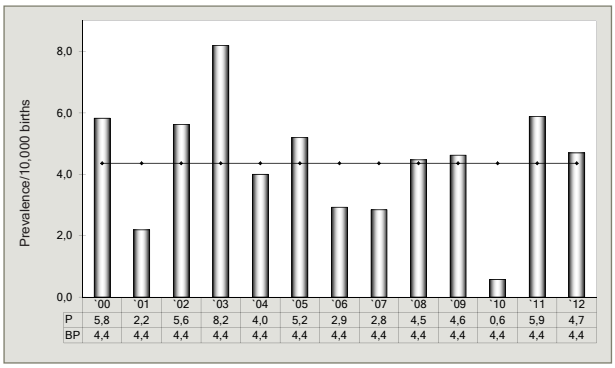


Fig. 18: Development of prevalence/10,000 births with transposition of great vessels in the registration area since 2000

In 2012 one transposition of great vessels per 2,128 births was registered in Saxony-Anhalt.

12.12 Hypoplastic Left Heart Syndrome (Q23.4)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Magdeburg	1	2.1	↔
Districts: 1 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 2 x Burgenlandkreis	4	3.3	↔
Saxony-Anhalt	**5**	**2.9**	↔

Hypoplastic Left Heart Syndrome (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	2.62	1.43 - 4.40
Districts	3.11	2.30 - 4.11
Region	2.98	2.29 - 4.82
EUROCAT	2.64	2.54 - 2.74
		1.19 S Portugal* 4.34 Styria (Austria)**

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

The appearance of hypoplastic left heart syndrome is similar to the previous year: It was registered in five cases.
Therefore we calculated a prevalence of 2.9 per 10,000 births. This value is within the confidence interval of the years 2000-2011.

Compared to EUROCAT centres the prevalence of Saxony-Anhalt lies above their calculated basis prevalence of 2.64 per 10,000 births.

additional information:

Pregnancy outcome	2 x live birth 2 x live birth, deceased after 7 days of life 1 x termination of pregnancy
Sex	5 x male
Number of isolated malformations/MCA	4 x MCA 1 x isolated

All births with hypoplastic left heart syndrome are male in 2012.

The following pregnancy outcomes could be observed:
One pregnancy was terminated after 23 weeks of gestation as the invasive prenatal diagnostics showed a Jacobsen-syndrome, i.e. a microdeletion in the q-arm of chromosom 11.
Four births were delivered in perinatal resp. cardiac centres, two of the four infants deceased postnatal. The diagnosis hypoplastic left heart syndrome was already confirmed prenatally in two cases. AVSD and a truncus ateriosus communis were confirmed during prenatal ultrasound screening at one live birth which deceased after 5 months of life and at the aborted foetus. We have no information about prenatal findings in case of the twin who deceased two weeks after birth.

Malformation combinations (MCA) or superordinated syndromes detected:

- Jacobsen syndrome with: Coarctation of the aorta, hypoplasia of the aorta, persistence of left vena cava superior, membranous syndactyly of both hands (right finger III to V), hypertelorism, lateral descending eyelids, low set ears
- Canalis atrioventricularis communis, persistent Truncus arteriosus
- VSD, DUP I. grade right, PFO at preterm infant
- ASD

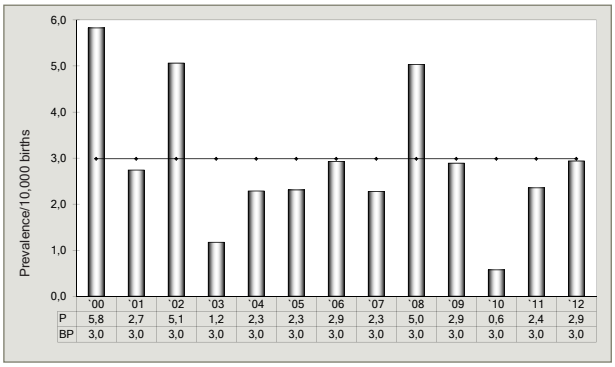


Fig. 19: Development of prevalence/10,000 births with hypoplastic left heart syndrome in the registration area since 2000

In 2012 one child with a hypolastic left heart syndrome per 3,405 births was registered in Saxony-Anhalt.

12.13 Coarctation of Aorta (Q25.1)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Halle 1 x Magdeburg	2	4.1	↔
Districts: 1 x Anhalt-Bitterfeld 2 x Burgenlandkreis 1 x Harz 1 x Mansfeld-Südharz 1 x Salzlandkreis 1 x Stendal	7	5.8	↔
Saxony-Anhalt	**9**	**5.3**	↔

Coarctation of Aorta (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	4.87	3.18 - 7.13
Districts	4.63	3.63 - 5.82
Region	4.69	3.81 - 5.71
EUROCAT	1.29	1.22 - 1.37
		0.14 S Portugal* 3.66 Vaud (Switzerland)**

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

As we registered nine births with coarctation of aorta the prevalence of 5.3 per 10,000 births remains on a similar level like in the years before. The prevalence also lies within the confidence interval in the major cities and in the districts.

A prevalence of 1.29 per 10,000 births is calculated when considering the registered values from all EUROCAT centres. The value we registered in Saxony-Anhalt is therefore to be classified as very high.

additional information:

Pregnancy outcome	8 x live birth 1 x termination of pregnancy
Sex	5 x male 4 x female
Number of isolated malformations/MCA	8 x MCA 1x isolated

The sex ratio is balanced.

When regarding the information about prenatal diagnostics of the nine births with coarctation of aorta, the diagnosis was made correctly in three cases. In one case only the additionally appearing oesophageal atresia was mentioned. In the remaining five cases we have no information about prenatal ultrasound screening results.

Eight infants were live births, one pregnancy was terminated after 23 weeks of gestation as a Jacobsen syndrome was diagnosed prenatal.

Malformation combinations (MCA) or superordinated syndromes detected:

- Jacobsen syndrome with: hypoplastic left heart syndrome, hypoplasia of the aorta, persistence of the left vena cava superior, membranous syndactyly of both hands (right finger III to V), hypertelorism, lateral descending eyelids, low set ears
- oesophageal atresia, tracheoesophageal fistula, vertebral body fusion (thoracic vertebra body 8/9 and lumbar vertebra body 4/5), DUP I. grade right
- ASD II, persistence of the left vena cava superior
- Stenosis of arteria subclavia, VSD, ASD
- Canalis atrioventricularis communis, bicuspid aortic valve, PFO at fullterm infant
- supravalvular pulmonary stenosis, solitary renal cyst left
- 2x PFO at fullterm infant

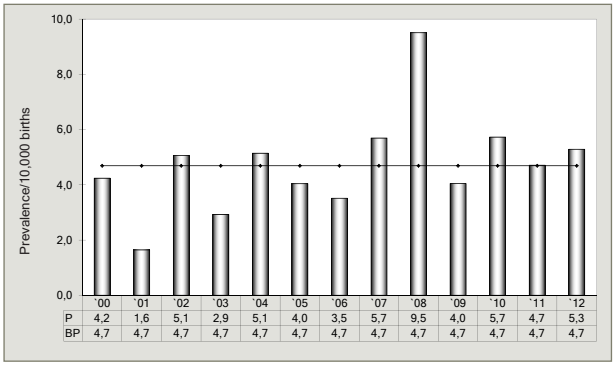


Fig. 20: Development of prevalence/10,000 births with coarctation of aorta in the registration area since 2000

In 2012 one coarctation of aorta per 1,891 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 basic prevalence
Major cities: 2 x Dessau-Roßlau 3 x Halle 6 x Magdeburg	11	22.6	↑
Districts: 3 x Anhalt-Bitterfeld 2 x Börde 2 x Harz 2 x Mansfeld-Südharz 3 x Salzlandkreis 1 x Stendal 1 x Wittenberg	14	11.5	↓
Saxony-Anhalt	**25**	**14.7**	↔

Cleft Lip With or Without Cleft Palate (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	13.67	10.72 - 17.18
Districts	14.08	12.38 - 16.00
Region	13.97	12.50 - 15.62
EUROCAT	8.94	8.75 - 9.13
		4.39 S Portugal* 14.38 Odense (Denmark)**

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

The number of registered births with cleft lip with or without cleft palate is in 2012 similar to the numbers we registered in the previous years. In the current year it is again obvious that clearly more cases were registered in the major cities than in the districts. 25 births were affected in 2012 which corresponds to a prevalence of 14.7 per 10,000 births. This prevalence confirms the high rate of appearance in Saxony-Anhalt again. However, the highest prevalences of up to 26.0 per 10,000 births were registered in the nineties.

Compared to EUROCAT data the high annual prevalence is also obvious, as they calculated a basis prevalence of 8.94 per 10,000 births. Similar high results are to find in Odense (Denmark).

additional information:

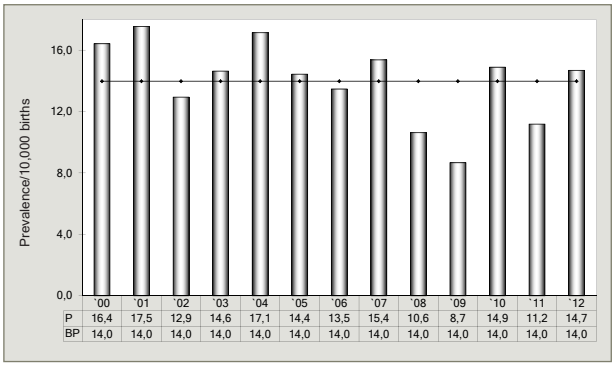
Pregnancy outcome	23 x live birth 2 x termination of pregnancy
Sex	17 x male 8 x female
Number of isolated malformations/MCA	9 x MCA 16 x isolated

As expected the sex ration shows that mainly male infants were affected.

Most infants were live births, however two pregnancies were terminated after 19 and 21 weeks of gestation. In one of these cases a Potter sequence was present, in the other case an amniotic band syndrome of the limbs was detected prenatally. In one case the mother suffered from a hypertonia and gestational diabetes and took the medicine Metoprolol as well as Insulin. In total, 16 births had an isolated cleft lip with or without cleft palate and nine births suffered from additional malformations.

Malformation combinations (MCA) or superordinated syndromes detected:

- parietal encephalocele, amniotic band syndrome at left hand and right leg, missing phalanges at left hand, amelia of left leg, clubfoot right, missing cranial bone, missing right eyelid, lateral descending left eyelid, low set ears
- holoprosencephaly, microcephalus, corpus callosum agenesia, cerebellar hypoplasia, hypophysis hypofuction, duplex right kidney, ASD II, haemodynamic not relevant PDA at preterm birth
- arhinencephaly, blt, polycystic kidney, megaureter left, corpus callosum agenesia, uncompletely lobed right lung, agenesia of nose, hypotelorism
- microcephalus, mandibular retrognathia
- unilateral radial aplasia
- blt not descended testes, DUP I. grade and low set ears
- VSD, ASD, sound conduction and perception disorder (right 50db, left 40dB)
- sound conduction disorder (blt 25-40 dB)
- sound conduction disorder (left 40-50dB)



	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	16,4	17,5	12,9	14,6	17,1	14,4	13,5	15,4	10,6	8,7	14,9	11,2	14,7
BP	14,0	14,0	14,0	14,0	14,0	14,0	14,0	14,0	14,0	14,0	14,0	14,0	14,0

Fig. 21: Development of prevalence/10,000 births with cleft lip with or without cleft palate in the registration area since 2000

In 2012 one child with cleft lip with or without cleft palate per 681 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 basic prevalence
Major cities: 1 x Dessau-Roßlau 2 x Halle 1 x Magdeburg	4	8.2	↔
Districts: 1 x Anhalt-Bitterfeld 1 x Burgenlandkreis 2 x Börde 3 x Harz 3 x Jerichower Land 1 x Saalekreis	11	9.1	↔
Saxony-Anhalt	**15**	**8.8**	↗

Cleft Palate (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	6.74	4.72 - 9.33
Districts	7.74	6.51 - 9.18
Region	7.48	6.43 - 8.70
EUROCAT	5.77	5.62 - 5.92
		2.86 S Portugal* 11.96 Malta**

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

A cleft palate, resp. a Pierre-Robin sequence which belongs per definition to this indicator malformation was registered in 2012 at 15 births.
Therefore the prevalence of 8.8 per 10,000 births slightly increased and lies now above the confidence interval of the registration period 2000-2011. However, the usually high prevalences of this malformation were not registered during the years 2008-2011.

In the European comparison the value we calculated for cleft palate is, similar to the cleft lip with or without cleft palate, above their basis prevalence of 5.8 per 10,000 births.

additional information:

Pregnancy outcome	15 x live birth
Sex	6 x male 9 x female
Number of isolated malformations/MCA	7 x MCA 8 x isolated

The sex ratio shows a clear gynaecotrophism as mainly female infants were concerned.

All 15 infants were live births. In three cases a Pierre Robin sequence was diagnosed. In eight cases cleft palate was the only malformation detected and seven births suffered from additional malformations.

Malformation combinations (MCA) or superordinated syndromes detected:

- dysostosis mandibulofacialis with: gastrochisis, hypoplastic toes right, blt triphalangeal thumbs, mandibular retrognathia, pes adductus left, retarded hip right, haemodynamic not relevant PDA at preterm birth
- atresia of jejunum and Ileum, intestinal malrotation, haemodynamic not relevant PDA at preterm birth
- scaphocephaly, haemodynamic not relevant PDA and PFO at fullterm birth, mandibular retroganthia, broad nose bridge, arachnodactyly (finger), retarded hip left
- ASD II, 2 VSD, mandibular retroganthia
- PFO at fullterm birth, sound conduction disorder (right 40dB, left 50dB), retarded hip left
- sound conduction and perception disorder (80dB right, 90dB left)
- sound conduction disorder blt

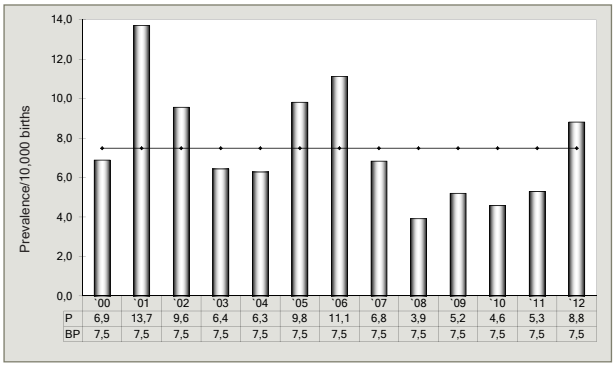


Fig. 22: Development of prevalence/10,000 births with cleft palate in the registration area since 2000

In 2012 one child with cleft palate per 1,135 births was registered in Saxony-Anhalt.

12.16 Choanal Atresia (Q30.0)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↓
Districts	0	0.0	↓
Saxony-Anhalt	**0**	**0.0**	↓

Choanal Atresia (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	0.56	0.12 - 1.64
Districts	0.51	0.22 - 1.00
Region	0.52	0.26 - 0.93
EUROCAT	0.88	0.82 - 0.94
		0.05 S Portugal* 2.11 Mainz (Germany)**

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

The rarely appearing malformation choanal atresia was not reported in 2012.

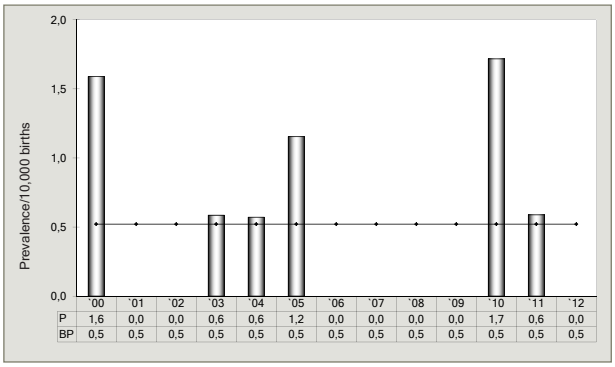


Fig. 23: Development of prevalence/10,000 births with choanal atresia in the registration area since 2000

In 2012 no child with a choanal atresia was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Dessau-Roßlau 1 x Halle 1 x Magdeburg	3	6.2	↗
Districts: 2 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 1 x Wittenberg	4	3.3	↗
Saxony-Anhalt	**7**	**4.1**	↑

Oesophageal Atresia/ Stenosis/ Fistula (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	3.56	2.14 - 5.55
Districts	2.35	1.65 - 3.23
Region	2.65	2.00 - 3.44
EUROCAT	2.34	2.24 - 2.44
		0.71 SE Ireland* 4.22 Mainz (Germany)**

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

Seven births with oesophageal atresia/ stenosis/ fistula were registered in 2012. The prevalence of the districts is lower than the prevalence of the major cities. In comparison to the previous years the prevalence of 4.1 per 10,000 births clearly increased and lies now above the confidence interval.

The European comparison shows that the prevalence we calculated in Saxony-Anhalt for oesophageal atresia/ stenosis/ fistula is higher than the basis prevalence calculated by EUROCAT. A similar high prevalence was reported from Mainz.

additional information:

Pregnancy outcome	6 x live birth 1 x live birth, deceased after 7 days of life
Sex	4 x male 3 x female
Number of isolated malformations/MCA	5 x MCA 2 x isolated

All infants were live births, one infant with an additional trisomy 21 deceased postnatal.

The oesophageal atresia/ stenosis/ fistula appeared in the most cases with additional malformations. Three of the seven oesophageal atresias had fistulas between trachea and upper oesophageal diverticulum. In one case a oesophagotracheal fistula was detected.

Malformation combinations (MCA) or superordinated syndromes detected:

- Down's syndrome with: duodenum atresia, ASD II, haemodynamic not relevant PDA at preterm infant, dilated and asymmetrical cerebral ventricles, macroglosia, lateral ascending eyelids and single transverse palmar crease
- coarctation of aorta, vertebral body fusion (thoracic vertebra body 8/9 and lumbar vertebra body 4/5), DUP I. grade right
- renal agenesis left, VSD, tricuspidal insufficiency, haemodynamic relevant PDA at preterm infant
- persistence of the vena cava superior, misjunction of portal vein
- cleft of trachea/ oesophagus

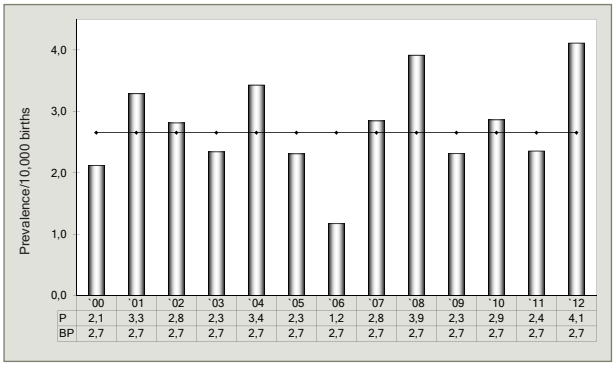


Fig. 24: Development of prevalence/10,000 births with oesophageal atresia/stenosis/fistula in the registration area since 2000

In 2012 one oesophageal atresia/fistula per 2,432 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 basic prevalence
Major cities	0	0.0	↓
Districts: 1 x Anhalt-Bitterfeld 2 x Börde 2 x Salzlandkreis 1 x Wittenberg	6	4.9	↑
Saxony-Anhalt	**6**	**3.5**	↑

Small Intestinal Atresia/Stenosis (2000-2011)			
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births	
Cities	1.50	0.65 - 2.95	
Districts	2.03	1.39 - 2.86	
Region	1.89	1.35 - 2.58	
EUROCAT	0.78	0.72 - 0.84	
		0.20	Wielkopolska (Poland)*
		1.78	Isle de la Reunion (France)**

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

Births with the indicator malformation small intestinal atresia were reported only from the districts in 2012. With six live births and a prevalence of 3.5 per 10,000 births is this value very high in comparison to the observation period 2000-2011. Only in 2004 we registered a similar high prevalence of 3.4 per 10,000 births.

The result from Saxony-Anhalt is clearly higher than the European basis prevalence of 0.8 per 10,000 births.

additional information:

Pregnancy outcome	6 x live birth
Sex	3 x male 3 x female
Number of isolated malformations/MCA	4 x MCA 2 x isolated

The sex ratio is balanced.

The small intestinal atresia occurred in four cases in combination with additional malformations, these were mainly cardiac defects.

Malformation combinations (MCA) or superordinated syndromes detected:

- incomplete median cleft palate, intestinal malrotation, haemodynamic not relevant PDA at preterm infant
- intestinal malrotation, haemodynamic not relevant PDA and PFO at fullterm infant
- intestinal malrotation, Ladd's bands
- haemodynamic not relevant PDA and PFO at preterm infant

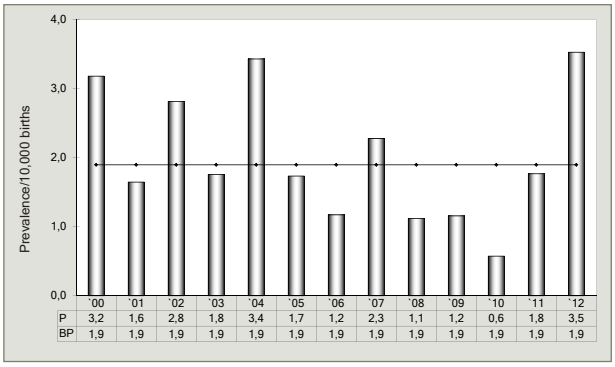


Fig. 25: Development of prevalence/10.000 births with small intestinal atresia/stenosis in the registration area since 2000

In 2012 one small intestinal atresia/stenosis per 2,837 births was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Halle 1 x Magdeburg	2	4.1	↔
Districts: 2 x Harz 1 x Mansfeld-Südharz 2 x Saalekreis	5	4.1	↔
Saxony-Anhalt	**7**	**4.1**	↘

Anorectal Atresia/Stenosis (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	5.62	3.79 - 8.02
Districts	5.07	4.02 - 6.31
Region	5.21	4.34 - 6.24
EUROCAT	3.05	2.94 - 3.16
		1.24 S Portugal* 7.33 Styria (Austria)**

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

The number of births with anorectal atresia/stenosis was very high in the years 2007-2010. In 2012 we have a slighly decreased number of seven births with this malformation. The number of registered cases lies under the confidence interval and corresponds to a prevalence of 4.1 per 10,000 births.

In the European comparison our indicator malformation prevalence for anorectal atresia/stenosis lies above their basis prevalence of 3.1 per 10,000 births.

additional information:

Pregnancy outcome	4 x live birth 3 x termination of pregnancy
Sex	5 x male 2 x female
Number of isolated malformations/MCA	6 x MCA 1 x isolated

The sex ratio shows an androtropism.

After detecting the anorectal atresia/stenosis three pregnancies were terminated. Four infants were live births.

All births had additional malformations resp. chromosomal anomalies. In two cases the anorectal atresia/stenosis appeared in combination with an omphalocele. In one case grave urogenital malformations were additionally present. It was prenatally diagnosed that one foetus suffered from an Edwards syndrome. A termination of pregnancy was the result of this diagnosis.

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome with: agenesia of the right kidney, duplex left kidney, partial hypoplasia of the 1st-3rd rib right, hypoplastic left thumb, rocker bottom foot, mesenterium ileocolicum commune, incompletely lobed right lung, mandibular retrognathia, high philtrum, short, broad nose, low set ears
- lumbosarcal spina bifida, persistence of sinus urogenitalis (at male gender), malformed os sacrum, cloacal extrophy, lipoma above tailbone, micropenis, cleft scrotum
- omphalocele, shortened muscles at right leg, clubfoot right, blt hip luxation, mandibular retrognathia, low set ears, hypertelorism
- omphalocele, bladder extrophy, epispadias, urethralatresia, mandibular retrognathia, low set ears, hypertelorism, epicanthus internus
- caudal regression syndrome: blt hip luxation, os sacrum agenesia, ASD II, VSD, mitral valve insufficiency, aplasia of tailbone and sacrum, DUP I. grade right
- ektopia ani, umbilical hernia, hepatomegaly

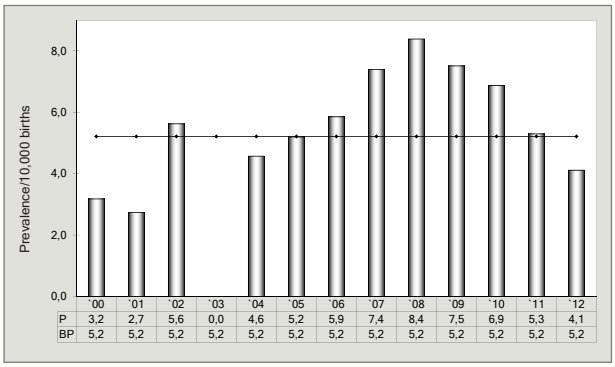


Fig. 26: Development of prevalence/10,000 births with anorectal atresia/-stenosis in the registration area since 2000

In 2012 one anorectal atresia/ stenosis per 2,432 births was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 4 x Halle 3 x Magdeburg	7	14.4	↔
Districts: 1 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 1 x Burgenlandkreis 2 x Börde 1 x Harz 1 x Salzlandkreis	7	5.8	↔
Saxony-Anhalt	**14**	**8.2**	↔

Undescended Testis (2000-2011)		
	Basic prevalence /10,000 births	Confidence interval (CI of 95%) /10,000 births
Cities	14.79	11.71 - 18.43
Districts	5.26	4.19 - 6.52
Region	7.67	6.60 - 8.91
EUROCAT	no informationn	no informationn

We calculated in 2012 a prevalence of 8.2 per 10,000 births, which means we registered 14 male infants/foetuses with undescended testis. Only fullterm infants are considered here, as only in case of a fullterm infant the undescended testis is registered as a major malformation.

During the last four years, we received fewer reports about this indicator malformation and therefore we have to assume that the congenital undescended testis is not reported in all cases.
In comparison to the previous years the current prevalence is within the confidence interval, both in the major cities and in the districts.

No EUROCAT data for comparison is present for undescended testis.

additional information:

Pregnancy outcome	13 x live birth 1 x live birth, deceased after 7 days of life
Sex	14 x male
Number of isolated malformations/MCA	5 x MCA 9 x isolated

The undescended testis occurred in five cases bilateral and in eight cases unilateral. In one case we received no information about the presence.

Malformation combinations (MCA) or superordinated syndromes detected:

- blt cleft lip with cleft palate, low set ears and DUP I. grade
- glandular hypopadias, blt. retarded hip
- ASD II, stenosis of arteria polmonalis, PFO at fullterm infant, blt pes adductus
- ASD II, dilated cerebral ventricles, blt small hands and single transverse palmar crease
- VSD

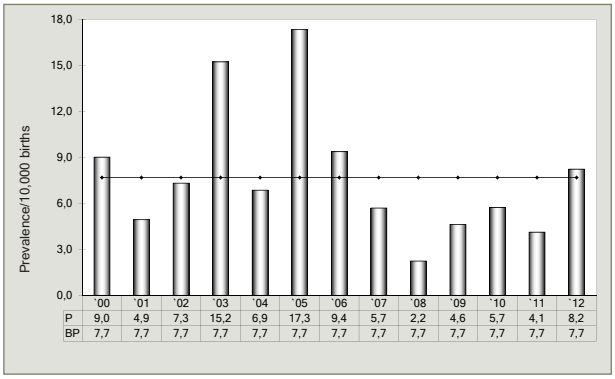


Fig. 27: Development of prevalence/10,000 births with undescended testis in the registration area since 2000

In 2012 one child with undescended testis per 1,216 births (619 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 basic prevalence
Major cities: 1 x Dessau-Roßlau 4 x Halle 2 x Magdeburg	7	14.4	↓
Districts: 1 x Altmarkkreis Salzwedel 3 x Anhalt-Bitterfeld 2 x Börde 6 x Harz 3 x Saalekreis 1 x Salzlandkreis 4 x Stendal	20	16.5	↔
Saxony-Anhalt	**27**	**15.9**	↓

Hypospadias (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	19.85	16.49 - 23.82
Districts	18.20	16.25 - 20.37
Region	18.62	16.90 - 20.51
EUROCAT	17.07	16.81 - 17.33
		3.84 Northern England (UK)* 35.64 Mainz (Germany)**

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

We registered 27 boys with hypospadias in 2012. Glandular, penile, scrotal and perineal hypospadias are included in our analysis by definition.
The prevalence of 15.9 per 10,000 births falls below the confidence level of the basis prevalence of 2000-2011. When comparing the major cities with the districts, their prevalences are nearly identical.

additional information:

Pregnancy outcome	27 x live birth
Sex	27 x male
Number of isolated malformations/MCA	6 x MCA 21 x isolated

All boys with hypospadias were live births and the malformation appeared in 21 cases isolated.

The main part of the hypospadias is the glandular form with 60%. We received no further specifications in a fourth of all cases.

Malformation combinations (MCA) or superordinated syndromes detected:

- Down's syndrome with: Hirschsprung's disease, ASD II, pulmonary valve stenosis, ASD, dilated cerebral ventricles, low set ears, macroglossia, single transverse palmar crease left, sandal's gap
- microcephaly
- blt undescended testis and retarded hip
- duplex kidney
- duplex left kidney, DUP I grade right
- duplex kidney, ventral apron prepuce

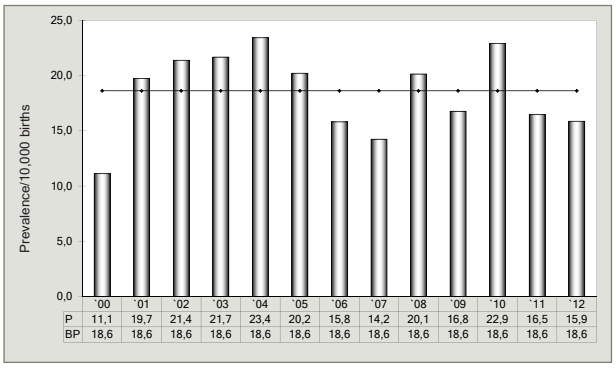


Fig. 28: Development of prevalence/10,000 births with hypospadias in the registration area since 2000

In 2012 one hypospadias per 630 births (321 boys) was registered in Saxony-Anhalt.

12.22 Epispadias (Q64.0)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↔
Districts	0	0.0	↓
Saxony-Anhalt	**0**	**0.0**	↓

Epispadias (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%) /10,000 births**
Cities	0.19	0.00 - 1.04
Districts	0.38	0.14 - 0.83
Region	0.33	0.13 - 0.68
EUROCAT	no informationn	no informationn

In 2012 no case of the rarely appearing malformation epispadias was registered.

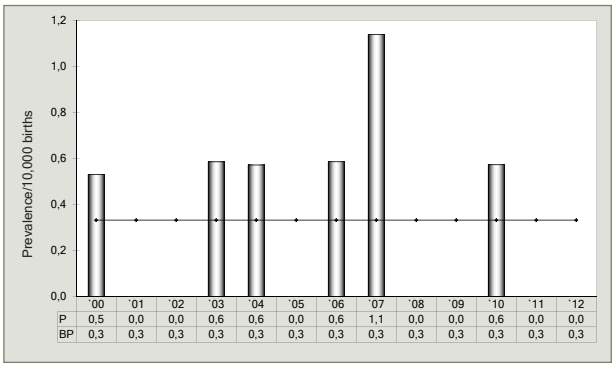


Fig. 29: Development of prevalence/10,000 births with epispadias in the registration area since 2000

In 2012 no birth with epispadias was registered in Saxony-Anhalt.

12.23 Indeterminate Sex (Q56.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↔
Districts: 1 x Saalekreis 1 x Wittenberg	2	1.6	↑
Saxony-Anhalt	**2**	**1.2**	↗

Indeterminate Sex (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	0.19	0.00 - 1.04
Districts	0.63	0.30 - 1.17
Region	0.52	0.26 - 0.93
EUROCAT	0.69	0.64 - 0.75
		0.32 Basque Country (Spain)*
		1.85 Isle de la Reunion (France)**

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

In 2012 two births with indeterminate sex were registered. Both originate from the districts.
In the current year we dedicate our "special topic" to this rarely appearing malformation under chapter 16 from page 74 on.
The prevalence of Saxony-Anhalt is at 1.2 per 10,000 births.

additional information:

Pregnancy outcome	2 x termination of pregnancy
Sex	1 x female 1 x unknown
Number of isolated malformations/MCA	2 x MCA

Both pregnancies were terminated.
In both cases a chromosomal analysis was made, in one case a turner syndrome was diagnosed, in the other case a trisomy 9. The autopsy of both foetuses presented as result of the histological examination the gonads as ovotestis.

In two cases additional malformations were present.

Malformation combinations (MCA) or superordinated syndromes detected:

- Trisomy 9 with: Dandy-Walker syndrome, diaphragmatic hernia, shortened left lower leg, missing distal phalanx of II. finger of both hands, corpus callosum agenesia, misjunction of pulmonary vein, membranous syndactyly of toes II to V at right foot
- Turner syndrome (caryotype 46,X0 with gonosomal anomalia) with: blt renal dysplasia, right incompletely lobed and left unlobed lung, aortic valve stenosis, hypoplastic arteria ilica communis, cleft uvula, low set ears

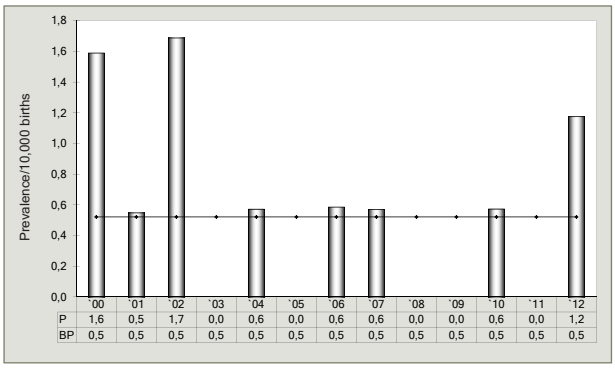


Fig. 30: Development of prevalence/10,000 births with indeterminate sex in the registration area since 2000

In 2012 one birth with indeterminate sex per 8,512 was registered in Saxony-Anhalt.

12.24 Potter Sequence (Q60.6)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Halle	1	2.1	↔
Districts: 1 x Salzlandkreis	1	0.8	↓
Saxony-Anhalt	**2**	**1.2**	↘

Potter Sequence (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	1.69	0.77 - 3.20
Districts	1.97	1.34 - 2.79
Region	1.89	1.35 - 2.58
EUROCAT	1.24	1.17 - 1.31
		0.58 Hungary* 5.00 Mainz (Germany)**

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

We registered two births with Potter sequence in 2012, one from the districts and one from the major cities.
The prevalence of 1.2 per 10,000 births lies under the basis prevalence of the registration period 2000-2011.

In comparison to EUROCAT data the annual prevalence of Saxony-Anhalt is within the confidence interval.

additional information:

Pregnancy outcome	2 x termination of pregnancy
Sex	1 x male 1 x female
Number of isolated malformations/MCA	2 x MCA

In the present cases the diagnosis was made by prenatal diagnostics. Both pregnancies were terminated after 20 resp. 22 weeks of gestation.

Malformation combinations (MCA) or superordinated syndromes detected:

- Prune belly sequence with clubfoot, blt megaureter and joint contracture, urethral stricture, blt hypoplastic and right incompletely lobed lung, megacyst, epicantus internus, mandibular retrognathie, slim thorax with widen costal arch, low set ears
- spina bifida (aperta)

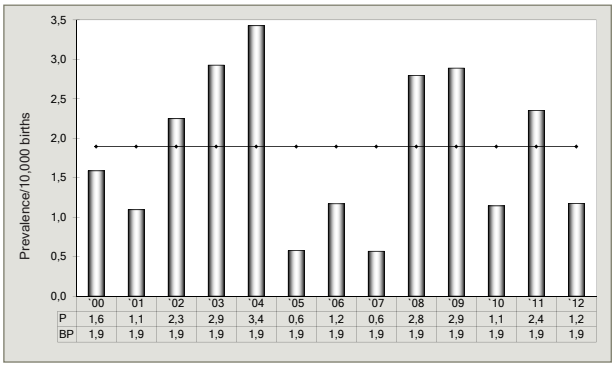


Fig. 31: Development of prevalence/10,000 births with Potter sequence in the registration area since 2000

In 2012 one Potter sequence per 8,512 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 the 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).

No secure data is present about an increased risk of fetopathie as a result of maternal intake of ACE inhibitors or sartans during the first trimenon of pregnancy.
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 basic prevalence
Major cities: 3 x Magdeburg	3	6.2	↔
Districts: 1 x Anhalt-Bitterfeld 1 x Harz 2 x Jerichower Land 3 x Mansfeld-Südharz 1 x Salzlandkreis 2 x Stendal 3 x Wittenberg	13	10.7	↑
Saxony-Anhalt	**16**	**9.4**	↑

Renal Agenesis, Unilateral (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%) /10,000 births
Cities	7.86	5.67 - 10.63
Districts	6.66	5.53 - 8.00
Region	6.96	5.95 - 8.14
EUROCAT	no informationn	no informationn

We registered 16 births with unilateral renal agenesis in 2012.
Therefore, the prevalence of 9.4 per 10,000 births lies above the basis prevalence. Our current value is the second highest within the registration period. Especially in the districts we observed an increasing trend since 2005.

No EUROCAT data is present here for comparison.

additional information:

Pregnancy outcome	15 x live birth 1 x termination of pregnancy
Sex	10 x male 6 x female
Number of isolated malformations/MCA	8 x MCA 8 x isolated

15 infants were live births. In the case of one infant, the presence of Trisomy 18 lead to a termination of pregnancy after 15 weeks of gestation. The diagnosis had been confirmed during an invasive prenatal diagnostic due to the maternal age of 35 years.

In eight cases renal agenesis occurred isolated and also in eight cases it occurred as MCA malformation.

Malformation combinations (MCA) or superordinated syndromes detected:

- anal atresia, duplex left kidney, partial hypoplasia of the 1st-3rd rib right, hypoplastic left thumb, rocker bottom foot, mesenterium ileocolicum commune, incompletely lobed right lung, mandibular retrognathia, high philtrum, short, broad nose, low set ears
- oesophageal atresia with fistula, VSD, tricuspidal insufficiency, haemodynamic relevant PDA at preterm birth
- Fallot tetralogy, accessory thumb
- VSD, accessory left thumb, haemanginoma under left axilla
- clubfoot right, renal dislocation, pes adductus left, hypoplastic left kidney
- sound conduction disorder left, hypoplastic right kidney
- DUP III grade, fetopathia diabetica
- VSD

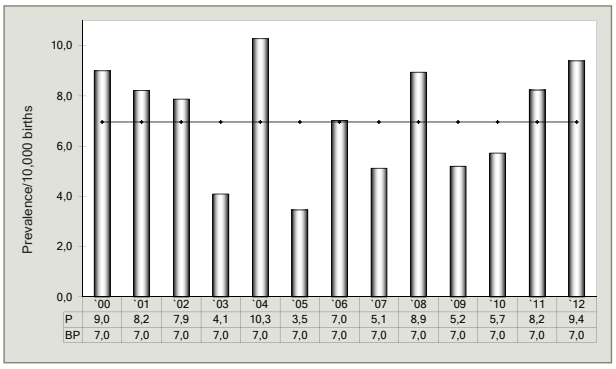


Fig. 32: Development of prevalence/10,000 births with unilateral renal agenesis in the registration area since 2000

In 2012 one renal agenesis, unilateral per 1,064 births was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Dessau-Roßlau 4 x Magdeburg	5	10.3	↔
Districts: 1 x Mansfeld-Südharz 1 x Salzlandkreis 1 x Wittenberg	3	2.5	↓
Saxony-Anhalt	**8**	**4.7**	↓

Cystic Kidney (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%) /10,000 births
Cities	9.92	7.43 - 12.98
Districts	8.18	6.92 - 9.66
Region	8.62	7.48 - 9.92
EUROCAT	no informationn	no informationn

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

In 2012 we registered only eight births with cystic kidneys and calculated a prevalence of 4.7 per 10,000 births. A similar small prevalence was registered in 2008. Consequentially, the current prevalence lies under the confidence interval, only in the major cities the prevalence remains on a similar level as in the previous years.

EUROCAT does not publish any data regarding this congenital malformation since 2006.

additional information:

Pregnancy outcome	5 x live birth 1 x live birth, deceased after 7 days of life 2 x termination of pregnancy
Sex	4 x male 3 x female 1 x indeterminate
Number of isolated malformations/MCA	3 x MCA 5 x isolated

The sex ratio is balanced.

In two cases the pregnancy was terminated after 19 weeks of gestation at presence of cystic kidneys and numerous additional malformations. One infant was delivered after 26 weeks of gestation, but deceased postnatal. Reason for the death were multiple malformations and also the preterm delivery. In this case the cystic kidneys were also diagnosed prenatally.

Malformation combinations (MCA) or superordinated syndromes detected:

- arhinencephalus, blt cleft lip with cleft palate, megaureter left, corpus callosum agenesia, incompletely lobed right lung, nasal agenesia, hypertelorism
- Turner syndrome (caryotype 46,X0 with gonosomal anomalia) with: hermaphroditism (ovotestis), right incompletely lobed lung, aortic valve stenosis, hypoplastic arteria ilica communis, cleft uvula, low set ears
- clubfoot, blt hernia inguinalis

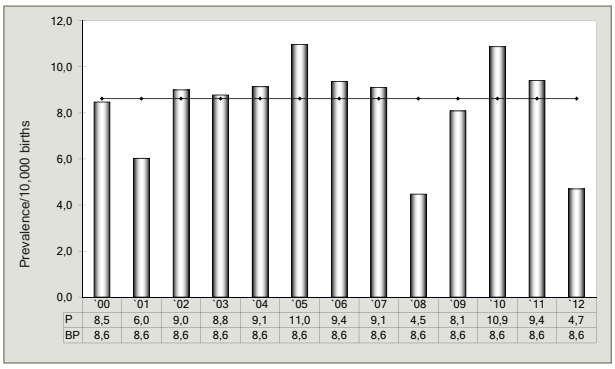


Fig. 33: Development of prevalence/10,000 births with cystic kidneys in the registration area since 2000

In 2012 one cystic kidney per 2,128 births was registered in Saxony-Anhalt.

12.27 Bladder Exstrophy (Q64.1)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↔
Districts: 1 x Harz 1 x Stendal	2	1.6	↑
Saxony-Anhalt	**2**	**1.2**	↑

Bladder Exstrophy (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%) /10,000 births**
Cities	0.00	0.00 - 0.56
Districts	0.19	0.04 - 0.56
Region	0.14	0.03 - 0.42
EUROCAT	no informationn	no informationn

We registered two births with bladder exstrophy from the districts. The rarely appearing malformation was registered in Saxony-Anhalt in 2005, 2009 and now again in 2012. We calculated a prevalence of 1.2 per 10,000 births.

No EUROCAT data is present for comparison.

additional information:

Pregnancy outcome	1 x live birth 1 x termination of pregnancy
Sex	1 x male 1 x female
Number of isolated malformations/MCA	2 x MCA

One girl with a bladder exstrophy-epispadias complex was born after 39 weeks of gestation. The other pregnancy was terminated after 18 weeks of gestation. The male foetus suffered from omphalocele and rectal atresia.

Malformation combinations (MCA) or superordinated syndromes detected:

- rectal atresia with fistula, omphalocele, epispadias, urethral atresia, mandibular retrognathia, low set ears, hypertelorism, epicantus internus
- epispadias, PDA and PFO at fullterm infant

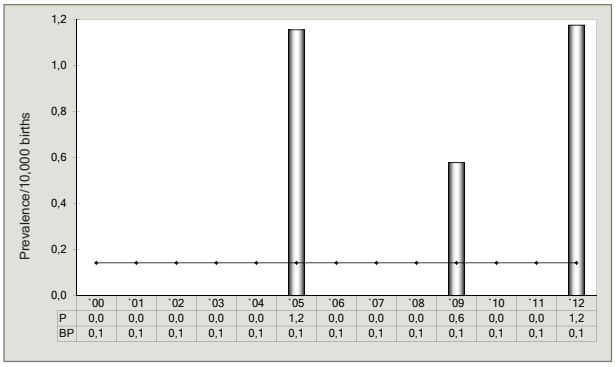


Fig. 34: Development of prevalence/10,000 births with bladder exstropy in the registration area since 2000

In 2012 one birth with a bladder exstrophy per 8,512 was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Dessau-Roßlau	1	2.1	↓
Districts: 1 x Anhalt-Bitterfeld 2 x Mansfeld-Südharz 1 x Salzlandkreis 1 x Stendal	5	4.1	↔
Saxony-Anhalt	**6**	**3.5**	↔

Preaxial Polydactyly (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%) /10,000 births
Cities	4.49	2.88 - 6.68
Districts	4.19	3.24 - 5.32
Region	4.26	3.43 - 5.24
EUROCAT	no informationn	no informationn

In 2012 six infants with preaxial polydactyly were registered in Saxony-Anhalt. In all cases an accessory thumb was present.
The prevalence of 3.5 per 10,000 births is identical to the previous year and lies within the confidence interval of the registration period 2000-2011 in Saxony-Anhalt. When regarding only the major cities we observe a descending trend.

Comparative EUROCAT data for preaxial polydactyly is not available.

additional information:

Pregnancy outcome	6 x live birth
Sex	4 x male 2 x female
Number of isolated malformations/MCA	3 x MCA 3 x isolated

All infants were live births.

The malformation occurred in three cases isolated and in three cases in combination with renal and cardiac malformations.

Malformation combinations (MCA) or superordinated syndromes detected:

- microcephaly
- renal agenesis right, Fallot tetralogy
- renal agenesis right, VSD, haemanginoma under left axilla

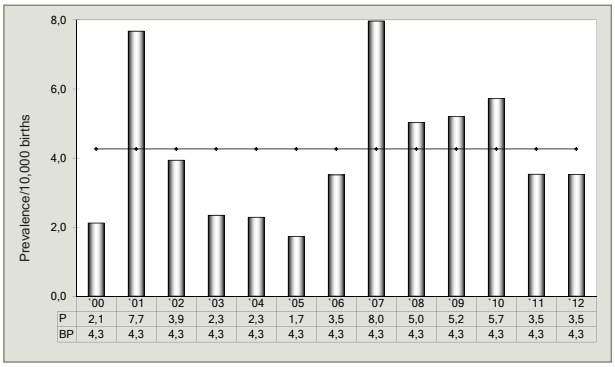


Fig. 35: Development of prevalence/10,000 births with preaxial polydactyly in the registration area since 2000

In 2012 one preaxial polydactyly per 2,837 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 basic prevalence
Major cities: 1 x Dessau-Roßlau 4 x Halle	5	10.3	↗
Districts: 2 x Anhalt-Bitterfeld 2 x Börde 4 x Harz 1 x Jerichower Land 2 x Mansfeld-Südharz 3 x Saalekreis 2 x Salzlandkreis 2 x Stendal	18	14.8	↑
Saxony-Anhalt	**23**	**13.5**	↑

Limb Reduction Defects of Upper and Lower Limbs (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	7.49	5.35 - 10.20
Districts	7.61	6.39 - 9.04
Region	7.58	6.52 - 8.80
EUROCAT	5.40	5.25 - 5.55
		1.91 S Portugal* 11.35 Mainz (Germany)**

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

In 2012 we registered 23 births with reduction defects of upper and lower limbs.
The prevalence of 13.5 per 10,000 births is clearly higher than the prevalence of the previous years and it is also the highest prevalence we calculated during the whole registration period.

The current prevalence of Saxony-Anhalt is clearly higher than the basis prevalence of the European malformation registers of 5.4 per 10,000 births.

additional information:

Pregnancy outcome	15 x live birth 1 x live birth deceased after 7 days of life 7 x termination of pregnancy
Sex	10 x male 13 x female
Number of isolated malformations/MCA	15 x MCA 8 x isolated

In seven cases the pregnancies were terminated at presence of grave malformations such as thanatophoric dysplasia, body-stalk-anomaly or amniotic band syndrome.
In the 16 cases of life birth, the indicator malformation occurred isolated eight times.

Malformation combinations (MCA) or superordinated syndromes detected:

- Edwards syndrome with: anal atresia, agenesia of the right kidney, duplex left kidney, partial hypoplasia of the 1st-3rd rib right, hypoplastic left thumb, rocker bottom foot, mesenterium ileocolicum commune, incompletely lobed right lung, mandibular retrognathia, high philtrum, short, broad nose, low set ears
- Trisomy 9 with: Dandy-Walker syndrome, diaphragmatic hernia left, hermaphroditism, corpus callosum agenesia, misjunction of pulmonary vein, membranous syndactyly of toes II to V at right foot
- Dysostosis mandibulofacialis with: Pierre-Robon sequence, median cleft of soft palate, gastrochisis, blt triphalangeal thumb, mandibular retrognathia, pes adductus left, retarded hip right, haemodynamic not relevant PDA and PFO at preterm birth
- analatresia, omphalocele, clubfoot right, hip luxation blt, mandibular retrognathia, low set ears, hypertelorism
- parietal encephalocele, clubfoot right, blt cleft lip with cleft palate, missing cranial bone, missing right eyelid, lateral descending left eyelid, low set ears
- Turner syndrome with: widely separated mamillas, DUP I. grade left, lateral descending eyelids, flat nose
- metatrophic dysplasia with: multiple extososes, kyphosis of thoracic spine, scoliosis as result of gaps between vertebral bodies and vertebral archs and blt short ribs, funnel chest, macrocephalus, blt plexus cyst, caudal annex, dilated vertebral ventricles, big hands and feet, adducted right thumb
- thanatophore dysplasia type I with: turricephaly, blt vaulted clavicula and deviated fermur, slim thorax, mandibular retrognathia, low set ears
- Body-Stalk anomalia, megacyst
- amniotic band syndrome, clubfoot, membranous syndactyly of toes II and III at right foot, I to IV toes at left foot and at right hand I and II finger, low set, dysplastic ears
- DUP II grade right and I grade left, syndactyly of toes II to IV at left foot, haemodynamic not relevant PDA and PFO at preterm birth
- neck fistula left, dysontogenetic ovarialcyst left, DUP I grade left
- cleft lip with cleft palate right
- clubfoot blt, retarded hip
- corpus callosum hypoplasia, mandibular retrognathia, haemodynamic not relevant PDA at preterm birth, posthaemorrhagic hydrocephalus

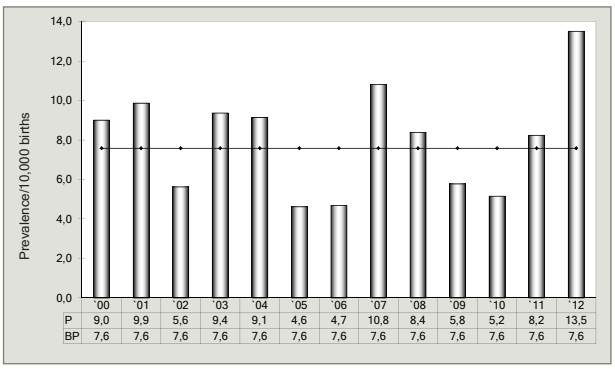


Fig. 36: Development of prevalence/10,000 births with limb reduction defects in the registration area since 2000

In 2012 one limb reduction defect per 740 births was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	0	0.0	↓
Districts: 1 x Anhalt-Bitterfeld 1 x Börde 1 x Saalekreis	3	2.5	↔
Saxony-Anhalt	**3**	**1.8**	↓

Diaphragmatic Hernia (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	4.49	2.88 - 6.68
Districts	2.22	1.55 - 3.09
Region	2.79	2.13 - 3.60
EUROCAT	2.72	2.61 - 2.82
		1.05 S Portugal* 4.51 Malta**

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

Three births from the districts with diaphragmatic hernia were registered in 2012. The prevalence of diaphragmatic hernia in Saxony-Anhalt is at 1.8 per 10,000 births and lies under the basis prevalence of the years 2000-2011. A descending trend can be observed since 2009.

In comparison with data from other EUROCAT centres, our prevalence in 2012 is one of the lower values.

additional information:

Pregnancy outcome	1 x live birth deceased after 7 days of life 1 x termination of pregnancy 1 x stillbirth
Sex	1 x male 2 x female
Number of isolated malformations/MCA	1 x MCA 2 x isolated

We received the following information regarding pregnancy outcomes of this malformation: One infant was born alive after 33 weeks of gestation but deceased postnatal, one infant was stillborn after 33 weeks of gestation. One pregnancy was terminated after 18 weeks of gestation, in this case a trisomy 9 was present. In two cases the diaphragmatic hernia was diagnosed prenatally and reported to us.

Malformation combinations (MCA) or superordinated syndromes detected:

- Trisomy 9 with: Dandy-Walker syndrome, diaphragmatic hernia, shortened left lower leg, missing distal phalanx of II. finger of both hands, corpus callosum agenesia, misjunction of pulmonary vein, membranous syndactyly of toes II to V at right foot

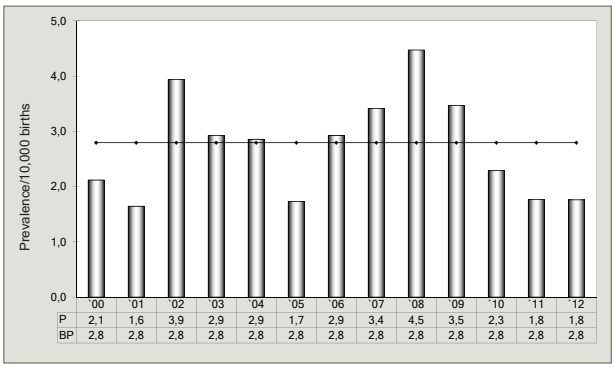


Fig. 37: Development of prevalence/10,000 births with diaphragmatic hernia in the registration area since 2000

In 2012 one diaphragmatic hernia per 5,674 births was registered in Saxony-Anhalt.

12.31 Omphalocele (Q79.2)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Halle	1	2.1	↔
Districts: 2 x Harz	2	1.6	↓
Saxony-Anhalt	**3**	**1.8**	↓

Omphalocele (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	2.81	1.57 - 4.63
Districts	3.30	2.46 - 4.32
Region	3.17	2.46 - 4.03
EUROCAT	2.87	2.76 - 2.98
		0.38 S Portugal* 5.81 Paris (France)**

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

The appearance of three cases with omphalocele in 2012 led to a descending prevalence in comparison to the previous two years. It is now similar to the prevalence we registered in 2008 and 2009.
The prevalence of 1.8 per 10,000 births lies under the confidence interval of the registration period 2000-2011. This is obvious when regarding the districts, at the same time the prevalence of the major cities remains unchanged in 2012.

In comparison with EUROCAT data the prevalence of Saxony-Anhalt lies within the middle range.

additional information:

Pregnancy outcome	3 x termination of pregnancy
Sex	3 x male
Number of isolated malformations/MCA	3 x MCA

In all three cases the diagnosis omphalocele was made during prenatal ultrasound screening. The pregnancies were terminated after 17 and 18 weeks of gestation.

As described by the literature omphalocele appears with additional malformations. Also the three registered cases in 2012 present additional malformations.

Malformation combinations (MCA) or superordinated syndromes detected:

- anal atresia, shortened muscles of the right leg, clubfoot right, blt hip luxation., mandibular retrognathia, epicantus internus, low set ears, hypertelorism
- rectal atresia with fistula, bladder extrophy, epispadias, urethral atresia, mandibular retrognathia, low set ears, hypertelorism
- Edwards-syndrome with: intestinal malrotation

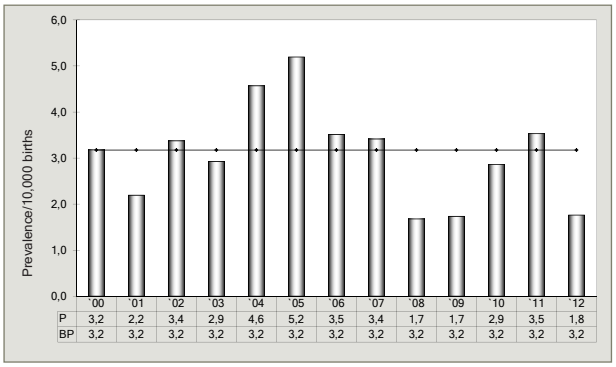


Fig. 38: Development of prevalence/10,000 births with omphalocele in the registration area since 2000

In 2012 one omphalocele per 5,674 births was registered in Saxony-Anhalt.

12.32 Gastroschisis (Q79.3)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Dessau-Roßlau	1	2.1	↓
Districts: 1 x Altmarkkreis Salzwedel 2 x Harz 2 x Mansfeld-Südharz 1 x Saalekreis	6	4.9	↗
Saxony-Anhalt	**7**	**4.1**	↔

Gastroschisis (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	4.49	2.88 - 6.68
Districts	3.61	2.74 - 4.68
Region	3.84	3.05 - 4.77
EUROCAT	2.55	2.45 - 2.65
		0.83 Hungary* 6.60 Mainz (Germany)**

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

The prevalence of gastroschisis remained unchanged during the last three years. In 2012 we registered seven births with this indicator malformation.
The prevalence of 4.1 per 10,000 births lies within the middle range of the basis prevalence. Affected births were mainly from the districts.

In comparison with EUROCAT the values from Saxony-Anhalt are high. However, the highest prevalence of 2004 with 8.6 per 10,000 births was not registered again.

additional information:

Pregnancy outcome	5 x live birth 1 x spontaneous abortion 1 x termination of pregnancy
Sex	2 x male 3 x female 2 x no information
Number of isolated malformations/MCA	3 x MCA 4 x isolated

Five infants were live births. Three infants with prenatally confirmed gastroschisis were delivered by caesarian section after 34 resp. 35 weeks of gestation in a perinatal centre. The gastroschises were operated postnatal. One infant of a 16-year old mother was delivered after 37 weeks of gestation, the diagnosis was not known prenatal in this case. Another infant was born after 27 weeks of gestation. One pregnancy was terminated after 20 weeks of gestation and one spontaneous abortion took place after 16 weeks of gestation.

The gastroschisis appeared in four cases as isolated malformation.

Malformation combinations (MCA) or superordinated syndromes detected:

- Dysostosis mandibulofacialis with: Pierre-Robon sequence, median cleft of soft palate, hypoplastic toes right, blt triphalangeal thumb, mandibular retrognathia, pes adductus left, retarded hip right, haemodynamic not relevant PDA and PFO at preterm birth
- haemodynamic relevant PDA at preterm birth, intestinal malrotation, blt DUP I. grade, asymmetric ventricle
- atresia of large intestine, PDA at preterm birth

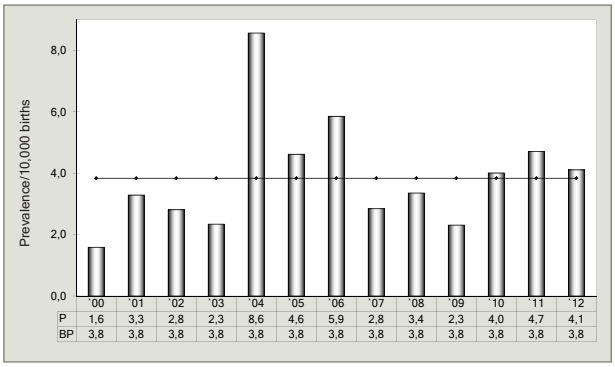


Fig. 39: Development of prevalence/10,000 births with gastroschisis in the registration area since 2000

In 2012 one gastroschisis per 2,432 births was registered in Saxony-Anhalt.

12.33 Prune Belly Sequence (Q79.4)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 1 x Halle 1 x Magdeburg	2	4.1	↑
Districts	0	0.0	↓
Saxony-Anhalt	**2**	**1.2**	↔

Prune Belly Sequence (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%) /10,000 births
Cities	1.12	0.41 - 2.44
Districts	0.82	0.44 - 1.41
Region	0.90	0.54 - 1.41
EUROCAT	no informationn	no informationn

We registered two births with Prune belly sequence from the major cities in 2012.
The prevalence of 1.2 per 10,000 births lies within the range of the basis prevalence of the previous years.

A European comparison is not possible in this case, as no EUROCAT data are present for this malformation.

additional information:

Pregnancy outcome	1 x spontaneous abortion 1 x termination of pregnancy
Sex	2 x male
Number of isolated malformations/MCA	2 x MCA

The diagnosis Prune belly sequence was prenatally confirmed in both cases. One pregnancy was terminated, one ended by spontaneous abortion.

Additional malformations were present at both male infants/foetuses.

Malformation combinations (MCA) or superordinated syndromes detected:

- Potter sequence (functionless kidneys) with blt clubfoot, megaureter and joint contracture, strictur of urethra, blt. hypoplastic and right incompletely lobed lung, megacystis, epicantus internus, mandibular retrognathia, slim thorax with widen costal arch, low set ears
- clubfoot, blt hypoplastic lung, megacystis, flat nose

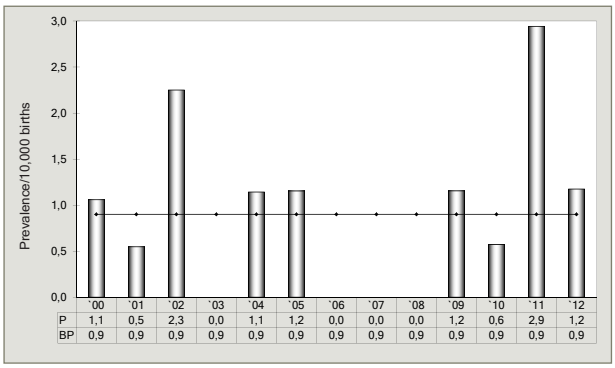


Fig. 40: Development of the prevalence/10,000 births with Prune belly sequence in the registration area since 2000

In 2012 one Prune belly sequence per 8,512 births was registered in Saxony-Anhalt.

12.34 Down Syndrome - Trisomy 21 (Q90.)

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 4 x Halle 3 x Magdeburg	7	14.4	↓
Districts: 1 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 2 x Burgenlandkreis 4 x Börde 1 x Harz 1 x Jerichower Land 4 x Mansfeld-Südharz 1 x Salzlandkreis 1 x Stendal 1 x Wittenberg	17	14.0	↔
Saxony-Anhalt	**24**	**14.1**	↓

Down Syndrome (2000-2011)		
	Basic prevalence /10,000 births	Confidence Interval (CI of 95%)/10,000 births
Cities	20.97	17.51 - 25.05
Districts	15.28	13.51 - 17.28
Region	16.72	15.10 - 18.51
EUROCAT	20.27	19.98 - 20.55
		7.63 S Portugal* 40.22 Paris (France)**

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

The Monitoring of Congenital Malformations registered 24 births with Down's syndrome in 2012.
The current prevalence of 14.1 per 10,000 births is lower than the confidence interval of the registration period 2000-2011. We registered a lower value mainly in the major cities.

EUROCAT calculated a prevalence of 20.3 per 10,000 births. In comparison, the data from Saxony-Anhalt of the previous years are lower than the EUROCAT basis prevalence. The number of registered cases of the chromosomal anomalie trisomie 21 differs very much between the single European malformation registers.

additional information:

Pregnancy outcome	11 x live birth 1 x live birth, deceased after 7 days of life 12 x termination of pregnancy
Sex	13 x male 9 x female 2 x no information
9Number of isolated malformations/MCA	14 x MCA 10 x isolated

50% of the infants/foetuses were live births. One infant deceased after 10 months, it suffered additionally from oesophageal and duodenal atresia. Ten live births had additionally a congenital cardiac defect, which is often related to trisomy 21.

Only in two cases of the twelve live births, we received information about the prenatal chromosomal analyses of trisomy 21.

In 12 cases the pregnancy was terminated between 13 and 22 weeks of gestation and after prenatal confirmation of the diagnosis. One termination of pregnancy took place after 30 weeks of gestation.

Malformation combinations (MCA) or superordinated syndromes detected:

- 2x microcephaly and canalis atrioventricularis communis
- oesophageal atresia, duodenal atresia, ASD II, haemodynamic not relevant PDA at preterm birth, dilated and asymmetric cerebral ventricle, macroglossy, lateral ascending eyelids and transverse palmar crease
- Hirschsprung disease, glandular hypospadias, ASD II, pulmonary valve stenosis, ASD, dilated cerebral ventricle, low set ears, macroglossy, transverse palmar crease left, sandal's gap
- ASD II, blt hydronephrosis
- VSD, stenosis of both arteriae pulmonalis, clubfoot, sound conduction disorder (right middle grade, left high grade)
- cardiac defects, sound conduction and perception disorder (blt 50 dB)
- VSD, ASD, haemodynamic not relevant PDA at full-term birth
- VSD, ASD II
- ASD II, stenosis of arteria pulmonalis
- cardiac malformations
- VSD, hygroma colli cysticum
- hygroma colli cysticum
- incompletely lobed right lung

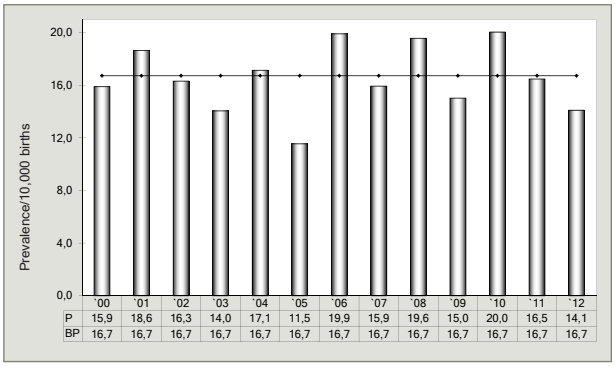


Fig. 41: Development of prevalence/10,000 births with Down syndrome in the registration area since 2000

In 2012 one Down´s syndrome (trisomy 21) per 709 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 basic prevalence
Major cities	0	0.0	↓
Districts: 1 x Stendal	1	0.8	↔
Saxony-Anhalt	**1**	**0.6**	↘

Patau Syndrome (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	1.50	0.65 - 2.95
Districts	0.82	0.44 - 1.41
Region	0.99	0.62 - 1.52
EUROCAT	1.81	1.72 - 1.89
		0.13 Zagreb (Croatia)* 3.79 Paris (France)**

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

In 2012 we registered one birth with trisomy 13 from the district Stendal. It was a female stillbirth after 25 weeks of gestation.
The prevalence of 0.8 per 10,000 births is lower than the basis prevalence of 2000-2011.

Our current prevalence from Saxony-Anhalt as well as the average of the previous years lies below the confidence interval of EUROCAT.

additional information:

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

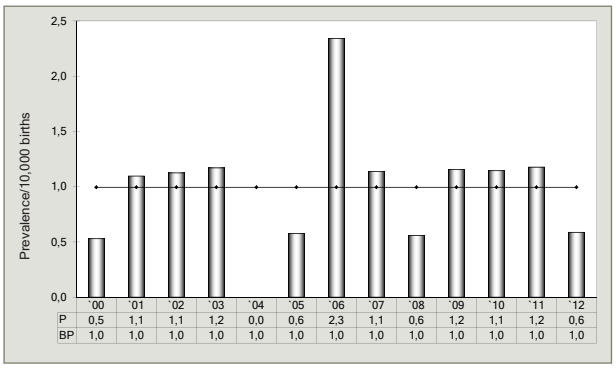


Fig. 42: Development of prevalence/10,000 births with a Patau syndrome in the registration area since 2000

In 2012 one Patau syndrome (trisomy 13) per 17,023 births was registered in Saxony-Anhalt.

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

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities: 3 x Halle	3	6.2	↔
Districts: 1 x Altmarkkreis Salzwedel 1 x Anhalt-Bitterfeld 1 x Mansfeld-Südharz	3	2.5	↘
Saxony-Anhalt	**6**	**3.5**	↔

Edwards Syndrome (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%)/10,000 births**
Cities	4.12	2.58 - 6.23
Districts	3.68	2.79 - 4.75
Region	3.79	3.01 - 4.72
EUROCAT	4.53	4.40 - 4.67
		0.95 S Portugal* 12.82 Isle de la Reunion (France)**

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

We registered six births with Edwards syndrome in 2012. The calculated prevalence of 3.5 per 10,000 births is within the middle range of the previous years basis prevalence and at the same time below the European average value.

additional information:

Pregnancy outcome	6 x termination of pregnancy
Sex	1 x male 3 x female 2 x no information
Number of isolated malformations/MCA	2 x MCA 4 x isolated

All pregnancies were terminated after 12 to 19 weeks of gestation.

Malformation combinations (MCA) or superordinated syndromes detected:

- anal atresia, agenesia of right kidney, duplex left kidney, partial hypoplasia of 1st to 3rd rip right, hypoplastic left thumb, rocker bottom foot, mesenterium ileocolicum commune, incompletely lobed lung right
- omphalocele, intestinal malrotation

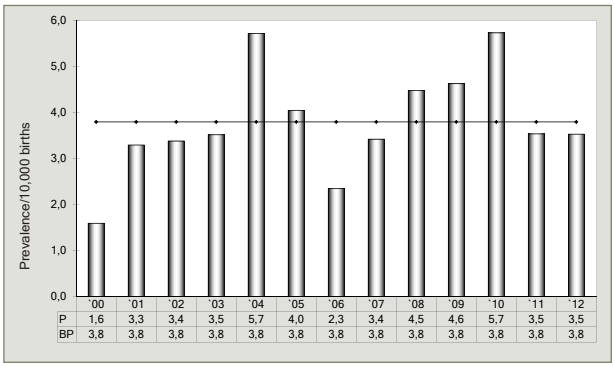


Fig. 43: Development of prevalence/10,000 births with Edwards syndrome in the registration area since 2000

In 2012 one Edwards syndrome (trisomy 18) per 2,837 births was registered in Saxony-Anhalt.

12.37 Indicator Malformations, In Total

We described in the previous chapters 12.1 to 12.36 36 indicator malformations which are exactly defined (see definitions in chapter 12.0) by the ICBDSR (International Clearinghouse for Birth Defects).

In 2012 we registered **252 births with an indicator malformation**. 204 (81.0%) of these 252 were live births. The number of live births increased continuously since 2009 (71.5%) and ranges during the whole registration period above the average value (76.7%). The percentage of spontaneous abortions is 2.0% (5 births) and the percentage of stillbirths 0.8% (2 births). As these are rather small numbers (between 1.9% and 6.8% in the registration period) we cannot describe any trend here. We registered currently less terminations of pregnancies with 16.3% (41 births) compared to the previous two years (2011: 17,8%, 2010: 22.3%).

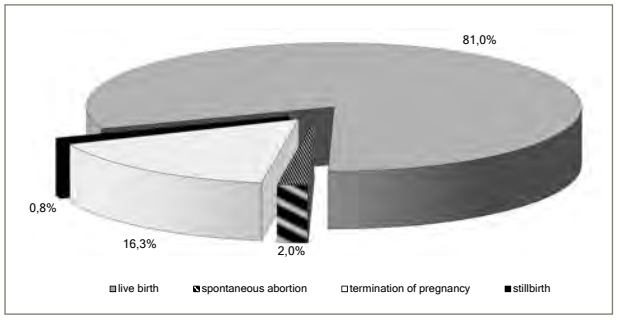


Fig. 44: pregnancy outcomes of births with indicator malformations 2012

To detect conspicuous accumulations of malformations, the current prevalence of each indicator malformation is compared to the basis prevalence of the years 2000-2011. The following table shows a comparison of all indicator malformations.

	Number	Prevalence /10,000 births	Trend in comp. to basic prevalence
Major cities	84	1.72	↔
Districts	168	1.38	↔
Saxony-Anhalt	**252**	**1.47**	↔

Indicator malformations, in total (2000-2011)		
	Basic prevalence /10,000 births	**Confidence Interval (CI of 95%) /10,000 births**
Cities	1.66	1.56 - 1.77
Districts	1.39	1.34 - 1.46
Region	1.47	1.42 - 1.52

252 births (1.5%) presented in total 308 indicator malformations in 2012. In the previous year the calculated prevalence was clearly smaller than the basis prevalence (2011: 226 births, 1.3%): However, in 2012 the prevalence lies again within the confidence interval of 2000 - 2011. The rate we registered in the major cities is about 18.3% higher than the rate registered in the districts.

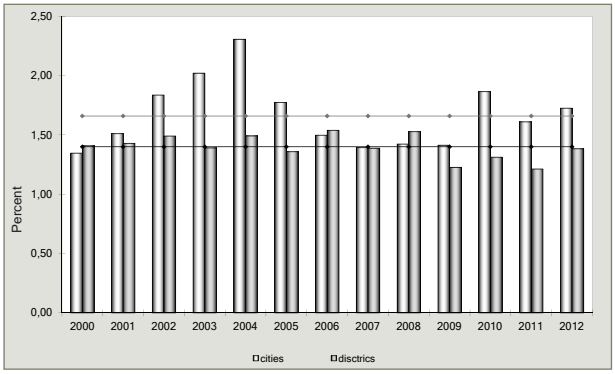


Fig. 45: Indicator malformations of ICBDSR in total (2000 to 2012), comparison of frequency (in %) in the major cities and districts

The analysis of the indicator malformation prevalence during the registration period allows to forecast the future development. As in our previous Annual Report we analysed again the trend of indicator malformation prevalences by considering the whole registration period (12 years).
Condition for the trend analysis is that we expect each malformation to appear at least five times or that we registered at least two cases of the corresponding malformation. Figure 46 on page 64 shows the average percentage changes of the annual prevalences of all indicator malformations that correspond to these conditions. They are rated by binary logistic regression analysis on the basis of the maximum-likelihood-estimation.
A **significant increasing trend** is indicated by a regression coefficient B, which is together with a confidence interval of 95% illustrated righthand of the axis of ordinates. The regression coefficient represents the strength and direction of the annual percentage change. Lefthand of the axis (in the negative area) descending trends are presented. If the confidence interval overlaps the zero value the percentage change is not significant.
We tested the temporary change of the trend-coordinate and the non-linear coordinate for heterogeneity by use of the chi-squared test. We rate the trend as non-linear at a probability of $p > 0,05$ for the linear ratio and $p < 0,05$ for the non-linear ratio. In these cases we **did not identify a linear trend**. This applies for **neural tube defects in total, spina bifida, microcephaly, undescended testis and preaxial polydactyly**.
The observed trend can be classified as significant at a probability of $p < 0,05$ for the linear ratio and $p > 0,01$ for the non-linear ratio. A **significant decreasing trend**, corresponding to a negative regression coefficient, can be observed for **congenital hydrocephalus and cleft palate**.

The malformation **anorectal atresia/stenosis** shows a **significant increasing trend** (6.09%, CI 1.21% to 11.61%). We observed an increasing number of anorectal atresia/stenosis in Saxony-Anhalt since we elaborated our Annual Report 2010. To identify possible reasons for this increasing trend and to analyse the recorded data, the Monitoring of Congenital Malformations Saxony-Anhalt cooperates with the Network for Congenital Uro-Rectal Malformations (CURE-Net).

All other indicator malformations do not show a significant positive or negative trend. The chi-squared test gives for the linear and non-linear component a probability of $p > 0,05$. For this reason, the non-linear ratio is not significant and it is also not decisive in regard to a disproportionate increase or decrease.

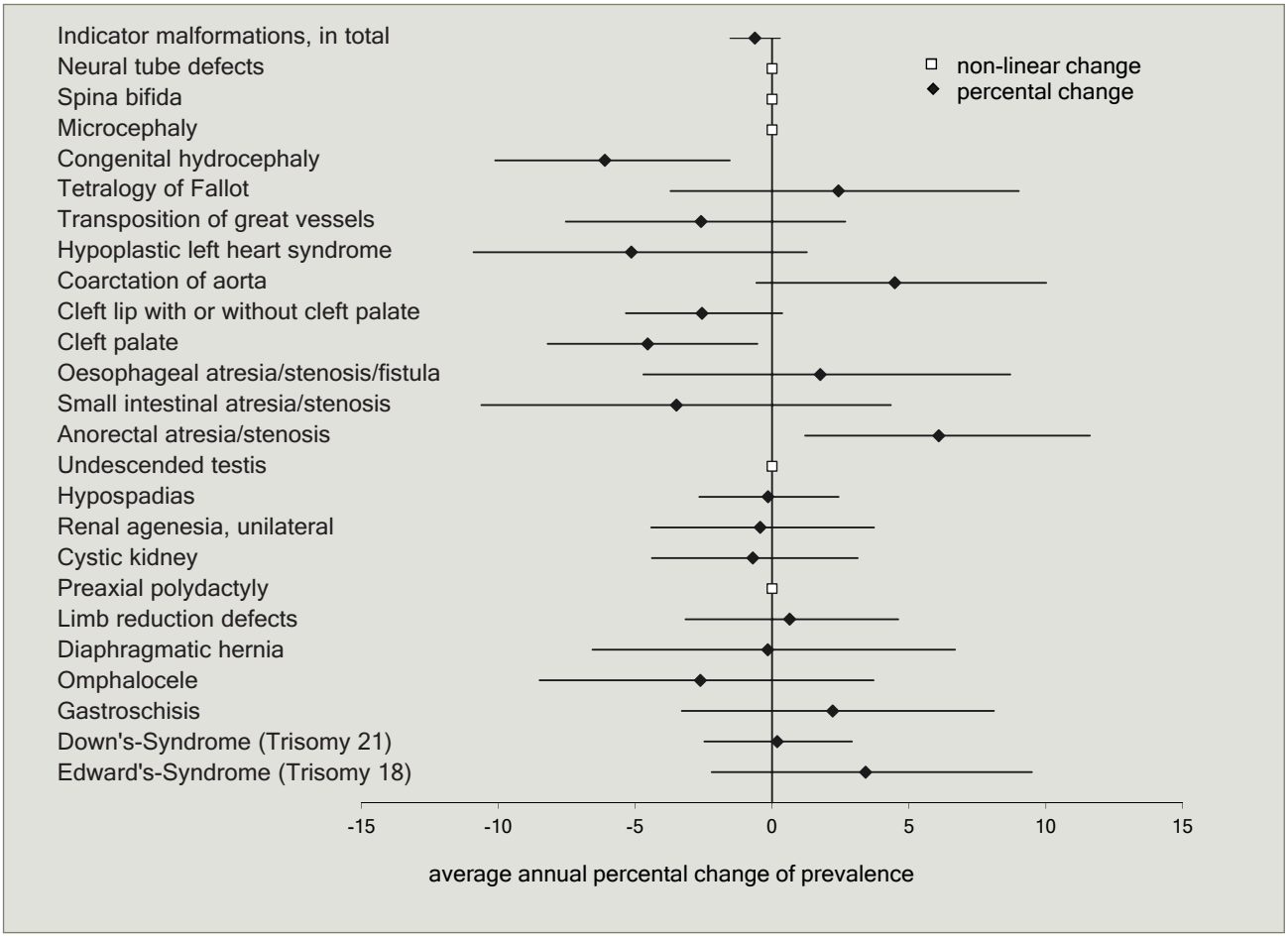


Fig. 46: Trend analysis 2000 - 2012 with average percental change of prevalence per year (95% confidence interval)

	regression coefficient B in %	confidence interval (CI of 95%)
Indicator malformations, in total	-0.62	-1.52 to 0.29
Congenital hydrocephaly	-6.11	-10.11 to -1.55
Tetralogy of Fallot	2.42	-3.71 to 9.01
Transposition of great vessels	-2.60	-7.53 to 2.67
Hypoplastic left heart syndrome	-5.14	-10.91 to 1.27
Coarctation of aorta	4.48	-0.57 to 10.01
Cleft lip with or without cleft palate	-2.56	-5.34 to 0.37
Cleft palate	-4.54	-8.19 to -0.54
Oesophageal atresia/stenosis/fistula	1.79	-4.70 to 8.70
Small intestinal atresia/stenosis	-3.49	-10.62 to 4.34
Anorectal atresia/stenosis	6.09	1.21 to 11.61
Hypospadias	-0.15	-2.66 to 2.43
Renal agenesia, unilateral	-0.43	-4.42 to 3.73
Cystic kidney	-0.70	-4.39 to 3.13
Limb reduction defects	0.64	-3.16 to 4.60
Diaphragmatic hernia	-0.16	-6.56 to 6.68
Omphalocele	-2.62	-8.49 to 3.71
Gastroschisis	2.22	-3.30 to 8.10
Down's-Syndrome (Trisomy 21)	0.19	-2.47 to 2.92
Edward's-Syndrome (Trisomy 18)	3.42	-2.21 to 9.49

15 Summary

The present Annual Report 2012 of the Monitoring of Congenital Malformations outlines registered data from Saxony-Anhalt about congenital malformations and anomalies as well as genetically caused diseases. We analysed the registered data statistically and present it now again in the approved manner, so that our analysed data can be compared to each other. At the same time, our analysis of data is population-based according to the official birth rate provided by the State Statistical Office in Halle. We have no data for comparison from other Federal States as there are no similar malformation registers existing in Germany. To classify the calculated prevalences anyway, we compare them to the European wide registered values, calculated by EUROCAT.

We register in Saxony-Anahlt a continuously decreasing birth rate. However, in 2012 with **16,888 infants** slightly more live births were born in Saxony-Anhalt in comparison to the previous year (2011: 16,837).
The officially registered number of **stillbirths** (2012: 63) is currently rather low in the absolute comparison to the whole registration period (2000-2011: 71.6 per year) as well as in relation to the number of live births (2012: 1 stillbirth per 268 live births, 2000-2011: 1 stillbirth per 243 live births).

According to the Federal Statistical Office, 673,544 infants were live births in Germany in 2012 (2011: 662,685; 2010: 677,947). The live births of Saxony-Anhalt represent 2.5% of all births in Germany in 2012.

The Monitoring of Congenital Malformations registered among data of live and stillbirths **52 terminations of pregnancy** and **20 spontaneous abortions after 16 weeks of gestation**. The prevalence calculations of the current report are therefore based on a **total number of 17,023 births** (see chapter 2).

597 births had at least one **major malformation** (3.5% of all births). Therefore, the malformation rate lies slightly above the rate of the previous two years (2011: 3.4%; 2010: 3.5%). At the same time it remains on a constant level in the 12-years-trend analysis (CI 3.3% to 3.5%) (see chapter 8).

89.5% of **infants with a major malformation** were live births in 2012 (2011: 88.2%; 2010: 87.3%). Since the end of the nineties we observed a slightly decreasing number of terminations of pregnancies (2012: 8.2%). The percentage of spontaneous abortions (2012: 1.5%) is on a constant level at 1.6% since 1996. The percentage of stillbirths is after a very high value in the previous year again very low (2012: 0.7%; 2011: 1.7%), (see chapter 7 and 8).

As expected, the analysis of **frequency of appearance of single diagnoses** in 2012 shows that atrial septal defect and ventricular septal defect are the most frequent and second most frequent single malformations. It is surprising that on rank three we registered in the current year the hearing disorder. Following are microcephaly, dilatative uropathy and clubfoot. Down's syndrome and hip subluxation appeared less frequently than in the previous years average (see chapter 11).

Approximately 1.5% of all births presented an **indicator malformation** in 2012 (see chapter 12). Furthermore, we calculated for the following ten indicator malformations **higher rates** in regard to the corresponding basis prevalence: encephalocele, microcephaly, Fallot-tetralogy, cleft palate, oesophageal atresia/stenosis/fistula, small intestinal atresia and stenosis, indifferent sex, unilateral renal agenesia, bladder extrophy and limb reduction defects. We calculated **lower rates** in comparison to the basis prevalence in 2012 for: hydrocephalus, microtia/anotia, anorectal atresia/stenosis, hypospadias, Potter-sequence, cystic kidney, diaphragmatic hernia, omphalocele, Down's syndrome and Patau-syndrome. The rarely appearing indicator malformations anencephaly, anophthalmos/microphthalmos and epispadias were not registered in Saxony-Anhalt in 2012.

Furthermore, we registered **52 terminations of pregnancies** in 2012. Most frequently, the pregnancies were terminated due to a chromosomal aberration (56.9%). A malformation of the central nervous system was decisive in one fourth (25.5%) of the cases. 3.9% of terminations of pregnancies took place after 23 weeks of gestation.

The analysis in chapter 13 shows that 30 infants and foetuses had a **genetically caused disease** in 2012. **Sequences, associations, resp. complexes** were present in 12 cases. 18 births had an **embryopathy or congenital infection**. Most frequently, the reason for presence of an embryopathy was a maternal diabetes mellitus resp. gestational diabetes. The average maternal age of 52 births with **chromosomal aberration** was 34.5 years in 2012. This is the highest average age we registered during our registration period.

Chapter 16 of the present Annual Report deals with the topic disorders of sexual development. Main symptoms, embryology and a possible connection with endocrine disruptors are outlined here. We examined epidemiologically the congenital adrenal hyperplasia, female and male genital malformations and the Turner-syndrome.

In 2012 the Monitoring of Congenital Malformations received data on 2,059 births from Saxony-Anhalt. At least one major malformation was present at 597 births. In 256 cases only minor malformations or anomalies were registered. The Monitoring of Congenital Malformations registers at the one hand data about infants and foetuses with congenital malformations and on the other hand data about infants without malformations as control cases. These control cases are necessary as the risk calculation in a scientifically founded analyses is only possible when both groups are compared.

The compilation of the present 2012 Annual Report was only possible due to ongoing voluntary reports about congenital malformations from various medical institutions of Saxony-Anhalt. By receiving these reports we created a solid data basis during the last years. **We would like to thank all "senders" and hope that this excellent cooperation will continue!**

16 Disorders of sexual development (DSD)

Definition

Disorders of sexual development are defined as missing coincidence between chromosomal, gonadal and phenotypical gender. DSD is a congenital disorder, however disorders of sexual development can appear at every stage of life. We outlined in the following the characteristics of sexual development and its variations as well as the malformations of external and internal genitalia which appear already at newborns or young babies. We do not analyse in this chapter complex processes such as morphologic-anatomical changes and disorders of sexual maturity as well as processes which are defined as "mental gender" (gender typical behaviour, sexual orientation, sexual identity).

Historically, there are different terms in the medical field that were used to describe a disturbed sexual development. The term hermaphrodite is obsolete and not used any longer. Currently, the term intersexuality that was used for many years was removed by a consensus conference (Chicago, USA, October 2005) and replaced by the term "disorder of sexual development: DSD". It was published within a monthly paediatrics journal in February 2008 and is now used in the paediatric endocrinology as well as in the clinical daily routine.

Nomenclature:
- DSD with aberration of sex chromosomes
- 46,XY DSD (assured diagnosis partly in 50% of all cases), complete or partial androgen resistance (CAIS, PAIS)
- one third of infants with DSD have additional malformations

Overview of disorders of the sexual development

Numerical aberrations of sex chromosomes:
- 47,XXY Klinefelter syndrome and variations
- 45,X0 Ulrich Turner syndrome and variations

Karyotype 46,XY
(male karyotype, phenotype female or indifferent):
- disorder of testicle development
  - complete gonadal dysgenesis
  - partial or mixed gonadal dysgenesis
- disorder of androgen biosythesis or androgen effect:
  - without adrenal insufficiency
    - 5alpha-reductase type II defect
    - complete androgen resistance (CAIS)
    - partial androgen resistance (PAIS)
    - endocrine disruptors
  - with adrenal insufficiency
- syndromal forms (hand-foot-genital syndrome)
- cloacal malformations
- isolated hypospadias
- cryptorchism
- 45,XY mosaic (mixed gonadal dysgenesis)
- 46,XX/46XY (chimerism)

Karyotype 46,XX
(female karyotype, phenotype male or indifferent):
- disorder of ovary development
- androgen excess
  - congenital adrenal hypoplasia (95% of all cases 21-hydroxylase deficiency)
  - glucocorticoid resistance
  - foetal placental androgen excess (for example aromatase deficiency)
  - maternal androgen excess (for example tumor, intake of androgen effective substances)
- syndromale forms (Mayer-Rokitansky-Küster-Hauser syndrome)
- cloacal malformations
- labial adhesion

Main symptoms

The majority of anomalies which are related to disorders of sexual development appear in connection with complex endocrinological variations. We register within the malformation registration only disorders of morphological-anatomical variations as valid guiding symptom.

Disorders of sexual maturity and processes such as development of a "mental gender" (gender typical behaviour, sexual orientation, sexual identity) are not analysed here. Following clinical findings which are made in the delivery room indicate a presence of DSD:

- clinical indifferent outer genitals
- female outer genital with:
  - clitoral hypertrophy
  - posterior fusion of labia
  - inguinal palpable or in labia palpable resistance (testis)
- male outer genitals with:
  - bilateral undescended testis
  - micropenis
  - perineal hypospadias
  - mild hypospadias, bilateral undescended testis
  - family history for DSD
  - discordance between prenatal karyotype and outer genitals

Basics of embryology

After fertilization, the gonads develop from the zygote as bipotent genitalridge after 4 weeks post conceptionem (p.c.). Bipotent means that a further differentiation into male and female characteristics is possible. Experts guess that after 6 weeks p.c. gender specific morphological differences of the embryo develop. Decisive for this development is the expression of the testicle determining factor (sex determining region Y) at 46,XY karyotype.

Development of inner genitals:

The sex differentiation takes place under control of a biosynthesis of sex hormones and cellular and tissue-specific effect transfer. Very important during this process is the effect of testosterone (generated by the Leydig-cells of the embryonic testis) and the effect of the anti-mullerian hormone (generated by Sertoli-cells of embryonic testis). Decisive for the female sexual differentiation is mainly the absence of testosterone and anti-mullerian hormone.

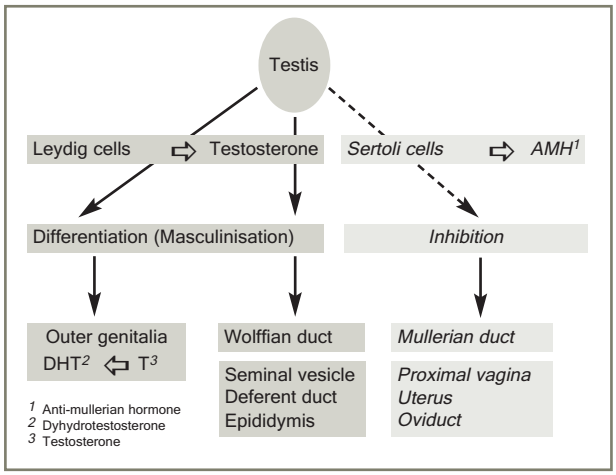


Fig.: 49: male sexual differentiation
source: Holterhus P (2012), Fig.25.2, p. 393

Development of outer genitals:

Decisive for the development of the male outer genitals is a testosterone biosynthesis after seven weeks of gestation. In this connection an enzyme called 5α-reductase type II has to be present, which activates testosterone to be transformed into dihydrotestosterone. Additionally, there have to be functioning androgen receptors at the genital target tissue. Under these conditions the penis develops from genital eminence until 12 weeks of gestation. The urethral line and labioscrotal bulge merge with each other and form the corpus cavernosum and scrotum. A disturbed androgen biosynthesis or receptor defect during this critical phase (7-12 weeks of gestation) may lead to an abnormal differentiation of outer genitals although a 46,XY karyotype is present (46,XY DSD). Conversely, an androgen excess at 46,XY may cause during this period of time a virilisation with different intensity of labioscrotal line fusion (46,XX DSD).
If no functioning testis are present (as common in female development or gonadal dysgenesia), the genital eminence forms a clitoris later and the labioscrotal lines form the labia.

Endocrine disruptors

The endocrine system of humans plays a key role from the beginning of life as it activates a sexual steriod biosynthesis which is a decisive factor for the presence of disorders of sexual differentiation. It is influenced by numerous inner processes. However, the influence of outer factors such as environmental influences increases continuously. These factors are able to influence hormonal procedures and are therefore named endocrine disruptors (environmental hormones).
These are natural substances (phytohormones) and synthetic products (alkylphenols, bisphenol A, chlorinated compounds, ethinyl estradiol, phtalates, pesticides). A contact with these substances is nearly unavoidable for humans. Already in the year 2000 the Monitoring of Congenital Malformations analysed this topic on behalf of the Federal Environment Agency. Currently, animal experiments were made which identified these substances as responsible agent for endocrine tumours as well as for genitalia malformations. However, an assured differentiation was not succeeded in clinical studies until now. Especially the different mixtures of substances (not only endocrine disruptors) which we face in our daily life make it difficult to identify the influence of one single substance as responsible factor for a genital malformation. Current analyses show that mainly lower concentrated mixtures of different disruptors and the period of time during which they influence an organism (partly already as foetus) are probably responsible. For this theory only animal experiments are present until now. A registration and analysis of the causality is nearly impossible due to the possible long period between time of influence of substances (intrauterine) and in the future life appearing clinical relevant disorders or negative effects.

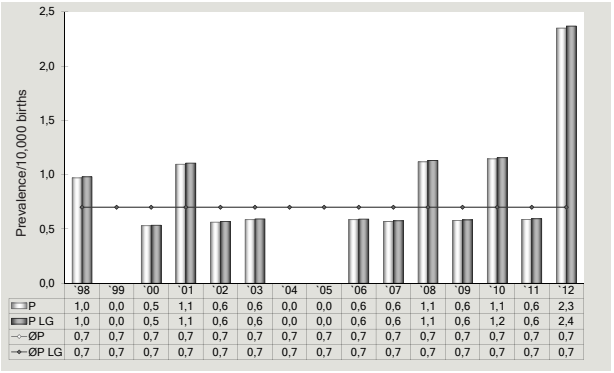
Epidemiology

An epidemiological evaluation of the situation is difficult as the disorders of sexual development concern a very heterogeneous group. Therefore a morphological-anatomical classification after ICD-10 that differs from the "endocrinological nomenclature" was used. We focus on disorders which attract the attention at birth by urogenital malformation or indifferent sex, including the divergence from phenotypical sex and karyotype.

We analysed the registrations of birth cohorts 1996 - 2012 in relation to a number of 268,572 births. Minor malformations were not excluded when forming the single groups.
The most frequent disorder with indifferent genital at birth is the congenital adrenal hyperplasia which is the responsible factor in half of the neonatal cases.

Congenital adrenal hypoplasia (CAH)

Valid data in regard to the frequency of a typical CAH with 21-hydroxylase deficiency is provided by the Federal newborn screening. CAH is potentially life-threatening (adrenal insufficiency). Therefore a newborn with indifferent sex urgently has to be tested for 17α-hydroxyprogesterone to eliminate the possible presence of a typical CAH with salt-losing syndrome.
A test for typical CAH is part of the newborn screening in Saxony-Anhalt since 1997. The calculated 15-years prevalence for the period of 1998-2012 is 0.7 per 10,000 births (based on 249,962). With 1:13,888 births the prevalence lies within the expected frequency. The prevalence for Germany is indicated with a value of 1:13,000 up to 15,000.

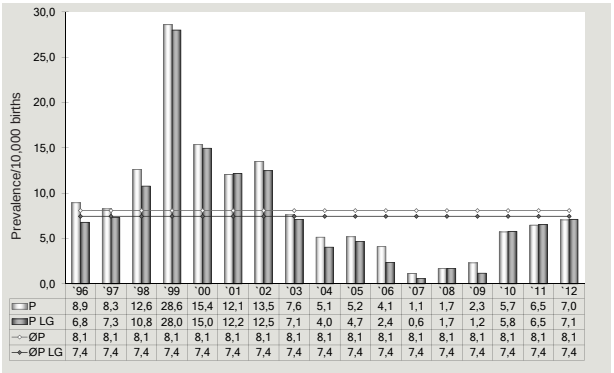


	`98	`99	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	1,0	0,0	0,5	1,1	0,6	0,6	0,0	0,0	0,6	0,6	1,1	0,6	1,1	0,6	2,3
P LG	1,0	0,0	0,5	1,1	0,6	0,6	0,0	0,0	0,6	0,6	1,1	0,6	1,2	0,6	2,4
ØP	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7
ØP LG	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7	0,7

Fig. 50: Development of prevalence/10,000 births with congenital adrenal hypoplasia in the registration area since 1998.

Female genital malformations

According to ICD -10 following malformations are summarised here: Q50.0-6 (congenital malformations of ovaries, of tubae uterinae and ligamenta lata uteri), Q51.0-9 (congenital malformation of uterus and cervix uteri) and Q52.0-9 (other congenital malformations of female genital organs). The 17-years prevalence is 8.1 per 10,000 births and the live births prevalence for the same period of time is 7.4 per 10,000 births.

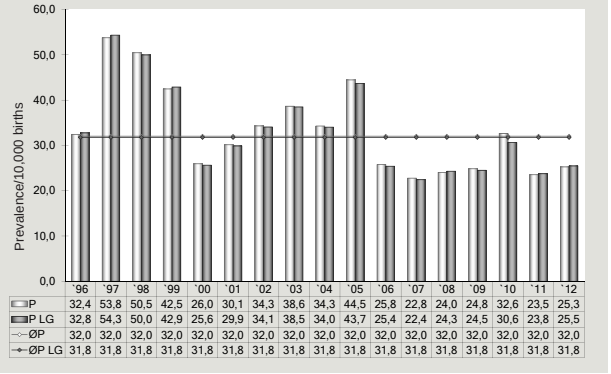


	`96	`97	`98	`99	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	8,9	8,3	12,6	28,6	15,4	12,1	13,5	7,6	5,1	5,2	4,1	1,1	1,7	2,3	5,7	6,5	7,0
P LG	6,8	7,3	10,8	28,0	15,0	12,2	12,5	7,1	4,0	4,7	2,4	0,6	1,7	1,2	5,8	6,5	7,1
ØP	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1	8,1
ØP LG	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4	7,4

Fig. 51: Development of prevalence/10,000 births with female genital malformation in the registration area since 1996.

Male genital malformations

According to ICD-10 these are the following male genital malformations: Q53.0-9 (nondescensus testis including ectopia at fullterm birth), Q54.0-9 (hypospadias including glandular hypospadias) and Q55.0-9 (other congenital malformations of male genital organs). The 17-years prevalence lies at 32.0 per 10,000 births and the live births prevalence for the same period of time is 31.8 per 10,000 births.

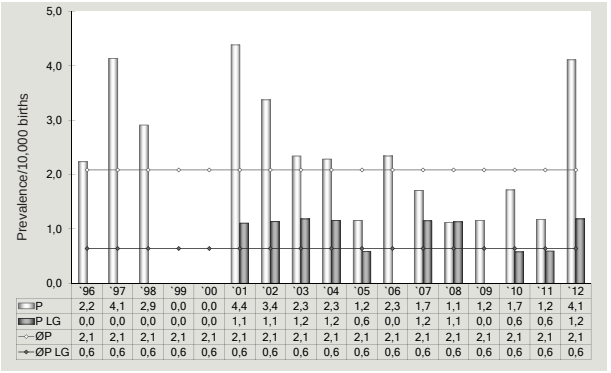


	`96	`97	`98	`99	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	32,4	53,8	50,5	42,5	26,0	30,1	34,3	38,6	34,3	44,5	25,8	22,8	24,0	24,8	32,6	23,5	25,3
P LG	32,8	54,3	50,0	42,9	25,6	29,9	34,1	38,5	34,0	43,7	25,4	22,4	24,3	24,5	30,6	23,8	25,5
ØP	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0	32,0
ØP LG	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8	31,8

Fig. 52: Development of prevalence/10,000 births with male genital malformation in the registration area since 1996.

Turner-syndrome

All types are included here (Karyotype 46,X0 with gonosomal anomaly or mosaic). A Turner-syndrome is most frequently the reason for a gonadal dysgenesis at female phenotype. In nearly 30% of all cases where a softmarker is prenatally detected, a Turner-syndrome is later present. The rate of spontaneous abortions is very high in these cases. In 18 (32%) of 56 registered cases between 1996 and 2012 there was at least one additional major malformation present (9x cardiovascular malformations (16%), 4x renal malformations (7%)).



	`96	`97	`98	`99	`00	`01	`02	`03	`04	`05	`06	`07	`08	`09	`10	`11	`12
P	2,2	4,1	2,9	0,0	0,0	4,4	3,4	2,3	2,3	1,2	2,3	1,7	1,1	1,2	1,7	1,2	4,1
P LG	0,0	0,0	0,0	0,0	0,0	1,1	1,1	1,2	1,2	0,6	0,0	1,2	1,1	0,0	0,6	0,6	1,2
ØP	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	2,1	2,1	2,1	2,1
ØP LG	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6	0,6

Fig.53: Development of prevalence/10,000 births with Turner-syndrome in the registration area since 1996.

The 17-years prevalence lies at 2.1 per 10,000 births and the live births prevalence is at 0.6 per 10,000 births. A study from Denmark shows that in 14.9% of the cases of Turner-syndrome the diagnosis was made at the age of <1 year and in 33.2% of the cases it was made between 10 and 17 years. In 38.5% of the cases the syndrome was diagnosed during adult age. That means that the births prevalence is lower than the "real" prevalence.

Indication of source:
Holterhus P: Störungen der Geschlechtsentwicklung. In: Hiort O, Danne T, Wabitsch M (Hrsg). Pädiatrische Endokrinologie und Diabetologie. 64 Tabellen Berlin, Heidelberg, New York, NY: Springer 2010: 391-409
further literature is available from the authors of the text

18 Newborn Hearing Screening 2012

Introduction

A general newborn hearing screening belongs to the recommended early detection examinations after the birth of a child since 01-01-2009. Aim of the newborn hearing screening 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).

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))
- for children at risk AABR examination is mandatory
- 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 at 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 Monitoring of Congenital Malformations 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
- 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

* Joint Committee on Infant Hearing (JCIH): Year 2007 Position Statement: Principles and Guidelines for Early Hearing Detection and Intervention Programs. Pediatrics. 120. 898-921 (2007) DOI: 10.1542/peds.2007-2333

Participating Institutions

In 2012, 27 maternity units existed in Saxony-Anhalt. In all these units, a newborn hearing screening is offered already for several years by TEOAE or AABR. Again, all 27 maternity units participated 2012 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-Anhalt.

The screening ID, which has to be assigned to each infant as condition to participate in the hearing screening tracking 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 units and the number of births with a screening ID.

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

Maternity units	Tracking period 2012	Births in this period*
Ameos Klinikum Aschersleben	01-01 to 31-12-2012	523
Ameos Klinikum Bernburg	01-01 to 31-12-2012	242
Gesundheitszentrum Bitterfeld/Wolfen gGmbH	01-01 to 31-12-2012	424
Krankenhaus Jerichower Land GmbH Burg	01-01 to 31-12-2012	381
Städtisches Klinikum Dessau	01-01 to 31-12-2012	805
Altmark-Klinikum gGmbH Krankenhaus Gardelegen	01-01 to 31-12-2012	343
Ameos Klinikum St. Salvator Halberstadt	01-01 to 31-12-2012	569
Sana Ohre-Klinikum GmbH Haldensleben	01-01 to 31-12-2012	258
Krankenhaus St. Elisabeth und St. Barbara Halle	01-01 to 31-12-2012	1,804
Universitätsklinikum Halle (Saale)	01-01 to 31-12-2012	1,117
Krankenhaus Köthen GmbH	01-01 to 31-12-2012	381
Klinik St. Marienstift Magdeburg	01-01 to 31-12-2012	841
Klinikum Magdeburg gGmbH	01-01 to 31-12-2012	1,186
Universitätsklinikum Magdeburg A.ö.R.	01-01 to 31-12-2012	1,262
Carl-von-Basedow-Klinikum Saalekreis GmbH Merseburg	01-01 to 31-12-2012	639
Saale-Unstrut Klinikum Naumburg	01-01 to 31-12-2012	332
Bördekrankenhaus GmbH Neindorf	01-01 to 31-12-2012	186
Harzklinikum Dorothea Christiane Erxleben GmbH Quedlinburg	01-01 to 31-12-2012	544
Altmark-Klinikum gGmbH Krankenhaus Salzwedel	01-01 to 31-12-2012	372
Helios Klinik Sangerhausen	01-01 to 31-12-2012	795
Ameos Klinikum Schönebeck	01-01 to 31-12-2012	509
Johanniter-Krankenhaus Genthin-Stendal gGmbH	01-01 to 31-12-2012	785
Asklepios Klinik Weißenfels	01-01 to 31-12-2012	494
Harz-Klinikum Wernigerode-Blankenburg GmbH	01-01 to 31-12-2012	636
Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg	01-01 to 31-12-2012	530
Georgius-Agricola Klinikum Zeitz	01-01 to 31-12-2012	371
Krankenhaus Anhalt-Zerbst gGmbH	01-01 to 31-12-2012	216
Total number of births* in Saxony-Anhalt		**16,545**

Home births / Births in a birthing centre resp. infants not born in Saxony-Anhalt	01-01 to 31-12-2012	**150**

Tracked infants, in total	**16,695**

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

In total, 16,545 births received a screening ID in a maternity department in Saxony-Anhalt in 2012.
Therefore, these infants participated in the hearing screening tracking.

Furthermore, 150 data records of infants which were home births or born in a birthing centre are included in the analyses. These infants received also a screening ID after birth, e.g. by the 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 unit and forward 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 108 senders in 2012.

The following table shows how much newborns received a screening ID per month and how many results were forwarded to the Monitoring of Congenital Malformations per month. Averagely, 1,750 results were registered per month, however in some cases we received multiple reportings for one child (e.g. from the maternity department, paediatric department, ENT department, ENT physician, paediatrist and from the parents).

Births with screening-ID and number of incoming result

2012	Infants with screening ID	Number of reportings
January	1,359	1,704
February	1,306	1,624
March	1,303	1,730
April	1,292	1,636
May	1,394	1,841
June	1,353	1,700
July	1,561	1,926
August	1,565	1,841
September	1,486	1,876
October	1,426	1,764
November	1,299	1,670
December	1,351	1,698
total	**16,695**	**21,010**

To carry out the tracking thoroughly, 2,736 letters resp. faxes were forwarded in 2012 (one up to nine letters per infant). With reference to all infants with screening ID this corresponds to an average of 0.16 letters per infant.

Additionally, the parents and attending physicians of the infants born in 2012 were contacted by telephone. In total 312 calls were made in connection with the hearing screening tracking (one up to five calls per infant).

Results (date July 2013)

All results of infants born in 2012, that were reported to the hearing screening tracking centre are included in the analyses 2012 of the newborn hearing screening:

14,128 infants out of 16,695 infants with screening ID had an unsuspicious newborn hearing screening.
In 2,567 cases the first hearing test had to be followed-up, resp. no newborn hearing screening took place in the maternity department (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 unit, transfer of the child to another unit or a defective hearing screening device.

The follow-up examination of the 2,567 infants showed in 2,009 cases an unsuspicious result. The remaining 558 infants had again a suspicious result.
124 of these 558 infants received a complete paediatric audiological confirmation diagnostics.
According to our knowledge, 168 infants did not receive a confirmation diagnostics and therefore are considered as lost to follow-up.

227 infants did not participate in the screening (no reaction of parents to reminder letters or refusal of examination) and in 10 cases the status is still pending, i.e. the examinations were not finished in August 2012 or the tracking process still requires more time.
In 29 cases the tracking was closed from our side without any result.

In total, the follow up-examinations of 144 infants who were born in 2012 could be completed (confirmations diagnostics). Among 124 infants with a suspicious result, 20 infants had an unsuspicious first screening. These infants possibly received a follow-up-examination due to present risk factors. Within the follow-up examination, a hearing disorder could be excluded in 96 cases, in 48 infants a unilateral/bilateral hearing disorder was diagnosed and the corresponding therapy was initiated. For instance, 27 infants received a hearing aid (20 times hearing aid bilateral, 10 times hearing aid unilateral).

19 Annual Report 2012 of the Newborn Screening Centre Saxony-Anhalt

according to §14 Note 2 of the valid Children Directive

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Competence net newborn-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 treatable types of these diseases. The details of the newborn screening (NS) are stipulated in the enclosures 2-4 of the Directives about the early detection of diseases at children up to their 6th year of life ("Children's directive").

The German Society of newborn screening (DGNS) compiles annually in cooperation with the German screening laboratories the national screening report. The screening data is analysed on the basis of several quality criteria for realisation of NS 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 are presented.

Screening samples from the single Federal States are divided to the laboratories as it is presented in figure 1. It shows that the screening laboratory completely handles all screening samples from Saxony-Anhalt.
Our laboratory works in due consideration of the diseases mentioned in the Directive. Table 1 shows these diseases with their corresponding frequency of appearance in Germany.

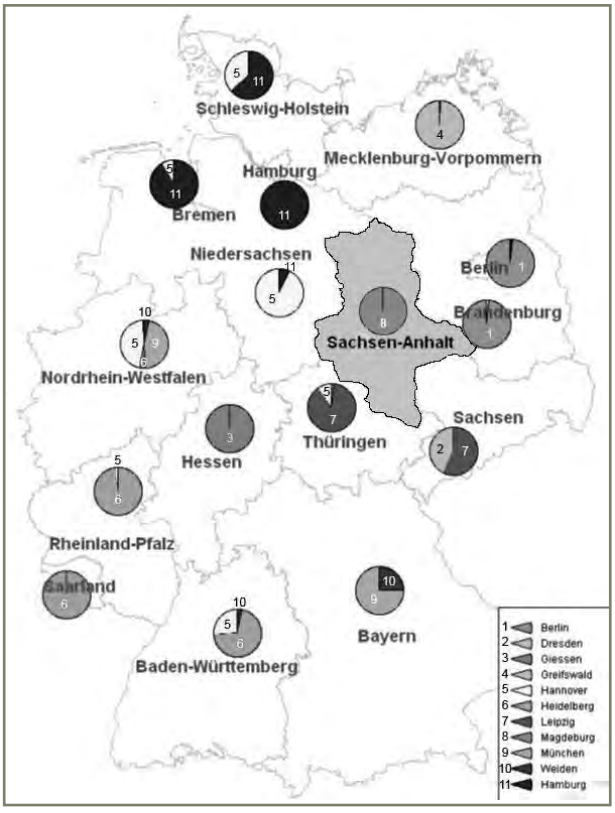

Fig. 1: Screening centres in Germany

Tab. 1: Frequency of diseases in Germany that are detected in the screening

Disease	Prevalence
Hypothyroidism	1 : 3,275
Congenital adrenal hypoplasia (CAH)	1 : 17,383
Biotinidase deficiency (incl. partial defects)	1 : 24,212
Galactosemia (classical)	1 : 112,991
Phenylketonuria (PKU)/ hyperphenylalaninemia (HPA)// cofactor deficiency	1 : 5,022
Maple syrup urine disease (MSUD)	1 : 112,991
Medium-Chain-Acyl-CoA-Dehydrogenase deficiency (MCAD)	1 : 10,761
Long-Chain 3-OH-Acyl-CoA-dehydrogenase deficiency (LCHAD)	1 : 135,589
(Very-)Long-Chain-Acyl-CoA-Dehydrogenase deficiency (VLCAD)	1 : 56,496
Carnitin-Palmitoyl-CoA-Transferase I deficiency (CPTI)	1 : 338,974
Carnitin-Palmitoyl-CoA-Transferase II deficiency (CPTII)	no information
Carnitin-Acylcarnitin-Translocase deficiency (CACT)	no information
Glutaric aciduria type I (GA I)	1 : 225,982
Isovaleric acidaemia (IVA)	1 : 56,496
total	**1 : 1,309**

Screening data of Saxony-Anhalt is outlined in the following:

Process quality

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

- complete coverage of population
  - coverage method and rate
  - blank card systems
- completeness of control (recall)- and following 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 (here only in the preanalytic and laboratory field: age at time of blood taking, time between blood taking, arriving at laboratory and result transmission)
- individual screening values of newborns, which have to be examined further on
- confirmation diagnostics
  - diagnostics type
  - diagnostics period of time
- final diagnosis
- start of therapy

Registration Rates

To assure that a screening is offered to every newborn, a tracking for completeness is necessary. This is done for children which are delivered in obstetric units by control of the consecutively numbers in the register of births and by means of a so called blank card system. According to the Childrens Directive the obstetric units have to document on a blank test card the total refusal of screening, the refusal of an early taking within the screening, the transfer to specialised institutions or death of the newborn. The test card has to be send to the laboratory, however the success of this method differs between the single Federal States.

We collected the following registration rates in Saxony-Anhalt in 2012:
According to the Federal Statistical Office 16,888 children were live births in Saxony-Anhalt (according to the residence of the mother).

Tab. 2: Registration rates of first tests

	Number	Difference/sum
first screening in Magdeburg	16,663	
not resident in Saxony-Anhalt	720	15,943
Screening refused by parents resp. probably not shown up for U2, no response	8	15,951

The discrepancy between the number of live births and screened infants amounts to 937.

Data of the Federal Statistical Office are based on the data of the Statistical Office of Saxony-Anhalt. All births (sorted according to maternal residence) that are reported by the materny units to the register office form the corresponding basis. However, the number of mothers with residence in Saxony-Anhalt who delivered their infants in another Federal State is not recorded in our screening statistics when the screening of the infant took also place in another Federal State.
We assume that newborns were screened in other Federal States, although they were born in Saxony-Anhalt and their mothers were resident in Saxony-Anhalt as well. We do not have further information about these cases.

Blank cards	Number
Received in total	331
Infant deceased / stillbirth	6 / 37
Refusal of early taking	238
Transfer to another clinic	50

Tab. 3: Registration rates by blank cards

No blood sample out of 79 blank cards (without descended infants) arrived at our laboratory. One reason among others is that the screening was done in another Federal State. The control of second examinations showed the following result:

Tab. 4: Completeness of control (recall) and following examinations

Second screening due to	suspicios first screening	early taking < 36h	preterm births < 32 WOG
requested	66	362	159
arrived at our own laboratory	63	347	155
deceased before control examination	1	1	4
arrived at other laboratory	2	6	

WOG = weeks of gestation

Examination Numbers, Recall Rates and Assured Cases

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

In total, 143 recalls had to be done in 2012.

Tab. 5: Samples, assured cases, recall-rate 2012, incidence 1992-2012

	First test	Second test*	Recall rate** 2012	Assured Cases	Incidence in Saxony-Anhalt 1992-2012
TSH	16,663	565	0.08 %	4	1/3,740
PHE***	16,663	565	0.02 %	3	1/5,489
GALT	16,663	565	0.01 %	-	1/170,168
BIO	16,663	565	0.00 %	-	1/223,000
17OHP	16,663	565	0.22 %	4	1/18,447##
AC, AS (TMS)	16,663	565	0.01 %	1 x MCAD#	1/14,539###

* Second transmissions, which were necessary because of an early blood withdrawal at term infant < 36 h or preterm infant < 32 weeks of gestation resp. positive first result (recall)
** Definition of recall: demand of a new blood sample because of a suspicious screenig result, when the first test took place at an age of > 36 h at term infant or >32 weeks of gestation at preterm infant
*** Phe = phenylalanine: parameter for the identification of a phenylketonuria and hyperphenylalaninemia
# MCAD: disorder in metabolizing medium-chain fatty acids
Screening of congenital adrenal hyperplasia syndrome (since 1997 in Saxon-Anhalt)
Enlarged screening (TMS) since May 2001 in Saxony-Anhalt

Process Times

Point of Taking Blood Samples

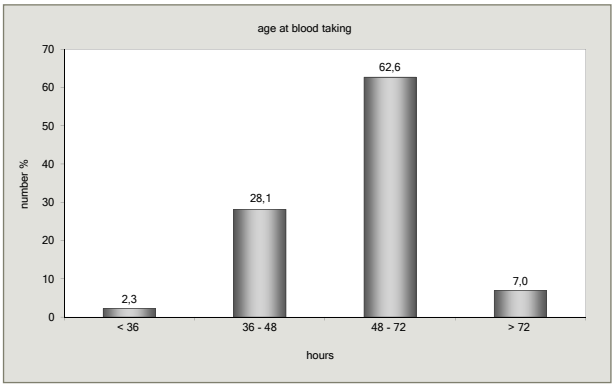

Fig. 2: Age at point of blood taking for first screening

The optimal point of taking blood samples for the newborn screening (36 –72 hours of life) took place within the required period of time at 90.7% of all cases (2011: 90.7%). At a total number of 9.3% the taking of blood samples took not place within the required period of time (2011: 9.3%). The data of 2012 remained on a same level as in the previous year.

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

Transmission Time

Figure 3 shows that 39.4% of all transmittals reached the laboratory more than two days after the blood taking (2011: 37.1%).

Problems with the transmission of blood samples occurred also in 2012.
The Children Directive requires a transmission of the pathological result by the laboratory back to the sender by no later than 72 hours after blood taking. The limiting factor is here the time from blood taking up to the receipt of the blood sample (delivery time). In this connection we want to point out again that the Children Directive requires a transmission of each blood sample at the day of taking.

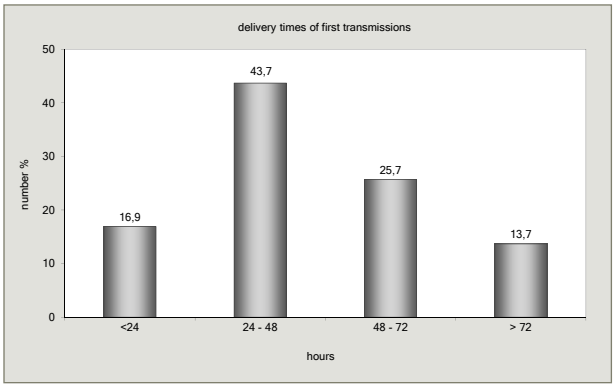

Fig. 3: Delivery time of transmittals

Transmission of Results

Figure 4 shows how much time the diagnostics of first examinations in the laboratory takes. Results which are finished after more than 36 hours are caused by internal repetitions. 2.8% of the results which were finished after more than 48 hours are the consequence of disturbances in the laboratory (maintenance of devices).

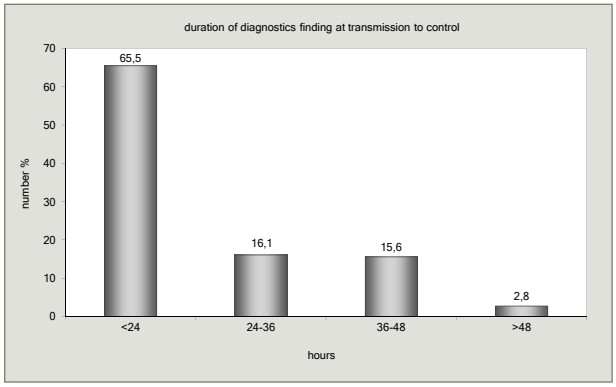

Fig. 4: Diagnostics time (date of result - date of arrival)

The result of first screenings which is shown by figure 4 reflects unfortunately also the diagnostics time of pathological results (in total 143) (figure 5).

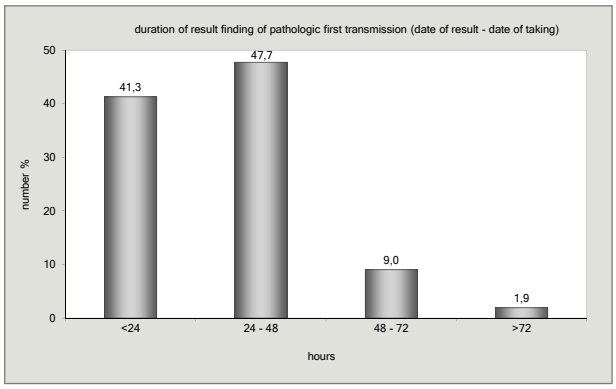

Fig. 5: Diagnostics time of pathological results

The following figure shows the time from oral transmission of 143 pathological results up to the arrival of a control sample. Generally, pathological results are transmitted orally and faxed as partial result after they were confirmed internally by the laboratory. All these activities are documented.
16 cases had a response time of more than 120 hours and concerned premature infants. In these cases, the taking of the sample to control was postponed to a gestational age of 32 weeks (timely second blood taking). As these infants are in custody of a hospital there is no risk implied in this procedure when the first result was discussed with the responsible physician.

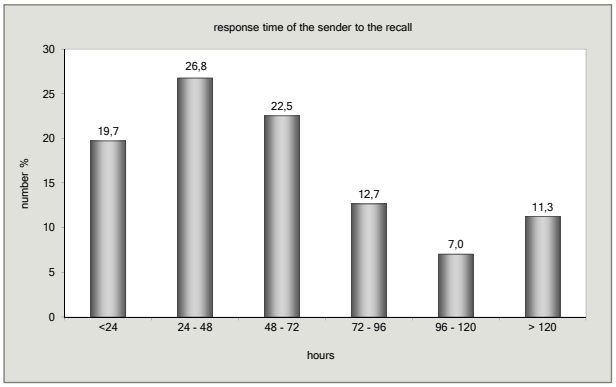

Fig. 6: Response time of sender to recall

12 suspicious screening cases were confirmed by confirmation diagnostics. These cases concerned four children with a hypothyreosis, three children with a phenylketonuria/hyperphenylalaninemia (PKU/HPA), one infant with a disorder in metabolising middle-chain fatty acids (MCAD) and four infants with congenital adrenal hyperplasia.

Therapy Starting at Patients with Positive Screening

Ten patients needed a therapy.

Tab. 6: Diagnosis, confirmation diagnostics and therapy starting

Diagnosis	Confirmation diagnostics	Age at start of therapy
4 x Hypothyroidism	Serum-TSH, T4, sonography	6-30 days
1 x Phenylketonuria	Serum-Phe, BH4-test	8 days
4 x Congenital adrenal hypoplasia	analysis of multiple steriods in dried blood or serum	2-5 days
1 x LCHAD deficiency	mutation analytics	7 days

Two infants with a HPA did not need a therapy.

Summary

In 2012 no changes took place in the specifications of the Federal Joint Committee of physicians and health insurances (G-BA).
Thereby, the Gene Diagnostics Act still is and remains the superordinated act with its own paragraphs of penalty.

The process quality was not improved in 2012 as our screening laboratory already has an optimal quality level in comparison to other German screening laboratories.

As usual, all patients with a positive first screening result were followed up and their diagnosis was assured resp. excluded.
Also the confirmation of a positive screening result (confirmation diagnostics) by the attending medical institution and the start of a therapy was documented in all cases.

We calculated an incidence of 1 : 1388 for all objective diseases of the newborn screening in Saxony-Anhalt in 2012.

For further information about the metabolic screening centre Magdeburg we kindly invite you to visit our website:

www.stoffwechselzentrum-magdeburg.de

We would like to inform senders, parents and interested people here about the Newborn Screening and the Newborn Hearing Screening and provide downloads. We update our website on a regular basis.

The national screening report of the DGNS is available on their own website two years after the concerned period of time.