Annual Report 2021

Malformation Monitoring Centre Saxony-Anhalt

OTTO VON GUERICKE UNIVERSITÄT MAGDEBURG

SACHSEN-ANHALT
Ministerium für Arbeit, Soziales, Gesundheit und Gleichstellung

Annual Report 2021
of the Federal State of Saxony-Anhalt
about the frequency of cengenital malformations
and anomalies as well as genetically cause dieseases

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Introduction

Dear reader,

it's a miracle and a joy every time parents finally hold their newborn in their arms. For
mothers and fathers, a new phase of life begins with a great deal of joy, but also effort, with excitement and uncertainty paired with the concern about the well-being of their child. This is where the support of experienced midwives, pediatric nurses and doctors can help. They stand aside to offer advice and support to young parents, even before birth.

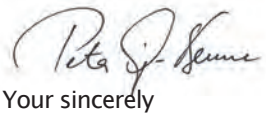
But not all children are born healthy. Affected infants and their parents face completely different challenges. Science shows us that approximately 4% of newborns are affected by a relevant malformation. Thereby „cardiac malformations" are the most common organ malformation in humans, up to 1% of newborns are affected. However, not every case presents a „severe" cardiac malformation. The spectrum ranges from a small hole in the ventricular septum (VSD, ventricular septal defect), which may close on its own during the growth of the child, to complex cardiac anomalies that can cause a serious threat to life without early detection and treatment. Increasingly, these treatments can be carried out via minimally invasive cardiac catheterization. Nearly 70% of all cardiac catheterizations in infants are therapeutic and complement or replace surgical intervention. Thanks to these good medical-technical possibilities, approximately 90% of infants with cardiac malformations reach adulthood.

Some cardiac malformations can also be detected prenatally by ultrasound screening. Therefore it is necessary to include all pregnancy outcomes in a valid evaluation of malformations. In this context, a malformation registry provides the epidemiological basis for the spatial and temporal analysis of congenital malformations. The malformation monitoring Saxony-Anhalt is an integral part of the health reporting system in our Federal State with its population-based malformation registration. The continuation of this interdisciplinary cooperation is only possible with the dedicated collaboration of all senders from the different outpatient and inpatient medical facilities.

According to data of the Federal Statistical Office, a total of 16,024 live births were counted in Saxony-Anhalt in 2021 (in 2020, the figure was 16,113). Nationwide there were 795,492 live births (in 2020, there were were 773,144). Compared to the previous year, the number of births rose by around 2.9% to the highest level since 1997 in Germany.

Nationally and internationally, the COVID 19 pandemic has presented us with new challenges. In the third year of the pandemic, the relevant scientific knowledge regarding SARS-CoV-2 infection during pregnancy, childbirth, and lactation is summarized in the guideline of the Association of the Scientific Medical Societies (AWMF) to improve patient care and to provide guidance to the medical staff.

I would like to thank all those who dedicate their professional or private lives to support children and their families who are affected by malformations.



Your sincerely

Petra Grimm-Benne

Federal Minister of Labor, Social Affairs, Health and Integration of the State of

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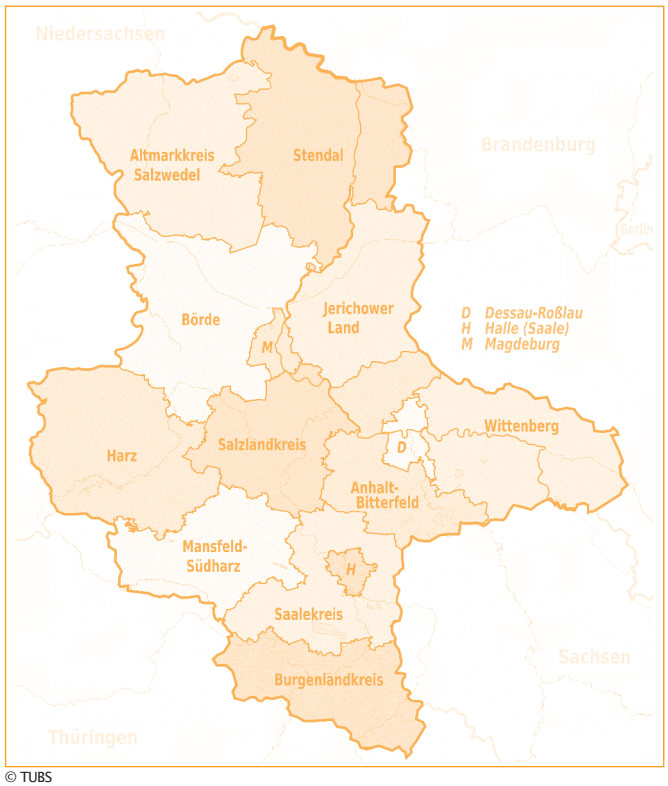
Abbreviations

AABR	automated auditory brainstem response (Hirnstammaudiometrie)
ASD	atrial septal defect
AVSD	Atrioventricular septal defect
ATC	Anatomical-Therapeutic-Chemical classification
AV-Block	atrioventricular block (= cardiac block)
blt	bilateral
BMI	Body-Mass-Index
BP	basis prevalence
cCMV	connatal cytomegalovirus infection
CHD	congenital heart defect
CI	confidence interval
CNS	central nervous system
dB	Dezibel
DIV	double inlet ventricle
DORV	double outlet right ventricle
DUP	dilated uropathy
EUROCAT	European Surveillance of Congenital Anomalies
ENT	ears, nose, throat
FAS	fetal alcohol syndrome
FASD	fetal alcohol spectrum disorder
G-BA	Federal Joint Committee
HLHS	hypoplastic left heart syndrome / left heart hypoplasia syndrome
ICBDSR	ICBDSR International Clearinghouse for Birth Defects Surveillance and Research
ICSI	intracytoplasmic sperm injection
IUGR	intrauterine growth restriction
LB	live births
MCA	multiple congenital anomalies
NHS	newborn hearing screening
NIPT	non-invasive prenatal test (cell-free DNA analysis)
NT	nuchal translucency
n. (o.) s.	not otherwise specified
OR	odds ratio
P	prevalence
PDA	persistent ductus arteriosus
PFO	persistent foramen ovale
SA	spontaneous abortion
SB	stillbirths
SD	Standardabweichung
TGV	transpositions of great vessels
TEOAE	transistoric evoked otoacoustic emissions
TOP	termination of pregnancy
UTS	urinary tract system
VSD	ventricular septal defect

1 Births and fetuses 2021 in the registration region

District/ major cities	Live births*	Stillbirths	Live births and stillbirths in total	*Spontaneous abortions (> 16 WOG)**	*Terminations of pregnancy**
Altmarkkreis Salzwedel	571	-	571	-	*3*
Anhalt-Bitterfeld	1,056	6	1,062	*1*	*1*
Börde	1,261	8	1,269	*1*	*7*
Burgenlandkreis	1,268	2	1,270	-	*1*
Dessau-Roßlau	536	1	537	-	-
Halle	2,137	15	2,152	*2*	*9*
Harz	1,434	8	1,442	*3*	*7*
Jerichower Land	622	6	628	-	*3*
Magdeburg	2,100	3	2,103	*12*	*10*
Mansfeld-Südharz	831	5	836	-	-
Saalekreis	1,305	7	1,312	-	*4*
Salzlandkreis	1,276	4	1,280	*3*	*9*
Stendal	777	5	782	*2*	*3*
Wittenberg	850	2	852	-	*1*
County in Saxony-Anhalt n.d.	-	-	-	*2*	-
Saxony-Anhalt	**16,024**	**72**	**16,096**	*26*	*58*

* Source: © Statistical Office Saxony-Anhalt, Halle (Saale), 2022
\# Data of the Monitoring of malformation registration Saxony-Anhalt



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https://de.wikipedia.org/wiki/Datei:Saxony-Anhalt,_administrative_divisions_-_de_-_colored.svg#filelinks

2 Participating institutioms of the region 2021

2.1 Maternity units / paediatric units / paediatric surgery / paediatric cardiology (ordered by location)

- AMEOS Klinikum Aschersleben
- Helios Klinik Jerichower Land Burg
- Städtisches Klinikum Dessau
- Altmark-Klinikum Krankenhaus Gardelegen
- AMEOS Klinikum Halberstadt
- Krankenhaus St. Elisabeth und St. Barbara Halle (Saale)
- Universitätsklinikum Halle (Saale)
- Helios Klinik Köthen
- Herzzentrum Leipzig - Universitätsklinik für Kinderkardiologie *(outside of Saxony-Anhalt)*
- Klinikum Magdeburg
- Krankenhaus St. Marienstift Magdeburg
- Universitätsklinikum Magdeburg A.ö.R.
- Carl-von-Basedow-Klinikum Saalekreis Merseburg
- SRH Klinikum Naumburg
- Harzklinikum Dorothea Christiane Erxleben Klinikum Quedlinburg
- Altmark-Klinikum Krankenhaus Salzwedel
- Helios Klinik Sangerhausen
- AMEOS Klinikum Schönebeck
- Johanniter-Krankenhaus Stendal
- Harzklinikum Dorothea Christiane Erxleben Klinikum Wernigerode
- Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg
- SRH Klinikum Zeitz

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

- Dipl. Heilpädagogin Schlote, Glindenberg/Magdeburg
- Dr. Perlitz, Fachärztin für Frauenheilkunde und Geburtshilfe, Haldensleben
- Krankenhaus St. Elisabeth und St. Barbara Halle, Pränatale Ultraschalldiagnostik: CA Dr. Seeger, OÄ Dr. Radusch
- Zentrum für Pränatale Medizin Halle: S. Rißе, N. Manthey
- Dr. Ababei, Fachärztin für Humangenetik, Magdeburg
- Dr. Blaschke, Fachärztin für Kinder- und Jugendmedizin, Magdeburg
- Dr. Jaekel, Fachärztin für Kinderchirurgie, Magdeburg
- Dr. Karstedt, Facharzt für Kinder- und Jugendmedizin, Kinderkardiologie, Magdeburg
- Dr. Karsten, Facharzt für Frauenheilkunde und Geburtshilfe, Magdeburg
- Klinikum Magdeburg, Pränatale Ultraschalldiagnostik: OÄ Dr. Schleef
- Universitätsklinkum Magdeburg A.ö.R., Institut für Humangenetik
- Universitätsklinkum Magdeburg A.ö.R., Universitätsfrauenklinik, Pränatale Ultraschalldiagnostik: OÄ Dr. Gerloff
- Universitätsklinkum Magdeburg A.ö.R., Institut für Klinische Chemie, Screeninglabor
- Trackingstelle Neugeborenen-Hörscreening Sachsen-Anhalt, Magdeburg
- Dr. Welger, Fachärztin für Frauenheilkunde und Geburtshilfe, Magdeburg
- Dipl.-Med. Fiedler und Giesecke, Fachärzte für Orthopädie, Merseburg
- Altmark-Klinikum Krankenhaus Salzwedel, Pränatale Ultraschalldiagnostik: CA Dr. Müller
- Dr. Achtzehn, Dr. Adams, Fachärzte für Kinder- und Jugendmedizin, Wanzleben
- Harzklinikum Dorothea Christiane Erxleben Klinikum Wernigerode, Pränatale Ultraschalldiagnostik: OÄ Dr. Schulze

2.3 Pathological-anatomical institutes (ordered by location)

- Institut für Pathologie Dr. Taege, Dr. Bilkenroth, Dr. Irmscher, Eisleben
- Klinikum Magdeburg, Institut für Pathologie
- Universitätsklinikum Magdeburg A.ö.R., Institut für Pathologie
- Harzklinikum Dorothea Christiane Erxleben Klinikum Quedlinburg, Institut für Pathologie
- Praxis für Pathologie PD Dr. Schultz, Dr. Lüders, Dr. Hainz, Stendal

3 Malformation registration in Saxony-Anhalt 2021

3.1 General informations

Our thanks for the continued interdisciplinary cooperation to you as sender should be placed again at the beginning of the current annual report (data evaluation birth cohort 2021).
Congenital malformations are structural or functional malformations or defects of the body that are present at the time of birth. The term „congenital" refers to the existence of the defect before or at birth. Although the malformations/diseases are congenital, the time of diagnosis for the individual malformation can be quite different. This may be prenatally, at the time of birth, during infancy or childhood (e.g., hearing impairment without newborn hearing screening) or only post-mortem. The majority of congenital malformations belongs to the group of rare diseases.
This prospective epidemiological data analysis about congenital malformations is part of the health reporting of the Federal State of Saxony-Anhalt. This would not be possible without the continuous support of the Ministry of Labor, Social Affairs, Health and Integration of the Federal State of Saxony-Anhalt. Special thanks are extended to the head of department Mrs. K. Müller. We would like to thank for the continuous good cooperation with Department 23, in particular with Dr. med. Henze and Mr. M. Schiener.

Even in the third year of the SARS-CoV-2 pandemic, we were able to continue the population-based malformation registration in Saxony-Anhalt, despite any special challenges. Under the continuing conditions of the pandemic, the focus still lies on possible teratogenic effects. The data analysis of the European network EUROCAT still does not provide any indication of this either. EUROCAT can draw on data from 38 active malformation registries of 18 European countries. Thus, 1.7 million births (29% of the European birth population) are evaluated in this way with regard to congenital malformations (https://eu-rd-platform.jrc.ec.europa.eu/eurocat). Also the WHO associated network organization International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR), a consortium of 42 malformation registries of 38 countries around the world (www.icbdsr.com), did not figure out any evidence of teratogenic effects of primary SARS-CoV-2 infection.

As a special topic in the current annual report we analysed „congenital cardiac malformations" as the most common organ malformation in newborns in Europe. The health political importance of congenital malformations and the benefits of good health care can be detected by the example of congenital cardiac defects.

We would also like to thank the Medical Faculty of the Otto-von-Guericke-University Magdeburg for the continuously cooperation in regard to the project „ monitoring of congenital malformations". In particular, we would like to thank the dean Prof. Dr. rer. nat. D. C. Dieterich for her support. We are pleased that the support of the Medical Director Prof. Dr. med. H.-J. Heinze and the Commercial Directorate, currently represented by Mr. M. Bohn, continued so productively.

3.2 Registration and analysis

Our present annual report contains data about children/fetuses with congenital malformations and chromosomal disorders of the Federal State of Saxony-Anhalt, whereby we refer to the place of residence of the mother during pregnancy respecively at the time of birth.

Basis of the annual prevalence calculations forms the total number of births, i.e. live and stillbirths, in Saxony-Anhalt. The prevalence of congenital malformations and anomalies as well as genetically caused diseases includes: live births, stillbirths, terminations of pregnancy (of all WOG) as well as spontaneous abortions from the 16th WOG.

The expected date of delivery is used as basis for analysing the termination of pregnancy, e.g. 2021 is considered the year of birth although some terminations of pregnancy after prenatal diagnostics took place at the end of 2020. 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. Data about live births and stillbirths is provided annually in mid-year by the Statistical Office in Halle for the previous year. The percentages and prevalences shown are rounded values.

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

The total number of infants with major malformations as well as the geographical distribution of appearance in the big cities and districts is outlined in chapter 6 and 7. Infants with only minor malformations or rather norm variations are not evaluated separately since this data is only collected incompletely in the end and not target of permanent observation.

Chapter 9 outlines the most frequent single diagnoses of major malformations registered from 2009 to 2021.
Similar to the previous years, we analysed the reported pathological prenatal screening results separately in Chapter 8.
Chapter 10 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 2021 in comparison to the last 12 years (2009-2020). Here, a total number of 206,371 births forms basis for the basis prevalence calculation 2009 to 2020.

The graphical presentation of the annual prevalences allows to identify frequent appearances and gives a good overview about rarely appearing indicator births defects. The exact calculation of confidence levels is based on the binominal distribution with a confidence probability of 95%. To discover a certain trend, the percentage change of an indicator malformation prevalence is presented as well for the whole publishing time of the Annual Report (Chapter 10.38).

Data regarding genetically caused diseases, chromosomal disorders, sequences, associations, complexes and embryopathies is outlined in chapter 11. Chapter 12 contains an analysis of malformation caused terminations of pregnancy. As usual, the Newborn hearing screening forms part of the Report of the Monitoring of Congenital Malformations Saxony-Anhalt and is outlined in chapter 16.
Chapter 17 presents the Annual Report of the department of newborn screening in Saxony-Anhalt with data regarding congenital metabolic disorders and endocrinopathies.

3.3 Data quality and completeness/reporting procedure

The malformation monitoring receives information about newborns and fetuses from the maternity and pediatric clinics and from colleagues of pre and postnatal diagnostics (chapter 4.2). These are evaluated, coded and entered into the database of the malformation monitoring, which forms a fundamental prerequisite for scientific projects and evaluations of malformations and also for the compilation of our annual reports. For the 2021 birth cohort, 1,733 records were newly recorded, corresponding to about 10.7% of all children and fetuses of Saxony-Anhalt. Since the last annual report was published, the number of children/fetuses reported has risen from 1,822 to 1,852 due to subsequent reports for 2020.

The malformation monitoring received 1982 reports for the birth year 2021, including 384 from outpatient facilities. For 11.2% of the children/fetuses, we received information from different facilities. To confirm or reject a suspected malformation or to classify multiple malformations more precisely, this redundancy is essential and very welcome.

In relation to the infants born in a hospital, we received the majority of reportings about children / fetuses from the HELIOS Klinikum Köthen and the AMEOS Klinikum Schönebeck. We would like to express our special thanks for this! Also the Magdeburg University Hospital and St. Marienstift Magdeburg submitted a great amount of data. Three hospitals which are located in Merseburg, Naumburg and Zeitz continue to send data about less than 0.5% of the infants born in the hospital. Expressly positive is the commitment of the outpatient facilities and colleagues from all medical fields. Thanks to all envolved people in the medical practices!

High data quality is achieved through complete information on the reporting sheets and detailed descriptions of diagnoses. They are a precondition for the correct entry of information into the database and have an impact on the quality of statistics. Therefore, complete and correct indication of all entities on the reporting sheet and the detailed description of the diagnoses are important. This year again, the proven cooperation and strength of all senders has resulted in very good data quality. Important data was reported almost complete: Gender at 99.0%, maternal age at 98.6% and district at 99.1% of all cases. Birth weight was not reported 62 times, but of these only 19 were live births. The head circumference, which is relevant for the assessment of a microcephaly, was not given for 32.4% of infants in 2019. These data was missing in only 22.1% of reports in 2021.

We ask all senders to continue to report all malformations, to indicate all accompanying malformations and to describe them as completely as possible. As of birth year 2021, 89 indicator malformations were found prenatally. Twice we did not receive a postnatal report that could be assigned. Since unconfirmed findings are not included in the evaluations, the resulting prevalence of rare malformations might be underestimated.

We receive two thirds of malformation registrations and indications of control cases by means of the „green documentation sheets“, which we provide free of charge to the reporting institutions. Documentation sheets may be ordered at any time by phone +49 391-6714174 or e-mail to monz@med.ovgu.de.
Additionally, it is also possible to report on so-called „white documentation sheets“. This form serves to register a basis data set. The indication of the above-mentioned information and possible risk factors like intake of medication or family histories and an exact description of the malformation and / or corresponding symptoms are important here.
Both documentation sheets are also available for download on our homepage www.angeborene-fehlbildungen.com. It is possible to complete the sheet manually or to enter the data directly into the PDF file, print it out and send it back to us. Mostly, we receive the reports by mail on our documentation form sheets. In many institutions fax reports have become the preferred method of transmission. Our fax number is: +49 391-6714176.
We will be at your disposal for answering any further questions about the reporting

5 Sex Ratio 2021

Sex ratio of all live births and stillbirths of Saxony-Anhalt according to the information of the Statistical Office, Saxony-Anhalt, Halle (Saale)

male	8,341 live births and stillbirths
female	7,755 live births and stillbirths
total	16,096 live births and stillbirths

Sex ratio m : f = 1.08

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

Male	334 births
Female	242 births
Unknown	12 births
Total	588 births

Sex ratio m : f = 1.38

Sex ratio of all births with only minor malformations and anomalies

Male	124 birth
Female	124 birth
Unknown	1 birth
Total	249 birth

Sex ratio m : f = 1.0

The Statistical Office of Saxony-Anhalt indicated a number of 16,024 live births in 2021. Since 2016, the number of live births in Saxony-Anhalt has been on a monotonously declining trend. In 2021, 72 children were stillborn. The ratio of the number of live births in contrast to the number of stillbirths in 2021 is slightly lower than the ratio of the years 2009-2020 (222.6 : 1 vs. 240.1 : 1).

Like every year, the gender distribution of live births and stillbirths in 2021, shows an androtrophy (m : w = 1.08). The average ratio during the reporting period amounts to m : w = 1.05 (2009-2020) with a maximum value of m : w = 1.09 (2006). Stillbirths showed an average sex ratio during the reporting period of m : w = 1.16 (2009-2020). More girls than boys were stillborn in the last three years. In 2021, the ratio amounts to m : w = 0.95.

Major malformations were diagnosed at 588 children/fetuses in 2021. This figure includes live and stillbirths, terminations of pregnancy and spontaneous abortions after 16 weeks of gestation. The sex ratio of all children/fetuses with major malformations in 2021 is as usual boyish (m : w minimum 1.18; maximum 1,47).

The sex ratio of the 249 children/fetuses who presented in 2021 exclusively minor malformations is balanced. In almost all years before, an andotropism could be noticed, which, however, is not as significantly represented as in the case of the children/fetuses with.

9 Organ system involvement and most frequent single diagnoses in infants and foetuses with major malformations

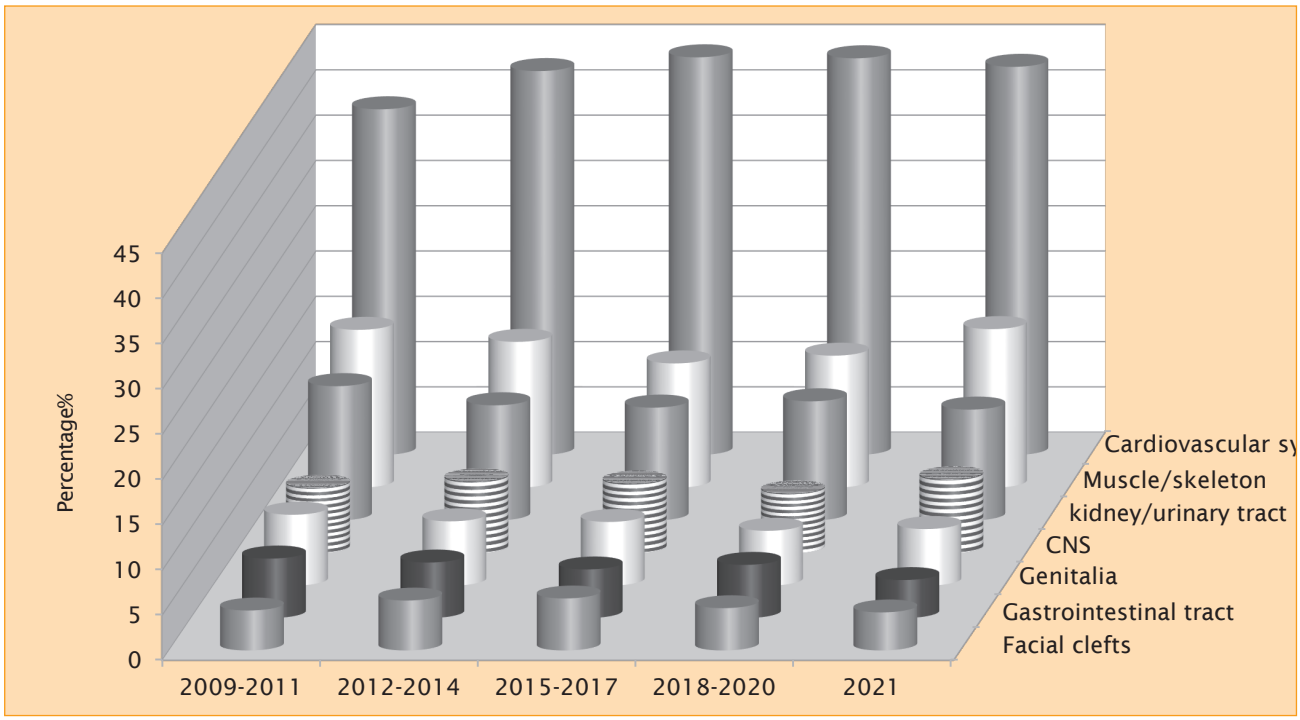


Fig. 5: Organ system involvement in major malformations (grouped)

The diagram above (Fig. 5) shows for seven selected organ systems the proportion of children/fetuses that are affected by a malformation in these organ systems during the reporting period 2009-2021 in Saxony-Anhalt.

508 infants were reported to have a major malformation in 2021 in Saxony-Anhalt. Nearly 60% of these children/ fetuses have an isolated malformation and slightly more than 40% (2021: 238) of them have malformations in multiple organ systems. Infants with multiple malformations are listed several times in the diagram. The timeline is divided from 2009-2020 into four 3-year periods, and 2021 is shown separately.

By far, the most frequently malformed organ system is the cardiovascular system. From 2009-2020 42.7% of the children/fetuses with a major malformation showed a cardiac malformation. The current value (2021: 42.9%) corresponds to the mean value of the previous years.

The musculoskeletal system is the organ system with the second highest incidence of malformations (2009-2020: 15.1% of all children/fetuses with major malformations). A customarily high proportion, as in the first half of the reporting period, was recorded in 2021 at 17.5%. The maximum proportion (19.1%) was recorded in 2010.

The proportion of children/fetuses with malformations of the renal and urinary tract in 2021 is on average at 12.2% (2029-2021: 13.1%). Over the years of the reporting period, the proportion decreases slightly.

A CNS malformation was diagnosed in 8.2% of all children/fetuses with major malformations in 2021. This proportion is high (2009-2020: 7.4% of all children/fetuses with major malformations), however, in 2014 (8.7%), an even higher proportion was observed. Neural tube defects (2009-2020: 8.5 per 10,000 children/ fetuses) and hydrocephalus (2009-2020: 5.7 per 10,000 fetuses) (Chapter 10.1) together account for about half of the CNS malformations (2009-2020: 28.2 per 10,000 children/fetuses).

The proportion of children/fetuses with malformations of the genital system (2021: 6.3%) has fluctuated from a high registered value in 2010 (9.2%) between 5.5% and 9.2% and lies averagely at 7,2% (2000-2020).

The proportion of children/fetuses with malformations of the intestinal tract of all those with major malformations amounts to 4.3% in 2021. This is the lowest proportion, that was registered during the reporting period. Maximum 7.4% (2011) of children/ fetuses with major malformations were affected by malformations of the digestive system. The average value lies at 6,0%.

Facial clefts are mainly divided into cleft palate (about 1/3) and cleft lip and palate (about 2/3). As of birth year 2021 4.3% of the children/fetuses with major malformations were diagnosed with a facial cleft, which is less than the mean value of 2009-2020 (5.3%). For cleft lip and cleft lip and palate, the current prevalence (2021: 7.5 per 10,000 children/fetuses) lies significantly below the basis prevalence (2009-2020: 13.2 per 10,000 children/fetuses) (Chapter 10.1).

Most frequent single diagnosis 2021 (only major malformations)

	ICD-10	diagnosis	children/foetuses 2021		children/foetuses 2009-2020**	
			number	prevalence /10,000*	prevalence /10,000	confidence intervall (CI 95%)
1.	Q21.1	Atrial septal defect (without PFO)	154	95.7	98.9	94.7 - 103.3
2.	Q21.0	Ventricular septal defect	80	49.7	47.2	44.3 - 50.3
3.	Q62.3	Dilated uropathy grade II-IV/ ureterocele	40	24.9	24.9	22.8 - 27.1
4.	Q90.	Down`s syndrome (trisomy 21)	35	21.7	20.5	18.6 - 22.6
5.	H90.	Conductive and sensorineural hearing loss	34	21.1	24.3	22.2 - 26.5
6.	Q66.0	Pes equinovarus congenitus (clubfoot)	28	17.4	13.8	12.2 - 15.5
7.	Q54.	Hypospadias	22	13.7	24.3	22.2 - 26.5
8.	Q69.	Polydactyly (pre- and postaxial)	21	13.0	12.5	11.0 - 14.1
9.	Q65.3-5	Subluxation of the hip joint (unilateral/bilateral/w.o. sidedness)	16	9.9	8.1	7.0 - 9.5
	Q62.2	Congenital megaureter	16	9.9	8.1	7.0 - 9.5
10.	Q63.0	Accessory kidney / duplex kidney	13	8.1	7.9	6.8 - 9.3
	Q62.1	atresia and stenosis of ureter	13	8.1	9.4	8.1 - 10.8
11.	Q35.	Cleft palate	10	6.2	3.9	3.1 - 4.8
12.	Q25.6	Stenosis of pulmonary artery (peripheral pulmonary stenosis)	9	5.6	2.7	2.1 - 3.5
	Q03.	Congenital hydrocephalus (without neural tube defect)	9	5.6	5.7	4.7 - 6.8
13.	Q02.	Microceplalus	8	5.0	3.9	3.1 - 4.9
	Q61.4	renal dysplasia	8	5.0	6.4	5.4 - 7.6
	Q20.3	discordant ventriculoarterial connection (incl. complete TGA)	8	5.0	3.5	2.7 - 4.4
	Q91.4-7	Patau syndrome (trisomy 13)	8	5.0	1.3	0.8 - 1.8
14.	Q37.	Cleft lip with cleft palate	7	4.3	10.4	9.0 - 11.9
	Q25.1	aortic valve stenosis	7	4.3	5.7	4.7 - 6.8
	Q25.0	patent ductus botalli (PDA), hemodynamically effective	7	4.3	10.2	8.9 - 11.7
	Q40.0	Hypoplasia/agenesis of the corpus callosum	7	4.3	5.0	4.1 - 6.1
	Q21.3	tetralogy of Fallot	7	4.3	3.4	2.8 - 4.3
15.	Q91.0-3	Edwards syndrome (trisomy 18)	6	3.7	4.6	3.7 - 5.6
	Q23.0	aortic valve stenosis/ -atresia	6	3.7	2.6	1.9 - 3.4
	Q00.	anencephaly	6	3.7	2.2	1.6 - 2.9
	Q04.2	holoprosencephaly	6	3.7	1.6	1.1 - 2.2

* in reference to 16,096 births
**in reference to 206,371 births

The table above presents the most frequently observed major individual malformations in Saxony-Anhalt. The list is sorted in descending order according to the current prevalence in 2021, with reference to a population of 16,096 births. 206,371 births form the basis for calculation of the basis prevalence (with confidence interval) over the years 2009-2020.

As usual, the first place in the frequency table is occupied by far ahead of all other malformations by atrial septal defect (2021: 95.7 per 10,000 births; 2009-2020: 98.9 per 10,000 births) as the most frequently diagnosed single malformation. Approximately one child/fet out of 100 is affected in Saxony-Anhalt. This is followed about half as often by another cardiac malformation, the ventricular septal defect (2021: 49.7 per 10,000 births; 2009-2020: 47.2 per 10,000 births). In 2021, the prevalence of both cardiac malformations lies within the tolerance range.

Three malformations ranked third to fifth in the years 2009-2020 and can be found also in 2021 on the third to fifth place of the frequency list of individual malformations: dilated uropathy II.-IV. grade/ureterocele (2021: 24.9 per 10,000 births), Down's syndrome (2021: 21.7 per 10,000 births) and congenital hearing disorders (2021: 21.1 per 10,000 births). The prevalence of dilated uropathy II.-IV. grade/ureterocele and the prevalence of the most common chromosomal disorder, Down's syndrome, are found to be 2021 inconspicuously within the normal range. For the first time in 2021, the prevalence of congenital hearing disorders lies, since the start of newborn hearing screening with tracking of congenital hearing impairment (2007), clearly below the lower confidence limit of the basis prevalence in Saxony-Anhalt (2009-2020: 24.3 per 10,000 births).

Although clubfeet were seen more frequently in Saxony-Anhalt in 2021 than expected (2021: 17.4 per 10,000 births; 2009-2020: 13.8 per 10,000 births), they occupy the usual sixth place in the ranking. Over the years, prevalences have fluctuated widely from 6.5 (2013) to 17.9 (2019) per 10,000 births.

For all severities of hypospadias, i.e., from glandular to scrotal form, the prevalence in 2021 is well below the normal level and occupies therefore the seventh place on the frequency list (2021: 13.7 per 10,000 births; 2009-2020: 24.3 per 10,000 births). During the years of the reporting period, the prevalence of all hypospadias was always observed to be above 20.0 per 10,000 births.

As usual on rank eighth and in the upper range of the prevalence 2021 we can find the prevalence of polydactyly (13.0 per 10,000 births). Polydactyly is divided into two forms, which can also occur in combination: postaxial polydactyly (2021: 8.7 per 10,000 births; 2009-2020: 9.3 per 10,000 births) and the rarer indicator malformation preaxial polydactyly (2021: 5.0 per 10,000 births; Chapter 10.27).

Subluxation of the hip joint and megaureter occurred more frequently in 2021 than in the previous year with 9.9 per 10,000 births (2009-2020: 8.1 per 10,000 births each). The maxima during the reporting period for megaureter (2016: 11.0 per 10,000 births) and for subluxation of the hip joint (2010: 17.3 per 10,000 births) were not reached.

On rank ten we can find two malformations of the urinary tract system, the duplex kidney and atresia or stenosis of the ureter. With the same prevalence (2021: 8.1 per 10,000 births), both values were inconspicuously in the range of the confidence interval.
This is followed more frequently than usual by the cleft hard palate (2021: 6.2 per 10,000 births; 2009-2020: 3.9 per 10,000 births). This year's prevalence represents a maximum during the reporting period.

Pulmonary artery stenosis occured also more often than expected in 2021 (2021: 5.6 per 10,000 births), which otherwise would not have been among the top 15 of the frequency list of individual malformations. With the same prevalence in 2021, hydrocephaly presents a value within the confidence interval of the basis prevalence.

A prevalence of 5.0 per 10,000 births and rank 13 resulted for four malformations in 2021. Renal dysplasia was reported less often than usual. More often than usual we registered microcephaly (2009-2020: 3.9 per 10,000 births) and another cardiac malformation, the discordant ventriculoarterial junction (2009-2020: 3.5 per 10,000 births). Extraordinarily often, we registered a Patau syndrome in 2021. For this trisomy, prevalences have been increased during the last years, but in Saxony-Anhalt a prevalence of more than 1.8 per 10,000 births (2019) has never been recorded.

Cleft lip and palate (2021: 4.3 per 10,000 births; 2009-2020: 10.4 per 10,000 births) can be found in 2021 only in 14th place. After two years above normal range, it occurred very rarely in 2021. Since cleft lip and palate, together with cleft lip form the indicator malformation cleft lip and palate (Chapter 10.14), the low prevalence also affects the annual prevalence of the indicator malformation.

An annual prevalence of 4.3 per 10,000 births (2021) was found for three cardiac malformations. Aortic coarctation (chapter 10.13) and hemodynamically effective PDA (2009-2020: 10.2 per 10,000 births) were both diagnosed less frequently than usual. This also applies for tetralogy of Fallot (Chapter 10.10), where the prevalence lies within the lower confidence limit of the basis prevalence. Also for hypoplasia/agenesia of the corpus callosum, the prevalence in 2021 is calculated to be with 4.3 per 10,000 births within the lower tolerance range.

The otherwise second most common trisomy, Edwards syndrome, is found at the usual rate of 3.7 per 10,000 births in 2021. Three further malformations with a calculated prevalence of 3.7 per 10,000 births (2021) that do not appear every year among the top ranks of the frequency list, were reported significantly more frequently than usual this year: aortic valve stenosis/atresia (2009-2020: 2.6 per 10,000 births), anencephaly (2009-2020: 2.2 per 10,000

10 Indicator Defects modified according to the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

10.0 Definitions

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

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

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

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

5. Microcephaly:
is characterized by a too small occipito frontal skull circumference (two standard deviations below the norm, www.intergrowth21.ndog.ox.ac.uk according to Villar et al. Lancet 2014, chapter 10.5), relative to the gestational age- and sex-dependent normal distribution. Exclusive microcephaly associated with a neural tube defect.

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 prenatally or at birth. Not counted when present with a neural tube defect. Exclusive macrocephaly without dilatation of ventricular system, skull of macerated fetus, hydranencephaly, 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. Not counted when present with a neural tube defect.

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/Pentalogy:
a condition characterized by ventricular septal defect, overriding aorta, infundibular pulmonary stenosis, and often right ventricular hypertrophy. Included is Fallot pentalogy, which has an additional ASD.

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

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

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

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

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. In addition, cleft palate is excluded in arhin- or holoprosencephaly.

16. Choanal atresia, bilateral:
congenital obstruction (membraneous or osseous) of the posterior choana or choanae. Excludes choanal stenosis that does not require therapy.

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 multiples areas of the jejunum or ileum. Exclusive duodenal atresia. In cases with an omphalocele or gastroschisis, small intestine atresia/stenosis is excluded.

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

20. Hypospadias:
a congenital malformation characterized by the opening of the urethra on the ventral side of the penis, distally to the sulcus. Inclusive penile, scrotal, and perineal hypospadias. Exclusive ambiguous genitalia (intersex or pseudo hermaphroditism).

21. 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.

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

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

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

25. 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.

26. 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.

27. 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.

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

29. 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.

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

31. 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. Excluded are aplasia or hypoplasia of the abdominal muscles, skin-enclosed umbilical hernia, and the omphalocele.

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

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

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

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

36. Turner syndrome:
Turner syndrome, also known as Ullrich-Turner syndrome or monosomy X, is caused by the partial or complete absence of one of the two X chromosomes in a girl (gonosomal monosomy). A mosaic or a gonosomal abnormality is possible.

37. Klinefelter syndrome/male gonosome abnormalities:

Klinefelter syndrome is caused by two or more X chromosomes in a male phenotype (Karoytype 47,XXY). Anomalies of the gonosomes in a male phenotype also include structural anomalies of the gonosomes or a gonosome mosaic.

Note:

The prevalences we calculated in the following chapters are population-based. The value indicates the number of births with malformations born in a certain population with reference to the total number of births in this population.
Since the birth cohort 2000, the coverage area of the malformation monitoring includes the entire Federal State of Saxony-Anhalt. The prevalence calculations starting with the birth cohort 2000 are based on live and stillbirths of mothers who have their place of residence in Saxony-Anhalt during pregnancy and at the time of birth. Between 1980 and 1993, the coverage area grew to include the former district of Magdeburg. After the district reform in 1993, it comprised 13 (1994/1995), 14 (1996/1997), 15 (1998) and 16 (1999) of 21 districts in Saxony-Anhalt. The calculation of the basic prevalences (2009 to 2020) is based on a total number of 206,371 births.

The analysis of indicator malformations is made in reference to the diagnosis. 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.

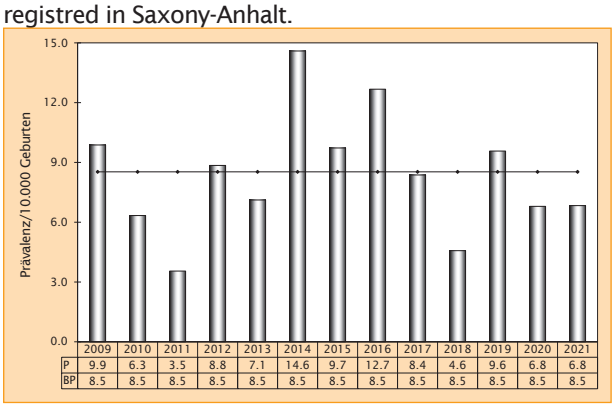
The in chapter 10 indicated comparison prevalences which correspond to the basis prevalences of Saxony-Anhalt are based on data of the years 2009-2020 of the 38 Full-Member-Register of European Surveillance of Congenital Anomalies (EUROCAT) from 18 different European countries. The calculation of the EUROCAT prevalence is based on a total number of 8,581,163 births (source: https://eu-rd-platform.jrc.ec.europa.eu/eurocat/eurocat-

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

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	11	6.83	↘
	Reporting period 2009-2020		
	Basis prevalence / 10,000 births	Confidence interval (CI 95%)	
	8.53	7.32 - 9.88	
EUROCAT (Full members)	Period 2009-2020		
	Prevalence/10,000 births	Confidence interval (CI 95%)	
	10.46	10.24 - 10.68	

With a **prevalence** of **6.8 per 10,000 births** births, neural tube defects were registered slightly below the basis prevalence in 2021 (2009-2020: 8.5 per 10,000 births). The prevalence values at the beginning of the reporting period resemble the current ones. After a very high prevalence 2014 (14.6 per 10,000 births), they decreased again. The change in prevalence over the period of trend analysis (2008-2021) is classified as nonlinear because of the rising values at the beginning of the reporting period and decreasing values in the last years (Chapter 10.38).

Neural tube defects include three types of neural occlusion defects: Anencephaly, spina bifida, and encephalocele, which are considered separately in chapters 10.2 to 10.4. In most cases, the children/fetuses with a neural tube defect are affected by spina bifida (2009-2020: 60.2% of neural tube defects). In 2021, there were six anencephalies, five spina bifidas and no encephalocele registred in Saxony-Anhalt.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	9.9	6.3	3.5	8.8	7.1	14.6	9.7	12.7	8.4	4.6	9.6	6.8	6.8
BP	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5

Fig. 6: Development of prevalence/10,000 births with neural tube defects in Saxony-Anhalt since 2009.

The tolerance range which was determined European wide by EUROCAT of the prevalence of the years 2009-2020 (10.5 per 10,000 births) lies above the confidence interval of the basis prevalence of Saxony-Anhalt. This year's value of the prevalence of Saxony-Anhalt is far below the confidence interval of the overall prevalence of the European registries.

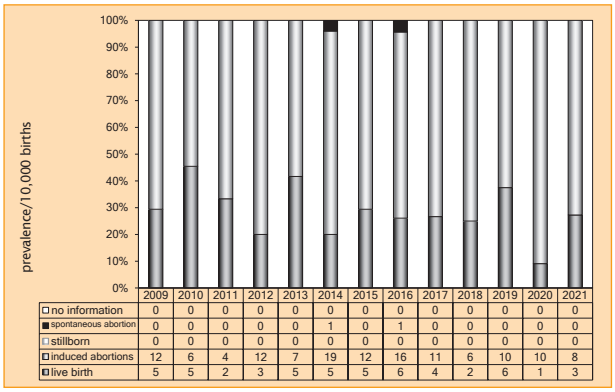
NOTE

After a pregnancy affected by a neural tube defect, increased folic acid prophylaxis according to the recommendations of the medical societies (preparation available in Germany with 5 mg folic acid equivalent per day) should be explained to those who wish to have children. This higher dose is also recommended today for women with antiepileptic medication and chronic absorption disorders.

additional information:

pregnancy outcome	2 x live births 1 x live births deceased after 7 days of life 8 x termination of pregnancy
sex	3 x male 4 x female 4 x no indication
number of isolated malformations/MCA	3 x MCA 8 x isolated

Three children with neural tube defects were live births in 2021. One child with anencephaly died on the first day of life. 8 times the pregnancy was terminated prematurely (2021: 72.7%, 2009-2020: 71.0% of children/fetuses with neural tube defect).



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
no information	0	0	0	0	0	0	0	0	0	0	0	0	0
spontaneous abortion	0	0	0	0	0	1	0	1	0	0	0	0	0
stillborn	0	0	0	0	0	0	0	0	0	0	0	0	0
induced abortions	12	6	4	12	7	19	12	16	11	6	10	10	8
live birth	5	5	2	3	5	5	5	6	4	2	6	1	3

Fig. 7: Pregnancy outcomes of neural tube defects in Saxony-Anhalt since 2009

In 2021, one neural tube defect per 1,463 births was registered in Saxony-Anhalt.

Neural tube defects are probably the most investigated congenital malformation within scientific studies. Already in 1995, several German specialist societies published their recommendation regarding primary prevention of folic acid sensitive neural tube defects. A periconceptional intake of 0.4 mg folic acid was recommended to women at child-bearing age. On the other hand, insufficient realisation of this recommendation is urged by recent studies as in case of unplanned pregnancy (first consultation of gynaecologist not before 5 to 7 WOGs) and by risk groups with low socio-economic status or migrants. An own sample confirmed this insufficient implementation [1].

*Literature
1 Wegner C, Kancherla V, Lux A, Köhn A, Bretschneider D, Freese K, Heiduk M, Redlich A, Schleef D, Jorch G, Rissmann A. Periconceptional folic acid supplement use among women of reproductive age and its determinants in central rural Germany: Results

10.2 Anencephaly (Q00.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	6	3.73	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.18	1.59 - 2.92	
EUROCAT (Full members)	Zeitraum 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.20	4.06 - 4.34	

Six anencephalies were observed in Saxony-Anhalt in 2021. After a very low prevelance in the last year with a value of 1.2 per 10,000 births, the current annual prevalence for 2021 is **3.7 per 10,000 births**. Therefore, the current **annual prevalence** lies above the confidence interval of the basis prevalence (2009-2020: 2.2 per 10,000 births).
The nonlinear change is substantial over the period of the trend analysis (2008-2021) in chapter 10.38 due to the fluctuating numbers in the trending assessment.

Comparing the confidence interval of the basis prevalence of Saxony-Anhalt with the value of the European registries (2009-2020: 4.2 per 10,000 births), it lies far below. The low basis prevalence of Saxony-Anhalt is a consequence of very low prevalences of the years 2009-2013. The current prevalence in Saxony-Anhalt for anencephaly is only slightly below the European normal range.

One child with anencephaly and multiple malformations was born alive but died within the first 24 hours. Anencephaly was diagnosed at five other fetuses between 11 and 15 weeks of gestation during prenatal ultrasound screening. These pregnancies were terminated.

additional information:

pregnancy outcome	1 x live birth deceased after 7 days of life 5 x termination of pregnancy
sex	1 x male 1 x female 4 x no indication
number of isolated malformations/MCA	1 x MCA 5 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- univentricular heart, unilateral renal agenesis, a rudimentary arm, hypoplastic thorax, hemivertebrae, scoliosis

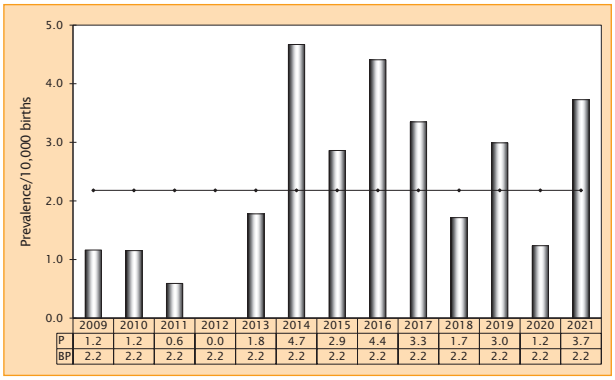


Fig. 8: Development of prevalence/10,000 births with anencephaly in Saxony-Anhalt since 2009

In 2021, one anencephalie per 2,683 births was registered in Saxony-Anhalt..

10.3 Spina bifida (Q05.)

	2021		
Saxony-Anhalt	Number	prevalence/ 10,000 births	Comparison to basis prevalence
	5	3.11	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.14	4.21 - 6.21	
EUROCAT (Full members)	Zeitraum 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.06	4.91 - 5.21	

In the year of birth 2021, only five children/fetuses with spina bifida were reported. From this we calculated an **annual prevalence** for Saxony-Anhalt of **3.1 per 10,000 births**, which significantly exceeds the basis prevalence of 5.1 per 10,000 births (2009-2020).
After a maximum value (8.2 per 10,000 births) was observed in 2014, prevalence values ranged around or below the average value. In the trend analysis in chapter 10.38, the nonlinear change can be observed over the years 2008-2021.

EUROCAT gives an overall prevalence for spina bifida of 5.1 per 10,000 births (2009-2020). The prevalence interval of the basis prevalence of Saxony-Anhalt is broader and spans due to the smaller numbers that of the European malformation registries, but the value of the prevalences is similarly high.

additional information:

pregnancy outcome	2 x live births 3 x termination of pregnancy
sex	2 x male 3 x female
number of isolated malformations/MCA	2 x MCA 3 x isolated

Two children with a lumbar and a lumbosacral spina bifida were affected by syringomyelia. Further three fetuses received the diagnosis of one lumbosacral and two sacral spina bifida between the 20th and 24th week of gestation during ultrasound screening. These three pregnancies were terminated.
In two of these fetuses, the spina bifida was accompanied by an Arnold-Chiari malformation and hydrocephaly.

Malformation combinations (MCA) or superordinated syndromes detected:

- 2 x syringomyelia (1 x with sacral dimple, nervus flammeus)

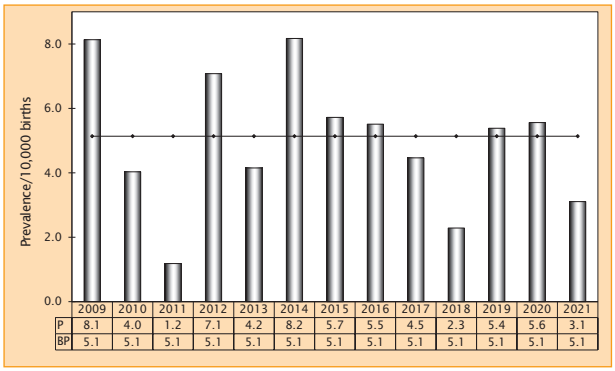


Fig. 9: Development of prevalence/10,000 births with spina bifida in Saxony-Anhalt since 2009

During the reporting period, there were no stillbirths or spontaneous abortion in relation to a spina bifida. Almost 60% of the children/fetuses were born alive, and in a good 40% the pregnancy was terminated. The proportion of live births decreases slightly over the period of 2009-2020.

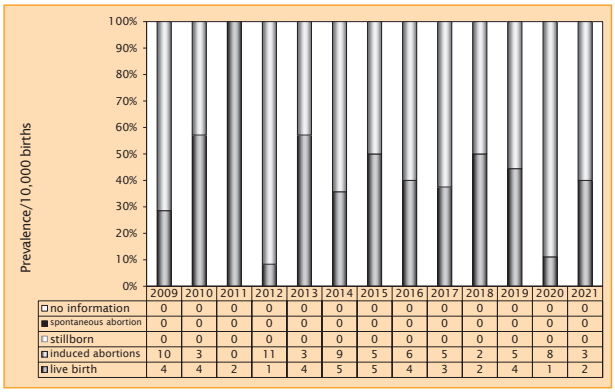


Fig. 10: Pregnancy outcomes of spina bifida in Saxony-Anhalt since 2009

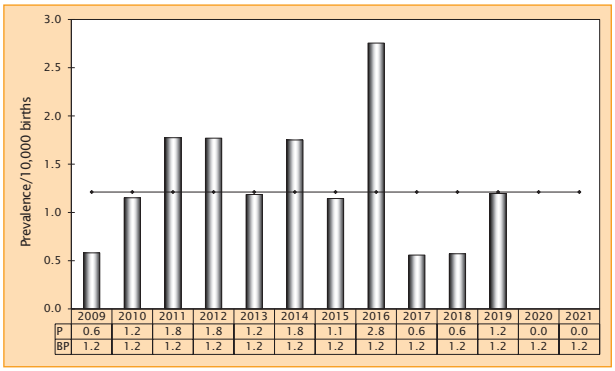
In 2021, one spina bifida per 3,219 births was registered in Saxony-Anhalt..

10.4 Encephalocele (Q01.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	0	0.0	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.21	0.78 - 1.79	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.20	1.13 - 1.28	

The indicator malformation encephalocele is with a basis prevalence of 1.2 per 10,000 births (2009-2020) in Saxony-Anhalt, one of the rare malformations. On average, two to three cases per year can be expected in Saxony-Anhalt. As in the previous year 2020, no encephalocele occurred in Saxony-Anhalt in the current year 2021.

The confidence interval of the basis prevalence of Saxony-Anhalt covers the somewhat wider limits of the confidence interval of the European prevalence, given by EUROCAT (2009-2020: 1.2 per 10,000 births). Both prevalences are similarly high over the reporting period. Accordingly, the annual prevalence of Saxony-Anhalt, also compared to that of EUROCAT, is to be assessed as low.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	0.6	1.2	1.8	1.8	1.2	1.8	1.1	2.8	0.6	0.6	1.2	0.0	0.0
BP	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

Fig.11: Development of prevalence/10,000 births with encephalocele in Saxony-Anhalt since 2009

In 2021, no encephalocele was registered in Saxony-Anhalt..

10.5 Microcephaly (Q02.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to Basis prevalence
	8	4.97	↗
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.92	3.12 - 4.88	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence intrval (CI 95%)	
	2.67	2.56 - 2.78	

Eight births with microcephaly were registered in Saxony-Anhlat in 2021. The head circumferences differed by more than -3 SD from normal in one fet with Patau syndrome, one with cCMV and two spontaneous abortions in the 24th week of gestation after taking into account gestational age and sex. Four additional children developed microcephaly during the first year of life. The malformation monitoring uses for the purpose of diagnosis finding available data from the INTERGROWTH-21st project study about internationally valid percentile curves. During the first year of life the diagnosis becomes definitive with the non-development of the brain and skull.

The current **prevalence** is shown to be **5.0 per 10,000 births** in 2021. After it could be found three years each below the basis prevalence (between 2.4 and 2.9 per 10,000 births), it lies again slightly above (2009-2020: 3.9 per 10,000 births).

When comparing the prevalences of Saxony-Anhalt of 2021, as well as of the reporting period, with the prevalence provided by EUROCAT for the European registers for 2009-2020 (2.7 per 10,000 births), the prevalence values are clearly higher.

additional information:

pregnancy outcome	4 x live births 2 x sponatneus abortion 2 x terminaton of pregnancy
sex	4 x male 4 x female
number of isolated malformations/MCA	4 x MCA 4 x isolated

Malformation combinations (MCA) or superordinated detected:

- Patau syndrome with: Diaphragmatic hernia, dextrocardia.
- 2 x cCMV (1 x with hydrocephalus internus, schizencephaly, pachymicrogyria, corpus callosum agenesis, VSD, PFO at full term infant, blt sensorineural hearing loss, hemangiomas)
- Alcohol embryopathy with: VSD, right ventricular myocardial hypertrophy

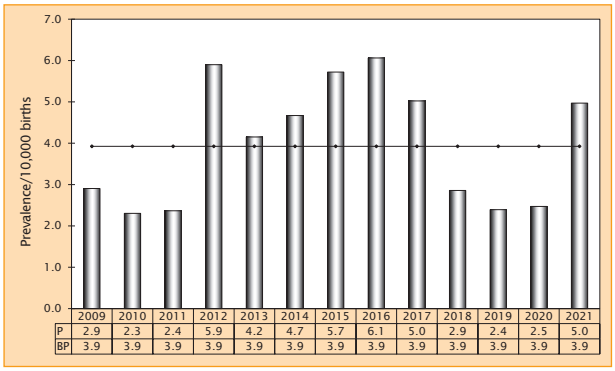


Fig. 12: Development of prevalence/10,000 births with microcephaly in Saxony-Anhalt in 2009

In 2021, one microcephalie per 2,012 births was registered in Saxony-Anhalt..

10.6 Congenital Hydrocephaly (Q03.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	9	5.59	↔
	Reproting period 2009-2020		
	Basis prevalence/ 10,000 Geburten	Confidence interval (CI 95%)	
	5.67	4.69 - 6.79	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.28	5.12 - 5.43	

In the case of the indicator malformation hydrocephaly, only congenital hydrocephalies are considered, which have not developed as a result of neural tube defects. In the 2021 birth cohort, nine births in Saxony-Anhalt were registered with a congenital hydrocephaly.

This year's **prevalence** of **5.6 per 10,000 births** (2021) is located inconspicuous within the range of the basis prevalence of Saxony-Anhalt (2009-2020: 5.7 per 10,000 births).

The basis prevalence of Saxony-Anhalt can be considered as equal with a slightly higher range to the prevalence reported by EUROCAT (5.3 per 10,000 births). The annual prevalence of Saxony-Anhalt lies within the normal range of the prevalence, however due to the narrower European confidence interval, it is slightly below.

additional information:

pregnancy outcome	6 x live births 1 x live births deceased after 7 days of life 2 x termination of pregnancy
sex	7 x male 2 x female
number of isolated malformations/MCA	7 x MCA 2 x isolated

Three times chromosomal defects were responsible for the congenital hydrocephaly and once a congenital infection. In the cases of fetuses with chromosomal abnormalities, the pregnancy was terminated prematurely in two cases, one child died shortly after birth.

Malformation combinations (MCA) or superordinated syndromes detected::

- Down`s syndrome with: Canalis atrioventricularis communis
- Trisomy 9 with: Diaphragmatic hernia, thoracic hypoplasia, clubfoot on the right
- thanatophoric dysplasia type I with: Micromelia of the arms and legs, limited mobility of the knees and elbow joints, blt bending of the humerus and femur, narrow thorax, sunken root of the nose
- cCMV with: Microcephaly, schizencephaly, pachymicrogyria,
- Corpus callosum agenesis, VSD, PFO at full term infant, blt sensorineural hearing loss, hemangioma
- Corpus callosum agenesis, cerebellar hypoplasia, sacral dimple
- Corpus callosum hypoplasia, cerebellar hypoplasia, dilated cerebral ventricles
- Pachygyria, kinked left foot

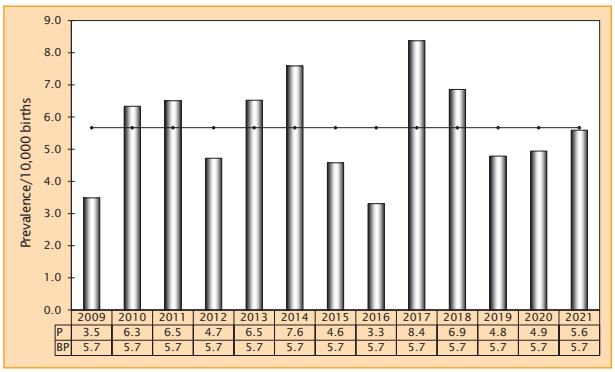


Fig 13: Development of prevalence/10,000 births with congenital hydrocephalus in Saxony-Anhalt since 2009

In 2021, one congenital hydrocephaly per 1,788 births was registered in Saxony-Anhalt.

10.7 Arhinencephaly/Holoprosencephaly (Q04.1/Q04.2/Q87.3)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	6	3.73	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.65	1.14 - 2.30	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.61	1.53 - 1.70	

With a basis prevalence of 1.6 per 10,000 births (2009-2020), the indicator malformation arhinencephaly/holoprosencephaly is one of the rarely seen malformations. During the reporting period, less than three cases were observed in six years in Saxony-Anhalt. In total, six cases of arhinencephaly/holoprosencephaly were registered in 2021.
The resulting **annual prevalence (3.7 per 10,000 births)** significantly exceeds the basis prevalence. However, there were significant higher values reached in the years 2010 and 2016 (4, 6, and 3.9 per 10,000 births, respectively). The trend analysis (Chapter 10.38) shows a significant nonlinear proportion. Therefore, the development of prevalence of the indicator malformation is considered as nonlinear change.

When comparing the prevalences of Saxony-Anhalt with the European prevalence provided by EUROCAT (2009-2020: 1.6 per 10,000 births), this year's prevalence of Saxony-Anhalt lies clearly higher. However, both confidence intervals of the 2009-2020 prevalence can be found on the same level. The confidence interval of Saxony-Anhalt's basis prevalence has a much larger range of variation than the confidence interval of the European prevalence due to the smaller population included.

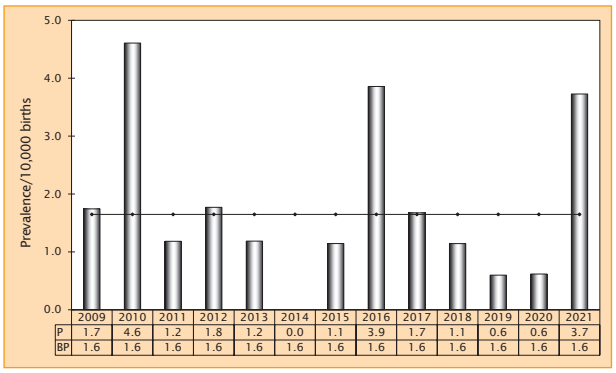
additional information:

pregnancy outcome	6 x termination of pregnancy
sex	4 x male 2 x female
number of isolated malformations/MCA	6 x MCA

Three fetuses showed holoprosencephaly, which is a developmental disorder of the forebrain and the face, along with other malformations, for example a Patau syndrome. The other three fetuses were also affected by holoprosencephaly.
Arhinencephaly or cyclopia were not found in 2021. All six holoprosencephalies were detected between the 12th and the 22nd week of gestation. On 4 occasions, the clinical feature of the face, a cleft lip and palate, was described.

Malformation combinations (MCA) or superordinated syndromes detected:

- 3 x Patau syndrome (1 x with: TGA, 1 x with: Cardiac malformation, polydactyly)
- Coffin-Siris syndrome
- Tetralogy of Fallot
- Microphthalmos



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.7	4.6	1.2	1.8	1.2	0.0	1.1	3.9	1.7	1.1	0.6	0.6	3.7
BP	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6	1.6

Fig. 14: Development of prevalence/10,000 births with arhinencephalie/holoprosencephalie in Saxony-Anhalt since 2009

In 2021, one arhinencephaly/holoprosencephaly per 2,683 birth was registered.

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

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	3	1.86	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.87	0.52 - 1.38	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.89	0.83 - 0.96	

The indicator malformation anophthalmia/microphthalmia is, with a basis prevalence of 0.9 per 10,000 births in Saxony-Anhalt (2009-2020), a rarely occuring malformation. Anophthalmia/ microphthalmia did not occur at all in the previous year. With three cases in 2021, the **annual prevalence** lies at **1.9 per 10,000 births** and is significantly higher than the basis prevalence. Only a number of one or two cases per year correspond to the normal range in Saxony-Anhalt.

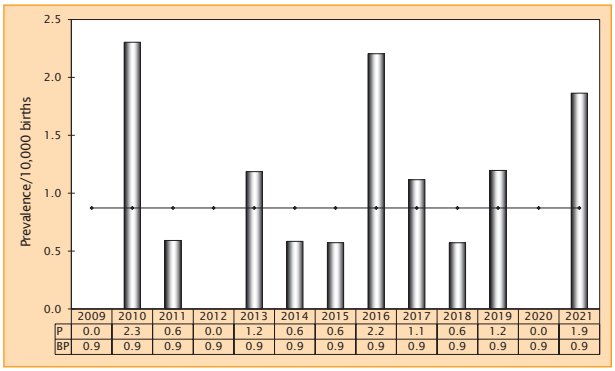
When comparing the indicated prevalence by EUROCAT of the years 2009-2020 (0.9 per 10,000 births) with the annual prevalence of Saxony-Anhalt, the latter is to be found far above. The confidence interval of the basis prevalence of Saxony-Anhalt lies with the
interval of the average prevalence of the European registries on a similar same level, but spans a larger safety range due to smaller numbers.

additional information:

pregnancy outcome	2 x live births 1 x termination of pregnancy
sex	3 x male
number of isolated malformations/MCA	2 x MCA 1 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- holoprosencephaly
- partial aniridia right, brain ventricle asymmetry



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	0.0	2.3	0.6	0.0	1.2	0.6	0.6	2.2	1.1	0.6	1.2	0.0	1.9
BP	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9

Fig. 15: Development of prevalence/10,000 births with anophthalmos/microphthalmos in Saxony-Anhalt since 2009

In 2021, one anophthalmos/microphthalmos per 5,365 births was registered in Saxony-Anhalt.

10.9 Microtia/Anotiea (Q16.0/Q17.2)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basisw prevalence
	2	1.24	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.00	2.30 - 3.85	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

In 2021, only two births with anotia were registered in Saxony-Anhalt. In both cases the anotia occured unilaterally. An ear dysplasia of II. to III. degree (microtia) was not observed. The resulting **annual prevalence (1.2 per 10,000 births)** is significantly lower than the basis prevalence of 3.0 per 10,000 births (2009-2020).

In both cases, the missing right auricle is associated to an atresia of the bony auditory canal. One child is affected by a reduced hearing ability, for the other child no information is available.

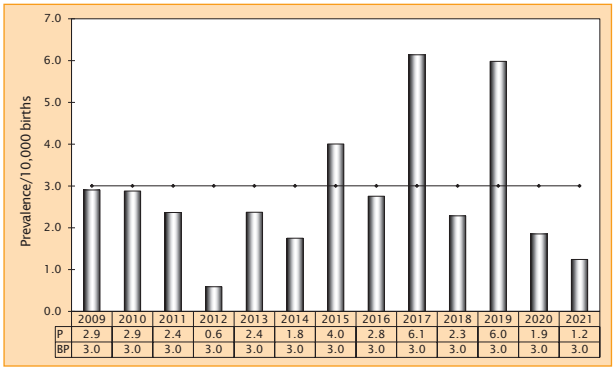
EUROCAT does not provide prevalence data for the indicator malformation microtia/annotia. For the less frequent malformation anotia or atresia/stricture of the bony auditory canal EUROCAT shows a prevalence of 0.83 per 10,000 births (2009-2020; CI 0.77-0.89). For Saxony-Anhalt, the calculated basis prevalence for anotia amounts to 0.53 per 10,000 births (2009-2020; CI 0.27-0.95).

additional information:

pregnancy outcome	2 x live births
sex	2 x male
number of isolated malformations/MCA	2 x MCA

Detected malformation combinations (MCA) or superordinate syndromes:

- renal agenesis on the right side, right-sided sound conductive disorder with atresia of the bony auditory canal
- atresia of the right bony auditory canal



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	2.9	2.9	2.4	0.6	2.4	1.8	4.0	2.8	6.1	2.3	6.0	1.9	1.2
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. 16: Development of prevalence/10,000 births with microtia/anotia in Saxony-Anhalt since 2009

In 2021, one microtia/anotia per 8,048 births was registered in Saxony-Anhalt..

10.10 Tetralogy of Fallot/ (Q21.3/Q21.80)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	7	4.35	↔
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.54	2.77 - 4.45	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.78	3.65 - 3.91	

Pulmonary stenosis, VSD, riding aorta and right heart hypertrophy form togehter the complex cardiac malformation tetralogy of Fallot. If aditionally, an ASD is diagnosed as a fifth malformation, it is referred to as a pentalogy of Fallot. As of this report, pentalogy is included as part of the indicator malformation tetralogy of Fallot.

The indicator malformation Fallot's tetralogy/ pentalogy was diagnosed at seven births in Saxony-Anhalt (**4.3 per 10,000 births)** in 2021. Therefore, this year's **prevalence** lies
inconspicuously in the range of the basis prevalence (2009-2020: 3.5 per 10,000 births).

The basis prevalence of Saxony-Anhalt for the years 2009-2020 and the provided European prevalence by EUROCAT (2009-2020: 3.7 per 10,000 births) are similarly high, whereas the Saxony-Anhalt confidence interval has a much wider range. The 2021 annual prevalence is therefore located above the upper confidence limit of the European prevalence.

additional information:

pregnancy outcome	6 x live births 1 x termination of pregnancy
sex	5 x male 2 x female
number of isolated malformations/MCA	5 x MCA 2 x isolated

In one case of a fet with tetralogy of Fallot and holoprosencephaly the pregnancy was terminated at 17 weeks gestation. In four cases the severe cardiac malformation was also known prenatally. Three of the six children with tetralogy of Fallot/ pentalogy were operated in Berlin and three in Leipzig. One heart surgery was performed in the first week of life, one at about two months of age, two at about six months of age and two at about eight months.

Malformation combinations (MCA) or superordinated syndromes detected:

- Down`s syndrome with: vascular ring of the great arteries
- holoprosencephaly
- DORV, laryngomalacia
- vascular ring through the anomalous right subclavicular artery, PFO at full term infant, malformation of the precerebral vessels
- persistent left superior vena cava

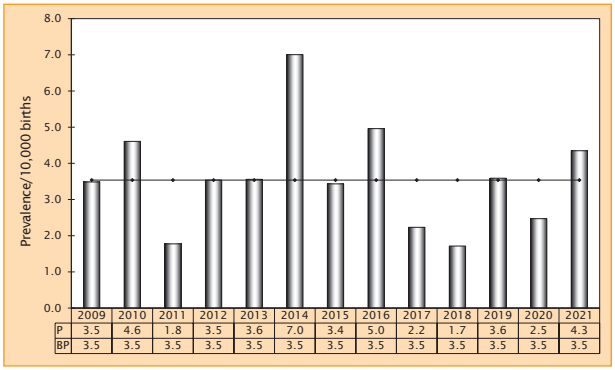


Fig. 17: Development of prevalence/10,000 births with Tetralogy of Fallot in Saxony-Anhalt since 2009

In 2021, one Tetralogy of Fallot per 2,299 births was registered in Saxony-Anhalt..

10.11 Transposition of great vessels - TGV (Q20.1/Q20.3)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	13	8.08	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.60	3.73 - 5.63	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.26	5.11 - 5.42	

One of the most severe cardiac malformations, transposition of the great arteries (TGA), oc-curs when the aorta and the pulmonary artery are interchanged. 13 births were registered in 2021 in Saxony-Anhalt with this cardiac malformation. The resulting **prevalence of 8.1 per 10,000 births** clearly exceeds the upper limit of the confidence interval of the basis prevalence of Saxony-Anhalt (2009-2020: 4.6 per 10,000 births).

EUROCAT gives a prevalence for transposition of great vessels of 5.3 per 10,000 births (2009-2020). The prevalence interval of the basis prevalence of Saxony-Anhalt is broader and covers due to a much smaller population of Saxony-Anhalt the interval of the by EUROCAT given overall prevalence of the European malformation registers.

additional information:

pregnancy outcome	11 x live births 2 x itermination of pregnancy
sex	10 x male 3 x female
number of isolated malformations/MCA	9 x MCA 4 x isolated

In one case, DORV was diagnosed in the 13th week of gestation in addition to a sirenomelia. In case of another fet, a discordant ventriculoarterial connection as additional malformation in relation to a prenatally confirmed Patau syndrome was diagnosed in the 12th week of gestation.

Both pregnancies were terminated prematurely. In all eleven life births the heart was affected by other malformations. Most of the children were operated during their first year of life in the Leipzig Heart Center.

Malformation combinations (MCA) or superordinated syndromes detected:

- Sirenomelia
- Patau syndrome with: holoprosencephaly
- Heterotaxy, persistent left superior vena cava, duodenal stenosis, cleft vertebrae, scoliosis, processus vaginalis peritonei on the left side, undescended right testis at full term infant
- Canalis atrioventricularis communis, persistent left vena cava superior, dextrocardia with situs inversus, total supradiaphragmatic malperfusion of the pulmonary veins, asplenia of the spleen
- postductal aortic isthmic stenosis, discordant atrioventricular connection, hypoplasia of the aorta
- tetralogy of Fallot, laryngomalacia
- corrected transposition of the great vessels, malformation of the coronary vessels, non-hemodynamically effective PDA at full term infant
- persistent left superior vena cava
- penile hypospadias, ankyloglosson

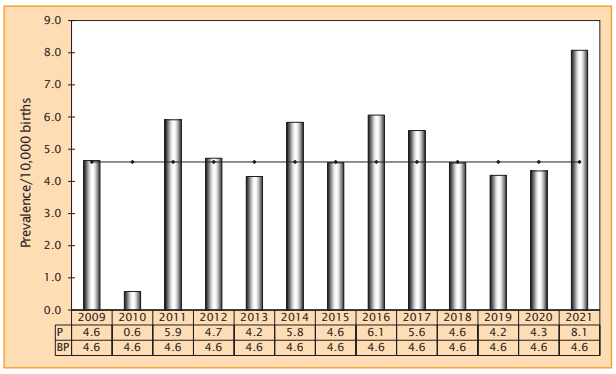


Fig. 18: Development of prevalence/10,000 births with transposition of great vessels in Saxony-Anhalt since 2009

In 2021, one transposition of great vessels per 1,238 births was registered in Saxony-Anhalt.

10.12 Hypoplastic left heart syndrom (Q23.4)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	3	1.86	↘
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.71	2.05 - 3.52	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.80	2.69 - 2.91	

In 2021, only three children in Saxony-Anhalt were registered with the most severe congenital cardiac malformation, the indicator malformation left heart hypoplasia. Due to modern surgical techniques and intensive treatment strategies, the unfavorable progno-sis of this very complex cardiac malformation improved, but there is a need for further medi-cal care after several operations, lifelong.
One child died in the second week of life and one at almost one year of age. The **prevalence** of Saxony-Anhalt for 2021 of **1.9 per 10,000 births** lies slightly below the calculated basis prevalence (2009-2020: 2.7 per 10,000 births).

The confidence interval of the basis prevalence of Saxony-Anhalt encloses due to the smaller numbers, the interval limits of the overall prevalence of the European registries given by EU-ROCAT (2009-2020: 2.8 per 10,000 births). The Saxony-Anhalt prevalence for the year 2021 is therefore, in comparison to the Europe-wide overall prevalence, rather low.

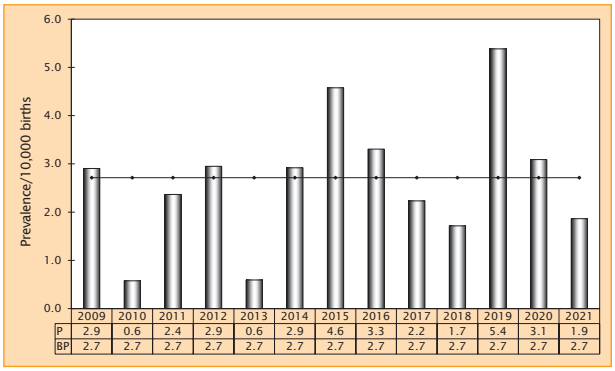
additional information:

pregnancy outcome	1 x live births 2 x live births, deceased after 7 days of life
sex	2 x male 1 x female
number of isolated malformations/MCA	2 x MCA 1 x isolated

In all three cases, left ventricular hypoplasia was discovered prenatally during ultrasound screening. For a heart surgery in the first days of life (Noorwood I), they were transferred to a specialized institution. One child was transferred prenatally and two children after birth.

Malformation combinations (MCA) or superordinated syndromes detected:

- vascular ring through the anomalous right subclavicular artery
- epilepsy



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	2.9	0.6	2.4	2.9	0.6	2.9	4.6	3.3	2.2	1.7	5.4	3.1	1.9
BP	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7

Fig. 19: Development of prevalence/10,000 births with hypoplastic left heart syndrome in Saxony-Anhalt since 2009

In 2021, one child with a hypoplastic left heart syndrome per 5,365 births was registered in Saxony-Anhalt.

10.13 Coarctation of aorta (Q25.1)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	7	4.35	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.77	4.78 - 6.90	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.04	3.90 - 4.17	

Seven children were born with aortic coarctation in Saxony-Anhalt in 2021. This corresponds to an **annual prevalence** of **4.3 per 10,000 births**. After a very high value in the previous year (2020: 8.6 per 10,000 births), we observed in 2021 again a value well below the calculated basis prevalence of Saxony-Anhalt (2009-2020: 5.8 per 10,000 births).

Compared to the prevalence of the EUROCAT registers (2009-2020: 4.0 per 10,000 births), the Saxony-Anhalt basis prevalence is, as well as the current annual prevalence (2021), to be regarded as high.

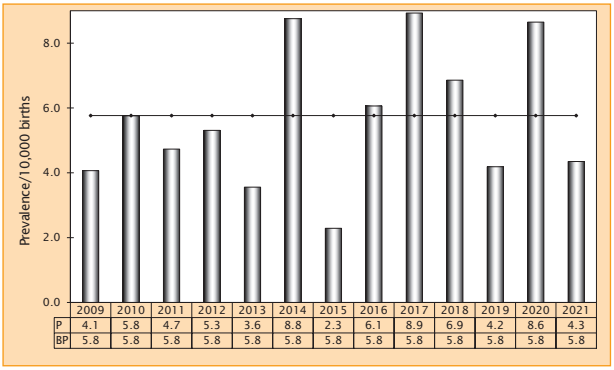
additional information:

pregnancy outcome	6 x live births 1 x live births, deceased after 7 days of life
sex	4 x male 3 x female
number of isolated malformations	6 x MCA 1 x isolated

Coarctation of aorta is often found postnatally as it is difficult to detect on prenatal ultrasound screening and occurs together with other cardiac malformations. Only twice, it was clearly diagnosed prenatally. In two other cases, other severe cardiac malformations were seen prenatally. One child who suffered in addition to aortic coarctation from diaphragmatic hernia with massive enterothorax, died a few days after birth.

Malformation combinations (MCA) or superordinated syndromes detected:

- Microduplication syndrome chromosome 10, right side DUP IV. degree, ureteral orifice stenosis and megaureter, epicanthus internus
- Cardiac urogenital syndrome with: hypoplasia of the aorta, VSD, PFO at full term infant, pulmonary sequestration and right lung hypoplasia, scimitar anomaly, sacral dimple, retarded hip maturity on the right side
- unilateral diaphragmatic hernia, hepatomegaly
- DORV, discordant atrioventricular connection, hypoplasia of the aorta
- 2 x hypoplasia of the aorta, ASD II



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	4.1	5.8	4.7	5.3	3.6	8.8	2.3	6.1	8.9	6.9	4.2	8.6	4.3
BP	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8	5.8

Fig. 20: Development of prevalence/10,000 births with coarctation of aorta in Saxony-Anhalt since 2009

In 2021, one coarctation of aorta per 2,299 births was registered in Saxony-Anhalt.

10.14 Cleft lip with or without cleft palate (Q36./Q37.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to bais prevalence
	12	7.46	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	13.18	11.66 - 14.84	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	8.73	8.53 - 8.93	

Cleft formations of the upper lip with or without cleft of the alveolar ridge or the hard palate are malformations, which together form the indicator malformation cleft lip and palate. In 2021, four births were registered with cleft lip and palate in Saxony-Anhalt, five with cleft upper lip, two with cleft lip and palate and one with cleft lip and palate. In 2021, a total of only twelve children were affected by cleft lip and cleft lip and palate. Since the maximum value of 2015 (16.6 per 10,000 births), the **prevalence** is decreasing again and reached this year a minimum of **7.5 per 10,000 births** during the reporting period, which can be located far below the confidence interval of the basis prevalence (2009-2020: 13.2 per 10,000 births).

Measured in relation to the European prevalence determined by EUROCAT (2009-2020: 8.7 per 10,000 births), the basis prevalence of Saxony-Anhalt is extraordinarily high. This year's annual prevalence is, however, still lower than the lower confidence limit of the European overall prevalence.

additional information:

pregnancy outcome	11 x live births 1 x live births, decesased after 7 days of life
sex	11 x male 1 x female
number of isolated malformations/MCA	3 x MCA 9 x isolated

A rare bilateral cleft lip and palate occurred in combination with a sound conductive disorder. All other eleven cleft lips and cleft palates were unilateral: 7 times on the left side, twice on the right side and twice without indication of the side. It is common that the left side is af-fected more frequently.

Malformation combinations (MCA) or superordinated syndromes detected:

- left diaphragmatic hernia, VSD
- Corpus callosum agenesis
- blt sound conductive disorder

Furthermore, a cleft lip and palate was diagnosed 4 times this year as a symptom of holoprosencephaly (chapter 10.7). When holoprosencephaly represents the superordinated syndrome, cleft lip and palate is not seen individually as indicator malformation.

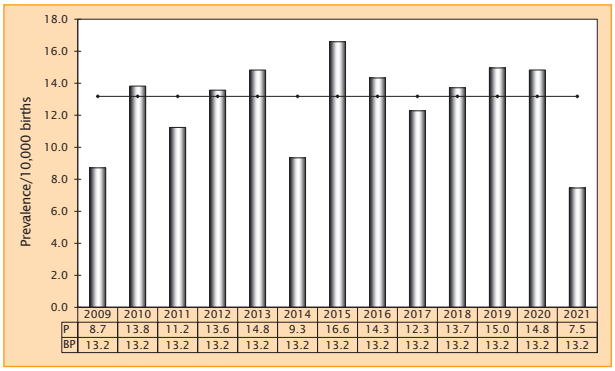


Fig. 21: Development of prevalence/10,000 births with cleft lip with or without cleft palate in Saxony-Anhalt since 2009

In 2021, one child with cleft lip with or without cleft palate per 1,341 births was registered in Saxony-Anhalt.

10.15 Cleft palate (Q35.1/Q35.3/Q35.5/Q35.9)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	13	8.08	↗
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	6.83	5.75 - 8.06	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.96	5.79 - 6.12	

In case of a cleft palate, there is a connection between the nasal cavity and the pharyngeal cavity with the oral cavity. The cleft palate with lip involvement (Chapter 10.14) is excluded from the indicator malformation cleft palate. As of birth year 2021, 13 births with cleft palate were observed in Saxony-Anhalt. Mostly they were reported as median (5 x) or bilateral (3 x), only once as unilateral.

After three very low annual prevalences for cleft palate during the period of 2018-2020, they were seen slightly more often again in the current year. For 2021, a **prevalence** value of **8.1 per 10,000 births** was calculated, which lies minimally above the upper confidence limit of the basis prevalence of Saxony-Anhalt for cleft palate (2009-2020: 6.8 per 10,000 births).

The confidence interval of the overall prevalence of the European malformation registries (2009-2020: 6.0 per 10,000 births) is at a slightly lower level, but is completely covered by the broader interval of the basis prevalence of Saxony-Anhalt. The Saxony-Anhalt annual prevalence is therefore also above the prevalence of the European registers.

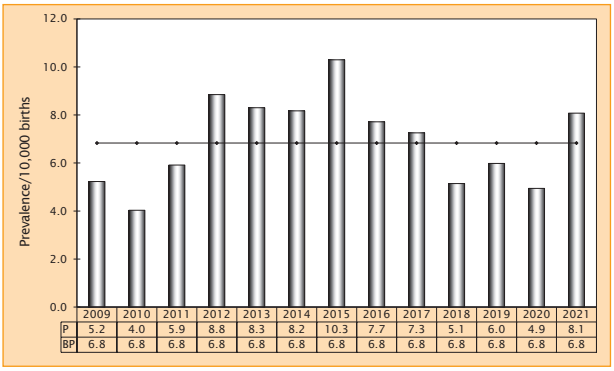
In one fet, cleft palate was identified as a symptom of an orofaciodigital syndrome with other severe malformations of the heart and extremities at 13 weeks of gestation. This pregnancy was terminated prematurely.

additional information:

pregnancy outcome	12 x live births 1 x termination of pregnancy
sex	5 x male 8 x female
number of isolated malformations/MCA	3 x MCA 10 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- orofaciodigital syndrome with: bilateral polysyndactyly, bilateral postaxial polydactyly of hands and feet and accessory big toes, ASD II, persistent left vena cava superior, sacral dimple
- polycystic kidneys of infantile type, midface hypoplasia, hepatomegaly
- bilateral conductive disorder



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	5.2	4.0	5.9	8.8	8.3	8.2	10.3	7.7	7.3	5.1	6.0	4.9	8.1
BP	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8	6.8

Fig. 22: Development of prevalence/10,000 births with cleft palate in Saxony-Anhalt since 2009

In 2021, one child with cleft palate per 1,238 births was registered in Saxony-Anhalt..

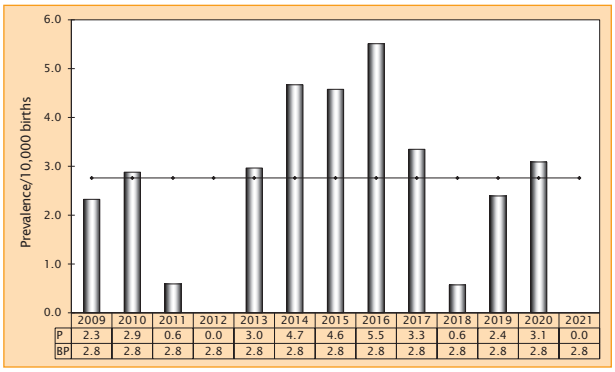
10.16 Choanal atresia (Q30.0)

Saxony-Anhalt	2021		
	Number	Prevalence/ 10,000 Geburten	Comparison to basis prevalence
	0	0.0	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.76	2.09 - 3.58	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.91	0.85 - 0.98	

The indicator malformation choanal atresia is defined as an obstruction in need of therapy of the transition between the nasal and pharyngeal cavities. The indicator malformation does not include low-grade stenoses. As it was the case in 2012, no birth with choanal atresia was registered in Saxony-Anhalt in 2021.

The annual prevalences vary due to the small numbers between 0.0 and 5.5 per 10,000 births. Furthermore, the change in prevalence over the reporting period is classified as nonlinear due to the increasing values up to the maximum in 2016 (5.5 per 10,000 births) and the subsequent decrease in falling values (chapter 10.38).

The basis prevalence of choanal atresia of Saxony-Anhalt exceeds the prevalence value given by EUROCAT considerably. The lower confidence limit of the basis prevalence of Saxony-Anhalt is far above the European confidence interval.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	2.3	2.9	0.6	0.0	3.0	4.7	4.6	5.5	3.3	0.6	2.4	3.1	0.0
BP	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8

Fig. 23: Development of prevalence/10,000 births with choanal atresia in Saxony-Anhalt since 2009

In 2021, no choanal atresia was registered in Saxony-Anhalt.

10.17 Oesophageal atresia/-stenosis/-fistula (Q39.0-Q39.4)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	5	3.11	↔
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.62	1.97 - 3.41	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.68	2.57 - 2.79	

In 2021, the indicator malformation esophageal atresia/ stenosis/ fistula occurred 5 times in Saxony-Anhalt. The **prevalence** of **3.1 per 10,000 births** lies unconspiciouly within the normal range of the basis prevalence (2009-2020: 2.6 per 10,000 births).
Over the reporting period, the prevalence of the indicator malformation esophageal atresia/stenosis/fistula varied between a minimum of 0.6 per 10,000 births (2013) and a maximum of 4.7 per 10,000 births (2012). However, in most cases, the value was within the confidence limits of basis prevalence.

Although this year's prevalence of Saxony-Anhalt is higher than the European average (2009-2020: 2.7 per 10,000 births), the confidence interval of Saxony-Anhalt's basis prevalence is consistent with that of the prevalence of the EUROCAT registers. However, it is wider than the interval of the European total prevalence, due to the smaller numbers.

additional information:

pregnancy outcome	4 x live births 1 x spontaneous abortion
sex	3 x male 2 x female
number of isolated malformations/MCA	3 x MCA 2 x isolated

Four children with atresia of the esophagus had a fistula between trachea and the lower esophageal pocket (type Vogt III b). For one child no information regarding a fistula was
given. In case of one fet with the very rare Costello syndrome, a spontaneous abortion occurred during the 26th week of gestation.

Malformation combinations (MCA) or superordinated syndromes detected:

- VATCERL association with: rectal atresia, Meckel's diverticulum, hemivertebrae, scoliosis, cervical ribs (14 rib pairs), persistent left superior vena cava
- Costello syndrome with: bilateral DUP, hypertelorism
- Feingold syndrome type 1

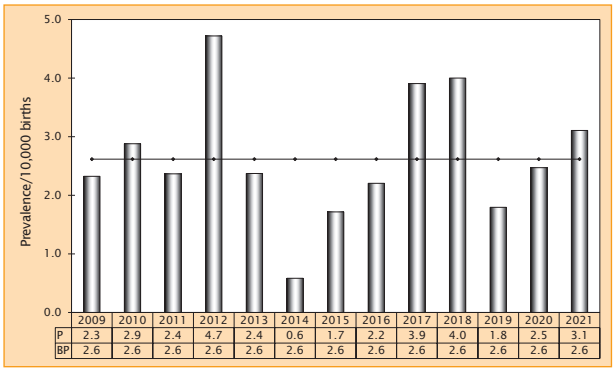


Fig. 24: Development of prevalence/10,000 births with oesophageal atresia/stenosis/fistula in Saxony-Anhalt since 2009

In 2021, one child with oesophageal atresia/-stenosis/-fistula per 3,219 births was registered in Saxony-Anhalt.

10.18 Small intestinal atresia/stenosis (Q41.1/Q41.2/Q41.8/Q41.9)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to bais prevalence
	4	2.49	↗
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.74	1.22 - 2.41	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence / 10,000 births	Confidence interval (CI 95%)	
	0.88	0.82 - 0.95	

Small intestinal atresia/stenosis is a rare malformation and is difficult to detect prenatally. In the current year, it was diagnosed at four births in Saxony-Anhalt after birth. The **annual prevalence (2021:2.5 per 10,000 births)** can be rated slightly higher than expected, and lies above the tolerance range of the basis prevalence (2009-2020: 1.7 per 10,000 births). In 2012, the maximum value of the prevalences during the reporting period was registered with 4.1 per 10,000 births. In contrast, the malformation was not registered at all in 2014.

The comparison with the prevalence provided by EUROCAT for 2009-2020 (0.9 per 10,000 births) suggests a prevalence value for Saxony-Anhalt for 2021, as well as for the reporting period, far above the European average.

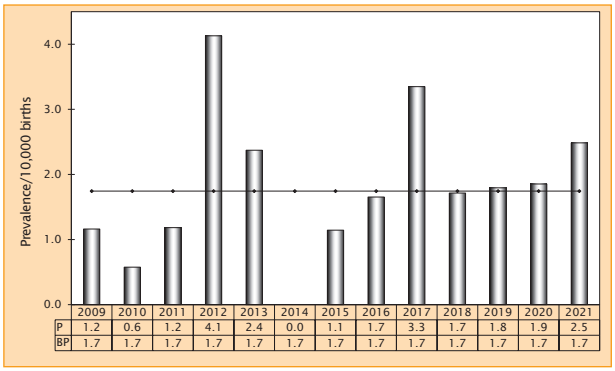
additional information:

pregnancy outcome	4 x live births
sex	2 x male 2 x female
number of isolated malformations/MCA	4 x MCA

Two births showed an atresia of the ileum, and two others had a stenosis of the small intestine. In one child who was affected by a gastroschisis, the gastrochisis was detected prenatally, but the stenosis of the small intestine was described postnatally.

Malformation combinations (MCA) or superordinated syndromes detected:

- gastroschisis, VSD
- malrotation of the intestine, hemodynamically effecti ve PDA in premature infant
- Hernia inguinalis on the right side at full term infant, ASD II
- malformation of the mesentery with mesenteric slit, retarded hip maturity on the right side



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.2	0.6	1.2	4.1	2.4	0.0	1.1	1.7	3.3	1.7	1.8	1.9	2.5
BP	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7	1.7

Fig. 25: Development of prevalence/10.000 births with small intestinal atresia/stenosis in Saxony-Anhalt since 2009

In 2021, one child with small intestinal atresia/stenosis per 4,024 births was registered in Saxony-Anhalt.

10.19 Anorectal atresia/ stenosis (Q42.0-Q42.3)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10.000 Geburten	Comparison to basis prevalence
	3	1.86	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.07	3.25 - 5.04	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.45	3.33 - 5.58	

In 2021, two births in Saxony-Anhalt were registered with rectal atresia, one with rectovaginal fistula and one without fistula. In one fet with caudal regression syndrome, anal atresia without fistula was detected prenatally beside other malformations.

A very low **annual prevalence** was calculated for the indicator malformation rectal and anal atresia/stenosis **(2021: 1.9 per 10,000 births) in 2021**. The highest rate of rectum and anal atresia/ -stenosis was seen at the beginning of the reporting period in 2009 (7.6 per 10,000 births). Since the peak in 2007-2010 with an extreme value of 8.4 per 10,000 births in 2008, the prevalence value decreased. As in recent years, this is reflected in the trend calculation over the period 2008-2021 (chapter 10.38), and can be discovered by a significant downward trend with a percentage change of -19.03% (CI -25.34% to -8.45%).

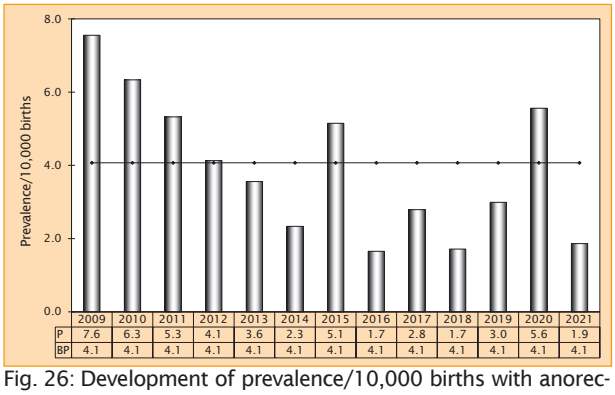
The confidence interval of the basis prevalence of Saxony-Anhalt covers due to the narrower population included, the confidence interval of the European prevalence (2009-2020: 3.5 per 10,000 births). The prevalence of Saxony-Anhalt of 2021 can be found below the European overall prevalence.

additional information:

pregnancy outcome	2 x live births 1 x termination of pregnancy
sex	1 x male 2 x female
number of isolated malformations/MCA	2 x MCA 1 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- caudal regression syndrome with: absent kidney on the left side and right dysplastic kidney, accessory finger on the left, abdominal muscle hypoplasia, low-set ears, wide nasal root, craniofacial dysmorphia
- VATCERL association with: esophageal atresia with fistula (Vogt IIIb), Meckel's diverticulum, hemivertebrae, scoliosis, cervical ribs (14 pairs of ribs), persistent left superior vena cava



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	7.6	6.3	5.3	4.1	3.6	2.3	5.1	1.7	2.8	1.7	3.0	5.6	1.9
BP	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1	4.1

Fig. 26: Development of prevalence/10,000 births with anorectal atresia/-stenosis in Saxony-Anhalt since 2009

In 2021. one anorectal atresia/ stenosis per 5.365 births was registered in Saxony-Anhalt.

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

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	35	21.74	↘
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	24.23	22.15 - 26.45	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	17.98	17.70 - 18.26	

Hypospadias is, with one up to two affected boys per 1,000 male children, not only one of the most frequent malformations, it is also the most frequent indicator malformation. In 2021, 35 births with hypospadias were registered in Saxony-Anhalt. This **year's prevalence (21.7 per 10,000 births)** is somewhat below the confidence interval of the basis prevalence (2009-2020: 24.2 per per 10,000 births).

When taking into account all live birth and stillbirths, a current annual prevalence is calculated (2021: 41.96 per 10,000 boys), which lies also slightly below the normal range of the corresponding basis prevalence (2009-2020: 47.27 per 10,000 boys; CI 43.22-51.60).

Ten boys were affected by severe forms of hypospadias in 2021: 7 times penile hypospadias and twice penoscrotal hypospadias and once perineal. Glandular hypospadias, the mildest form of hypospadias, occurred most frequently in 20 boys and once a hypospadias coronaria was described. It is possible that the monitoring of malformations may not cover the less severe forms, as these are often only noticed in the course of the first year of life. 4 times the severity of hypospadias was not reported.

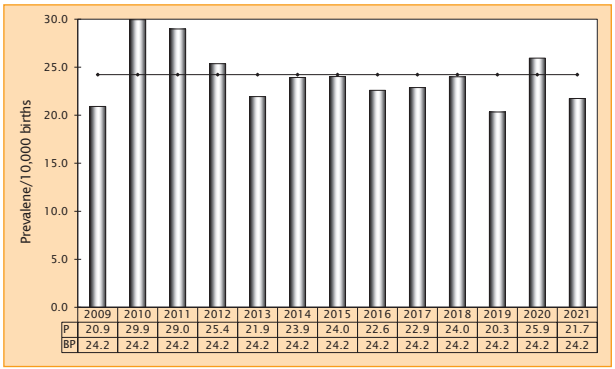
Compared with the average prevalence of EUROCAT (2009-2020: 18.0 per 10,000 births), the basis prevalence of Saxony-Anhalt is far above the normal range of the values of the European registries. Also the low annual prevalence of 2021 of Saxony-Anhalt exceeds the European prevalence provided by EUROCAT. All boys who suffered from hypospadias were born alive in 2021 and were born as full term infants, except for six boys.

zusätzliche Angaben:

pregnancy outcome	35 x live births
sex	35 x male
number of isolated malformations/MCA	4 x MCA 31 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- embryofetopathy due to sartans
- dextro-transposition of the aorta, ankyloglosson
- accessory right thumb, sacral dimple, sandal gap, PFO at preterm infant, umbilical hernia, deviation of the nasal septum
- VSD, left ventricular myocardial hypotrophy, PFO at preterm infant



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	20.9	29.9	29.0	25.4	21.9	23.9	24.0	22.6	22.9	24.0	20.3	25.9	21.7
BP	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2	24.2

Fig. 27: Development of prevalence/10,000 births with hypospadias in Saxony-Anhalt since 2009

In 2021, one hypospadias per 460 births (238 boys) was registered in Saxony-Anhalt.

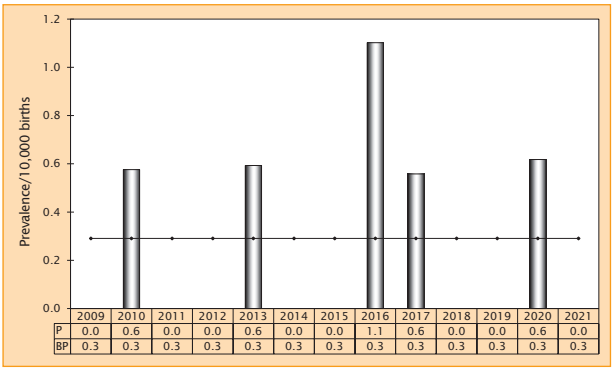
10.21 Epispadias (Q64.0)

Saxony-Anhalt	Jahr 2021		
	Number	Prevalence/ 10,000 births	Comparison to bais prevalence
	0	0.0	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.29	0.11 - 0.63	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

Epispadias is a malformation that is seen extremely rarely. As in more than half of the years of the reporting period (2009-2020) epispadias was not observed in Saxony-Anhalt. This also applies for the current year (2021). Only in one year (2016) a maximum of two cases occurred, which means that in this year the upper confidence limit of the basis prevalence (2009-2020: 0.3 per 10,000 births) was already far exceeded.

In reference to all live and stillbirths, the basis prevalence for epispadias is calculated to be 0.57 per 10,000 boys (2009-2020).

European comparative values for the prevalence of epispadias are not available from EUROCAT.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	0.0	0.6	0.0	0.0	0.6	0.0	0.0	1.1	0.6	0.0	0.0	0.6	0.0
BP	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Fig. 28: Development of prevalence/10,000 births with epispadias in Saxony-Anhalt since 2009

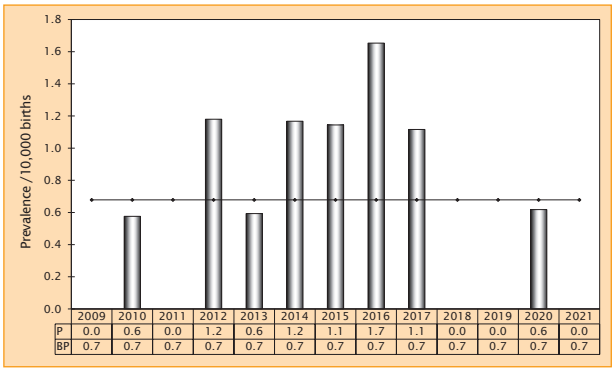
In 2021, no epispadias was registered in Saxony-Anhalt.

10.22 Indeterminate sex (Q56.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	0	0.0	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.68	0.37 - 1.14	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.54	0.49 - 0.59	

The indicator malformation indeterminate sex was diagnosed in total only 14 times during the reporting period (2009-2020). The malformation does only occur occasionally and not in every year in Saxony-Anhalt. Thus, even in 2021 in Saxony-Anhalt, no child/fet was found to be of indifferent sex. The maximum prevalence value was registered with 1.7 per 10,000 births in 2016.

The confidence interval of the basis prevalence of Saxony- Anhalt spans due to the smaller numbers a larger safety range than the interval of the average prevalence of the European registries (0.5 per 10,000 births). The prevalence value of Saxony-Anhalt matches the European prevalence.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	0.0	0.6	0.0	1.2	0.6	1.2	1.1	1.7	1.1	0.0	0.0	0.6	0.0
BP	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. 29: Development of prevalence/10,000 births with indeterminate sex in Saxony-Anhalt since 2009

In 2021, no indeterminate sex was registered in Saxony-Anhalt.

10.23 Potter sequence (Q60.6)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	2	1.24	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.86	2.18 - 3.69	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.28	1.21 - 1.36	

This **year's prevalence** for the indicator malformation Potter sequence **(2021: 1.2 per 10,000 births)** can be rated as very low. Only in two other years of the reporting period (2012, 2019), two cases were recorded, as it was the case in 2021. The current annual prevalence is significantly below the confidence interval of the basis prevalence (2.9 per 10,000 births). In 2016, the annual prevalence increased to a maximum value of 5.0 per 10,000 births and has been falling since then.

The European confidence interval determined by EUROCAT of the prevalence 2009-2020 (1.3 per 10,000 births) lies well below the confidence interval of the basis prevalence of Saxony-Anhalt. This year's prevalence value of Saxony-Anhalt lies within the European comparative values.

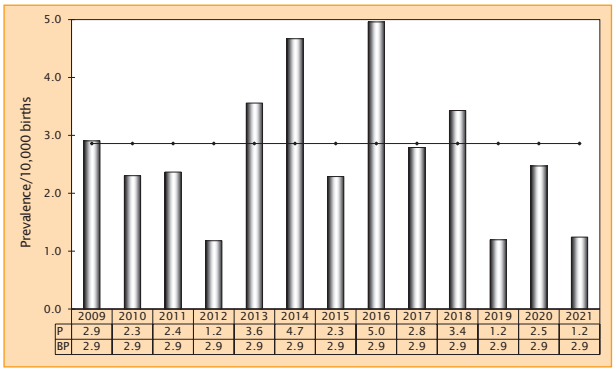
additional information:

prgenancy outcome	1 x live births, deceased until 7 days of life 1 x termination of pregnancy
sex	2 x male
number of isolated malformations/MCA	1 x MCA 1 x isolated

One live birth with bilateral nonfunctioning hypoplastic kidneys died after one day of life. In another case of a fet with bilateral nonfunctional cystic dysplastic kidneys the pregnancy was terminated after 20 weeks of gestation after discovery of the Potter sequence. Both were affected by pulmonary hypoplasia as a result of anhydramnios. Medication use by the mothers was not reported to the malformation monitoring.

Malformation combinations (MCA) or superordinated syndromes detected:

- urethral valves in the posterior part of the urethra, urinary bladder neck obstruction, megacystis, bilateral megaureter, DUP IV. grade right, sandal gap left



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	2.9	2.3	2.4	1.2	3.6	4.7	2.3	5.0	2.8	3.4	1.2	2.5	1.2
BP	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9	2.9

Fig. 30: Development of prevalence/10,000 births with Potter sequence in Saxony-Anhalt since 2009

In 2021, one Potter sequence per 8,048 births was registered in Saxony-Anhalt.

NOTE

What are ACE inhibitors and what is Sartan fetopathie?

The group of pharmaceuticals „sartans" were developed from ACE inhibitors. Mainly used in the antihypertensive therapy, they have a teratogenic effect in case of maternal intake during second and third trimenon of pregnancy. The suspected pathomechanism of both substances results in a reduced perfusion of the foetal organs, in particular of the kidneys. That means both substances interrupt the renin-angiotensin system at different points. The result of such a fetal damage is an intrauterine oliguria. Since amniotic fluid production depends from the second trimenon on mainly from fetal 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, limbs deformity, 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).

For further detailed information about this topic, please visit the website of the pharmacovigilance and advisory centre for embryonic toxicology (www.embyotox.de).

10.24 Renal agenesis, unilateral (Q60.0/Q60.2)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	5	3.11	↓
	Reporting period 2009-2020		
	Basis prevalnce/ 10,000 births	Confidence interval (CI 95%)	
	5.62	4.65 - 6.74	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.81	3.68 - 3.94	

This **year's prevalence** for a unilateral missing kidney **(2021: 3.1 per 10,000 births)** is similar to the value of the previous year (2020) and, with a basis prevalence of 5.6 per 10,000 births (2009-2020), it is considered very low. In the 2021 birth cohort of Saxony-Anhalt unilateral renal agenesis was found in only five births.

The confidence interval of the overall prevalence of the European registers (3.8 per 10,000 births) and the basis prevalence of Saxony-Anhalt do not overlap. The basis prevalence of Saxony-Anhalt is much higher. Compared to the European overall prevalence, the annual prevalence of Saxony-Anhalt of 2021 lies rather below.

The maximum prevalence value for unilateral renal agenesis was registered during the reporting period in 2012 (9.4 per 10,000 births). Since then, decreasing numbers have been reported and the prevalences are in or below the normal range. Figure 31 shows, similar to the previous year, the significant downward trend over the years 2008-2021 with a percentage change of -11.80% (CI -18.41% to -3.21%) (Chapter 10.38).

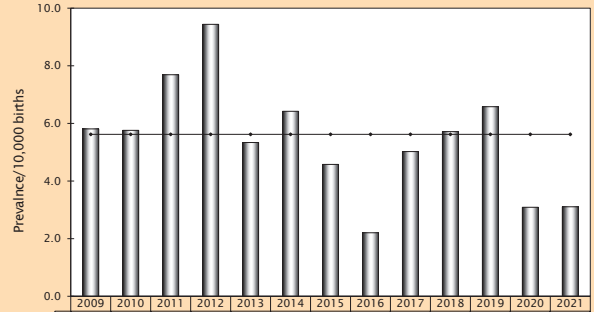
additional information:

prgenancy outcome	3 x live births 2 x termination of prgenancy
sex	3 x male 1 x femlae 1 x no inducation
number of isolated malformations/MCA	3 x MCA 2 x isolated

The left kidney was missing twice and once the right one. No information about the sidedness of the agenesis is available in two cases. In another two cases the unilateral renal agenesis was found among other severe and complex malformations in the 13th week of gestation during prenatal ultrasound screening. The pregnancy was terminated.

Malformation combinations (MCA) or superordinated syndromes detected:

- caudal regression syndrome with: rectal atresia, dysplastic right kidney, accessory finger on the left side, abdominal hypoplasia, low-set ears, wide nasal root, craniofacial dysmorphia
- anencephaly, univentricular heart, one rudimentary attached arm, hypoplastic thorax, hemivertebrae, scoliosis
- right anotia (grade IV), right-sided sound conduction disorder with atresia of the bony auditory canal



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	5.8	5.8	7.7	9.4	5.3	6.4	4.6	2.2	5.0	5.7	6.6	3.1	3.1
BP	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6	5.6

Fig. 31: Development of prevalence/10,000 births with unilateral renal agenesis in Saxony-Anhalt since 2009

In 2021, one child with cystic kidney per 3.219 births was registered in Saxony-Anhalt.

10.25 Cystic kidney (Q61.1-Q61.9)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	10	6.21	↔
	Reportin period 2009-2020		
	Basis prevalence 10,000 births	Confidence interval (CI 95%)	
	7.32	6.20 - 8.58	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

Polycystic kidneys are characterized by numerous fluid-filled cysts in the kidneys. The progressive kidney degeneration leads to the loss of function due to malformation and to a sooner or later kidney failure. With ten births affected by this malformation in the birth year of 2021 in Saxony-Anhalt, this **year's prevalence (2021: 6.2 per 10,000 births)** corresponds to the basis prevalence (2009-2020: 7.3 per 10,000 births). It is close to the lower confidence limit, just within the interval of the basis prevalence.

Europe-wide comparative values for the prevalence of the indicator malformation cystic kidneys are not available from EUROCAT.

additional information:

pregnancy outcome	9 x live births 1 xtermination of pregnancy
sex	4 x male 6 x female
number of isolated malformations/MCA	6 x MCA 4 x isolated

One fet showed in the 12th WOG as a symptom of a caudal regression syndrome, beside the cystic kidney on the right side also a missing kidney on the left side. This pregnancy was terminated prematurely. In three full term births in 2021, bilateral cystic kidney degeneration was registered. Another six children were affected by unilateral polycystic kidney.

Malformation combinations (MCA) or superordinated syndromes detected:

- caudal regression syndrome with: rectal atresia, dysplastic right kidney, accessory finger on the left side, abdominal hypoplasia, low-set ears, wide nasal bridge, craniofacial dysmorphia
- Laurence-Moon-Biedl-Bardet syndrome with: PFO at full term infant, postaxial polydactyly
- cleft soft palate, midface hypoplasia, hepatomegaly
- bilateral DUP III. degree, ureterocele on the right side, bilateral retarded hip maturity
- hexadactyly, macrocephaly
- multiple renal arteries left

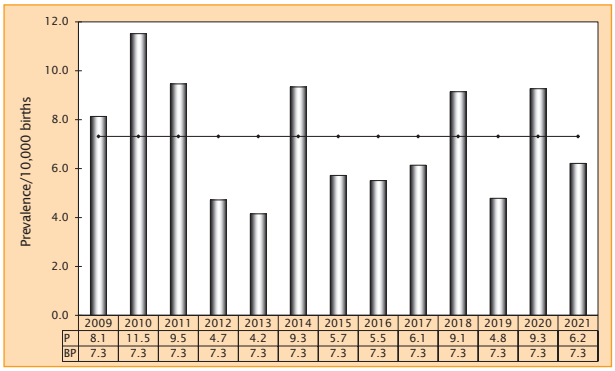


Fig. 32: Development of prevalence/10,000 births with cystic kidneys in Saxony-Anhalt since 2009

In 2021, one child with cystic kidney per 1,610 births was registered in Saxony-Anhalt.

10.26 Bladder Exstrophy (Q64.1)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	1	0.62	↔
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.34	0.14 - 0.70	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

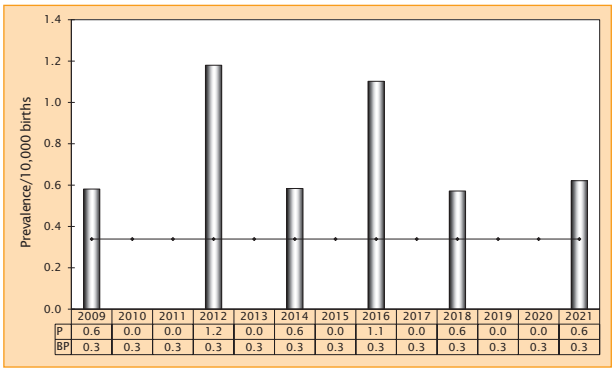
In 2021, one birth with this extremely rare malformation was registered, after two years in which no exstrophy of the urinary bladder was diagnosed in Saxony-Anhalt. The resulting **annual prevalence (2021: 0.6 per 10,000 births)** is in the upper normal range of the basis prevalence of Saxony-Anhalt (2009- 2020: 0.3 per 10,000 births).

During the years of the reporting period, a total of only eight children/fetuses were found with urinary bladder exstrophy. In five cases, as well as in the current year, the bladder exstrophy developed in addition to the also very rare malformation epispadias. In case of a combined occurrence of both malformations, they are classified only as indicator malformation exstrophy of the urinary bladder.

EUROCAT does not provide European-wide prevalence values separately for the malformation exstrophy of the urinary bladder. For the urinary bladder exstrophy-epispadias complex, EUROCAT indicates a prevalence of 0.65 per 10,000 births (2009-2020; CI 0.60-0.71).

additional information:

prgenancy outcome	1 x live births
sex	1 x male
number of isolated malformations/MCA	1 x isolated



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	0.6	0.0	0.0	1.2	0.0	0.6	0.0	1.1	0.0	0.6	0.0	0.0	0.6
BP	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

Fig. 33: Development of prevalence/10,000 births with bladder exstrophy in Saxony-Anhalt since 2009

In 2021, one bladder exstrophy per 16,096 births was registered in Saxony-Anhalt.

10.27 Preaxial polydactyly (Q69.1/Q69.2)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	8	4.97	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.30	2.56 - 4.18	
EUROCAT (Full members)	period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

As in the previous year, the current **annual prevalence (2021: 5.0 per 10,000 births)** for the indicator malformation preaxial polydactyly is significantly higher than the basis prevalence of Saxony-Anhalt (2009-2020: 3.3 per 10,000 births). After high prevalence values between 2008 and 2010, the values remained in the normal range in the following years and from 2016 to 2019 they could be found always below the confidence interval of the basis prevalence. In our trend analysis of the last report, this development led to a clear downward trend. The trend is currently no longer supported by the high prevalences which were registered during the last two years.

Comparative EUROCAT data for preaxial polydactyly is not available.

In only about one third of births with polydactyly, supernumerary thumbs or big toes were reported, which are characteristic of the indicator malformation preaxial polydactyly. For preaxial and postaxial polydactyly overall, the prevalence of 2021 lies at 13.0 per 10,000 births, which is within the normal range (2009-2020: 12.5 per 10,000 births) (Chapter 9).

Three children had an additional right thumb and three an additional left thumb. One child showed an accessory left big toe. One fet had bilateral toes in addition to bilateral polysyndactyls and postaxial hexadactylia of the hands and feet. Aditionally, symptoms of an orofaciodigital syndrome were registered.

additional information:

pregnancy outcome	7 x live births 1 xtermination of pregnancy
sex	4 x male 4 x female
number of isolated malformations/MCA	2 x MCA 6 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- orofaciodigital syndrome with: bilateral polysyndac tyly, postaxial polydactyly of hands and feet, cleft of the hard and soft palate, ASD II, persistent left superi or vena cava, sacral dimple
- penoscrotal hypospadias, sacral dimple, sandal gap, PFO at preterm infant, umbilical hernia, deviation of the nasal septum

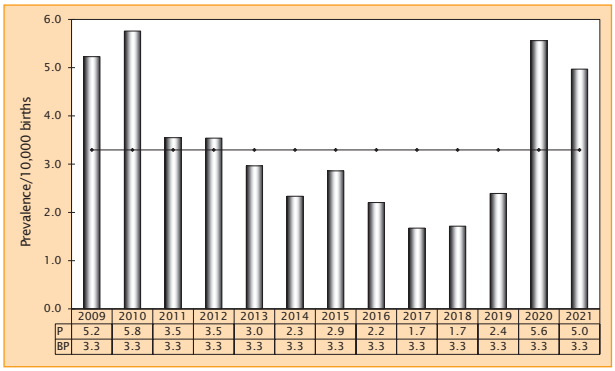


Fig. 34: Development of prevalence/10,000 births with preaxial polydactyly in Saxony-Anhalt since 2009

In 2021, on preaxial polydactyly 2.012 births was registered in Saxony-Anhalt.

10.28 Limb reduction defects of both upper and lower limbs (Q71./Q72./Q73.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	8	4.97	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence intervall (CI 95%)	
	7.85	6.69 - 9.16	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	5.10	4.95 - 5.25	

In 2012, a maximum value of 14.7 per 10,000 births was registered for reduction malformations of the extremities. Since then, the indicator malformation **prevalence** has been decreasing and shows up in 2021 **(5.0 per 10,000 births),** similar to the last four years, considerably lower than the basis prevalence (2009-2020: 7.8 per 10,000 births). The decreasing prevalence we registered during the time period of 2007-2020 has weakened in the trend analysis of the last report. The value of the current analysis from 2008-2021 is just barely no longer significant (chapter 10.38).

EUROCAT gives an overall prevalence for reduction malformations of the extremities of only 5.1 per 10,000 births (2009-2020). The prevalence interval of the total prevalence of the European malformation registries lies far below that of the basis prevalence of Saxony-Anhalt. Therefore, this year's very low prevalence of Saxony- Anhalt is still in the lower range of the European average prevalence

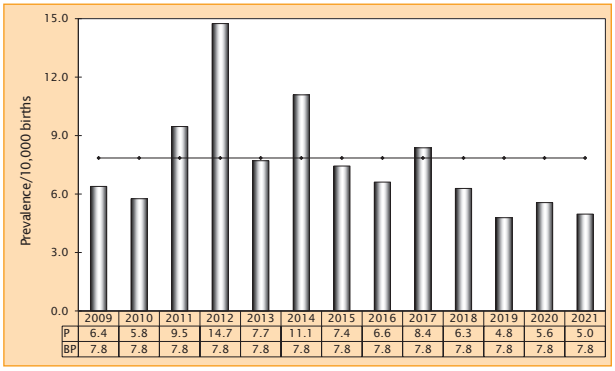
additional information:

pregnancy outcome	4 x live births 4 xtermination of pregnancy
sex	3 x male 3 x female 2 x no indication
number of isolated malformations/MCA	5 x MCA 3 x isolated

Reduction malformations of the extremities were seen in 2021 in two births bilaterally and in six births unilaterally, whereby twice only the right side was affected and three times only the left side. Once the side was not indicated. Reduction malformations of the arms, hands and fingers were reported more frequently (5 x) than those of legs, feet and toes (2 x). One fet showed as a symptom of thanatophoric dysplasia type I a micromelia of all four extremities.

Malformation combinations (MCA) or superordinated syndromes detected:

- thanatophoric dysplasia type I with: hydrocephalus internus, limited mobility of the knees and elbow joints, bilateral bending of humerus and femur, narrow thorax, sunken root of the nose
- omphalocele, amniotic ligaments, missing pectoral muscle on the right, hemivertebrae, scoliosis
- amniotic furrows, clubfoot on the right side, bony syndactyly of left thumb and finger (digit I / digit II)
- megalencephaly, brain ventricle asymmetry, macrocephaly



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	6.4	5.8	9.5	14.7	7.7	11.1	7.4	6.6	8.4	6.3	4.8	5.6	5.0
BP	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8

Fig. 35: Development of prevalence/10,000 births with limb reduction defects in Saxony-Anhalt since 2009

In 2021, one limb reduction defect per 2.012 births was registered in Saxony-Anhalt.

10.29 Diaphragmatic hernia (Q79.0)

Saxony-Anhalt	2021		
	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	8	4.97	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.42	1.80 - 3.19	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.0	2.88 - 3.12	

Eight children/fetuses with diaphragmatic hernia were registered. The resulting maximum **annual prevalence** during the reporting period **(2021: 5.0 per 10,000 births)** exceeds the current annual prevalence and the basis prevalence for diaphragmatic hernia in Saxony-Anhalt (2009-2020: 2.4 per 10,000 births) substantially. However, no trend can be identified.

A comparison across Europe shows that the confidence interval of the overall prevalence reported by EUROCAT (2009-2020: 3.0 per 10,000 births) is in the upper range of the confidence interval of the Saxony-Anhalt basis prevalence for diaphragmatic hernia. Because of the larger observed population, the European confidence interval is narrower. The annual prevalence of Saxony-Anhalt of 2021 can be found accordingly also far above.

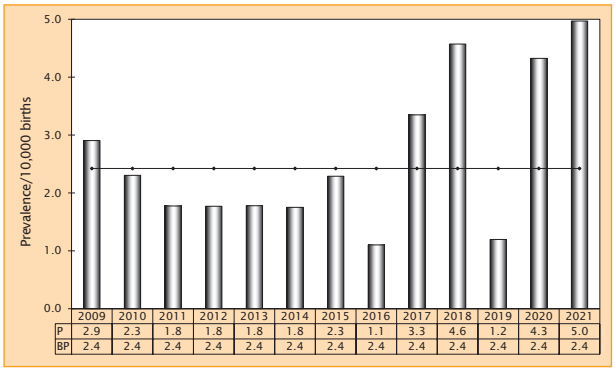
additional information:

pregnancy outcome	3 x live births 3 x live births deceased until 7 days of life 1 x termination of pregnancy 1 x no indication
sex	6 x male 2 x female
number of isolated malformations/MCA	6 x MCA 2 x isolated

Six of the eight diaphragmatic hernias were described as unilateral, four of them on the left side and two without laterality. Diaphragmatic hernias develop between 8 and 10 weeks of gestation. In five infants/fetuses, the diaphragmatic hernia was discovered prenatally between the 17th and 22nd week of gestation and in two births it was diagnosed postnatally. For one child no information is available about the time of diagnosis.

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: microcephaly, dextrocardia, sandal gap(s)
- Edwards syndrome
- Trisomy 9 with: Dandy-Walker syndrome, thoracic hypoplasia, clubfoot on the right
- preductal aortic isthmus stenosis, hepatomegaly
- unilateral cleft lip, VSD
- bilateral DUP II. grade, megaureter and ureteral orifice stenosis, bilateral undescended testis at full term infant



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	2.9	2.3	1.8	1.8	1.8	1.8	2.3	1.1	3.3	4.6	1.2	4.3	5.0
BP	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4	2.4

Fig. 36: Development of prevalence/10,000 births with diaphragmatic hernia in Saxony-Anhalt since 2009

In 2021, one diaphragmatic hernia per 2.012 births was registered inSaxony-Anhalt.

10.30 Omphalocele (Q79.2)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	5	3.11	↔
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.44	2.69 - 4.34	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.74	3.61 - 3.87	

As in the previous year, omphalocele occurred in five cases in Saxony-Anhalt in 2021. The resulting **annual prevalence (3.1 per 10,000 births)** for the indicator malformation
lies in the middle of the normal range of the basis prevalence of Saxony-Anhalt (2009-2020: 3.4 per 10,000 births).

The confidence interval of the basis prevalence of Saxony-Anhalt corresponds to the overall prevalence of the European malformation registries (2009-2020: 3.7 per 10,000 births). However, since the confidence interval of Saxony-Anhalt has wider limits than that of the European prevalence, the annual prevalence of Saxony-Anhalt for 2021 is somewhat lower.

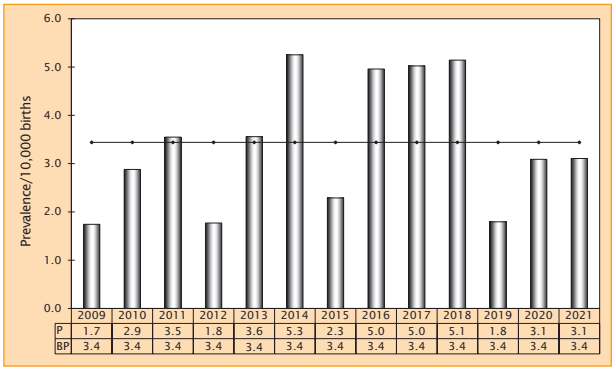
additional information:

pregnancy outcome	2 x live births 3 xtermination of prgenancy
sex	1 x male 1 x female 3 x no indication
number of isolated malformations/MCA	3 x MCA 2 x isolated

An omphalocele occurs when the umbilical hernia, which is physiologically present until the 10th week of gestation, does not regress. 4 times the abdominal wall defect omphalocele was detected between the 11th and 13th week of gestation during prenatal ultrasound screening.

Malformation combinations (MCA) or superordinated syndromes detected:

- Patau syndrome with: cardiac malformation
- complete amelia of the right arm, amniotic lacerations, absent pectoral muscle on the right, hemivertebrae, scoliosis
- Meckel's diverticulum



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.7	2.9	3.5	1.8	3.6	5.3	2.3	5.0	5.0	5.1	1.8	3.1	3.1
BP	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4

Fig. 37: Development of prevalence/10,000 births with omphalocele in Saxony-Anhalt since 2009

In 2021, one omphalocele per 3.219 birth was registered in Saxony-Anhalt.

10.31 Gastroschisis (Q79.3)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	2	1.24	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	3.73	2.95 - 4.66	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.68	2.57 - 2.79	

In 2021, only two births in Saxony-Anhalt were diagnosed with the indicator malformation gastroschisis. The abdominal wall defect was diagnosed in one child in the 13th and in the other child in the 17th week of gestation during prenatal ultrasound screening. Both children were delivered by primary sectio at 34 and 35 weeks of gestation, in a university hospital and subsequently operated.

In the past 30 years, not such a low **annual prevalence** for gastroschisis has been registered than in this year **(2021: 1.2 per 10,000 births)**. This minimum value lies significantly below the normal range of the basis prevalence of Saxony-Anhalt (2009-2020: 3.7 per 10,000 births). births). In the years 2011, 2014 and 2018, values far above the confidence interval were observed.

The Europe-wide comparison shows that the confidence interval of the Saxony-Anhalt basis prevalence for gastroschisis is significantly above the confidence interval of the overall prevalence reported by EUROCAT (2009-2020: 2.7 per 10,000 births). The prevalence of Saxony-Anhalt is lower than the lower confidence limit of the European prevalence.

additional information:

prgenancy outcome	2 x live birth
sex	2 x female
number of isolated malformations/MCA	1 x MCA 1 x isolated

Malformation combinations (MCA) or superordinated syndromes detected:

- small intestinal stenosis, VSD

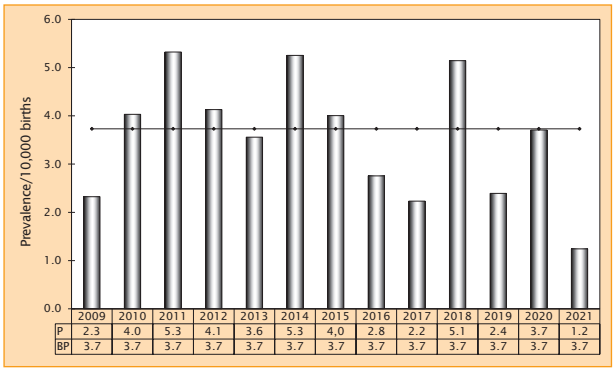


Fig. 38: Development of prevalence/10,000 births with gastroschisis in Saxony-Anhalt since 2009

In 2021, one gastroschisis per 8.048 births was registed in Saxony-Anhalt.

10.32 Prune-Belly syndrome (Q79.4)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	1	0.62	↔
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.82	0.48 - 1.32	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	0.14	0.12 - 0.17	

The indicator malformation prune-belly sequence is observed only in isolated cases. After it was not diagnosed at all in Saxony-Anhalt during the last two years, a prune-belly sequence was detected during a spontaneous abortion in the 16th week of gestation in 2021. A prune-belly sequenmce was regsitrered since the year 2000 only once, and in 2011 in five children/fetuses per year (maximum) in Saxony-Anhalt.

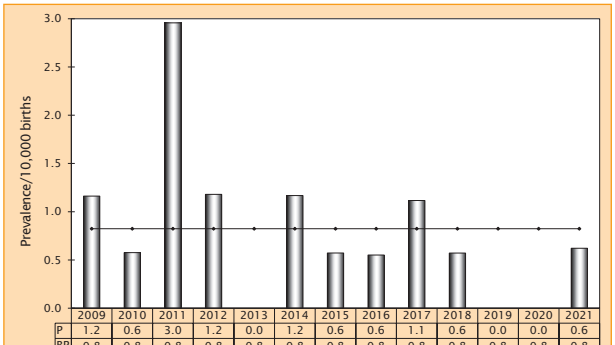
This year's **annual prevalence** in Saxony-Anhalt **(2021: 0.6 per 10,000 births)** lies within the range of the basis prevalence (2009-2020: 0.8 per 10,000 births). Even with three affected children/fetuses per year, the prevalence would no longer be within the normal range.

Since this year, European prevalence figures for the prune-belly sequence are available for comparison.

The 2021 annual prevalence of Saxony-Anhalt exceeds the European prevalence provided by EUROCAT (2009-2020: 0.1 per 10,000 births) significantly. Also the confidence interval of the basis prevalence of Saxony-Anhalt lies above the overall prevalence of the European registries (2009-2020) of this rare malformation.

additional information:

pregnancy outcome	1 x spontaneous abortion
sex	1 x male
number of isolated malformations/MCA	1 x isolated



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.2	0.6	3.0	1.2	0.0	1.2	0.6	0.6	1.1	0.6	0.0	0.0	0.6
BP	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8

Fig. 39: Development of the prevalence/10,000 births with Prune belly syndrome in Saxony-Anhalt since 2009

In 2021, on Prune-Belly syndrome per16.096 births was registered in Saxony-Anhalt..

10.33 Down´s Syndrom - Trisomy 21 (Q90.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	35	21.74	↔
	Reporting period 2009-2020		
	Basis Prevalence/ 10,000 births	Confidence interval (CI 95%)	
	20.55	18.64 - 22.60	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	24.55	24.22 - 24.88	

Trisomy 21 represents, with a basis prevalence of 20.5 per 10,000 births (2009-2020), one of the five most common malformations in Saxony-Anhalt. In the year 2021 it was detected in 35 children/fetuses. The resulting **prevalence (2021: 21.7 per 10,000 births)** lies in the middle range of the basis prevalence. When taking into account both, the prevalence of all pregnancy outcomes and the number of live births (2009-2020: 9.3 per 10,000 births), the European criterion for a rare disease of < 5.0 per 10,000 births is not given.

The basis prevalence as well as the annual prevalence 2021 of Saxony-Anhalt lies clearly below the European prevalence determined by EUROCAT of 24.5 per 10,000 births (2009-2020). Since the probability of Down`s syndrome increases with the age of the mother, it is possible that the lower prevalences of Saxony-Anhalt may result from the lower materal average age at birth of children in comparison to the EU average (2013-2020: 29.4 years vs. 30.6 years*).

additional information:

pregnancy outcome	14 x live births 1 x live births , deceased after 7 days of life 1 x sponatneous abortion 19 x termination of pregnancy
sex	16 x male 18 x female 1 x no indication
number of isolated malformations/MCA	15 x MCA 20 x isolated

More than half of the pregnancies (54.3%) were terminated in 2021. They were terminated prematurely at Ø 17.0 WOG (median 17.0 WOG), after averragely at Ø 14.8 WOG the first prenatal diagnosis was made. The earliest termination occurred at 14 WOG and the latest at 20 WOG.

Malformation combinations (MCA) or superordinated syndromes detected:

- duodenal stenosis, pancreas anulare, syndactyly of fingers (digit III / IV) right
- DUP III. degree left, DUP I. grade right
- Gerbode defect, DUP III grade right, DUP I. grade left, transient abnormal myelopoiesis
- Tetralogy of Fallot, vascular ring of the great arteries
- VSD, bilateral conductive disorder with stricture of the osseous auditory canals
- ASD, bilateral combined sound conduction and sensation disorder, umbilical hernia
- Canalis atrioventricularis communis, midface hypoplasia, non-hemodynamically effective PDA at preterm infant
- Canalis atrioventricularis communis, hydrocephalus internus
- Canalis atrioventricularis communis
- ASD II
- cardiac malformation
- bilateral sound sensation disturbance
- VSD, umbilical hernia, deep nuchal-hairline boundary, damage due to gestational diabetes and COVID-19 infection of the mother
- 2 x clubfeet

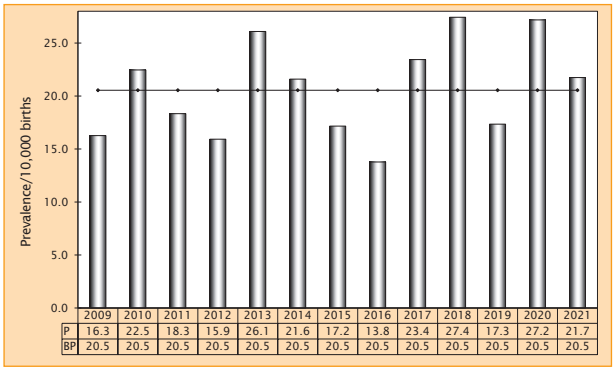


Fig. 40: Development of prevalence/10,000 births with Down`s syndrome in Saxony-Anhalt since 2009

In 2021, one Down`s syndrome per 460 births was registered in Saxony-Anhalt.

* Source: https://ec.europa.eu/eurostat/databrowser/view/DEMO_FORDAGEC__custom_3743023/default/table
Titel: Live births by mother‘s age and birth order

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

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	8	4.97	↑
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	1.26	0.82 - 1.85	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.27	2.17 - 2.37	

Patau syndrome is normally the third most common trisomy, this year the second most common. As of birth year 2021, it was diagnosed exceptionally often in eight births. The **annual prevalence** determined from this value **(2021: 5.0 per 10,000 births)** significantly exceeds the basis prevalence of Saxony-Anhalt (2009- 2020: 1.3 per 10,000 births). During the observation period since 1980, there has never been such a high prevalence. The previous maximum was reached in 1998 with 3.9 per 10,000 births.

The confidence interval of the basis prevalence of Saxony-Anhalt for Patau syndrome lies below the average European prevalence provided by EUROCAT (2009-2020: 2.3 per 10,000 births). This year's prevalence value of Saxony-Anhalt lies also considerably above the upper confidence limit of the prevalence given by EUROCAT.

Trend analysis from 2008-2021 (Section 10.38) shows a significant increasing trend with a percent change of 20.86% (CI 3.37% to 46.83%). Although the annual prevalences since 2008 have always been within the confidence interval of the basis prevalence, it is unmistakable that in the early years of the reporting period (until 2014) the annual prevalences were always located in the lower half of the confidence interval of the basis prevalence and from 2015 onwards mostly above it.
It is possible that due to diagnosis at an increasing earlier stage of pregnancy, the number of confirmed Patau syndromes is increasing as well. The development remains to be observed.

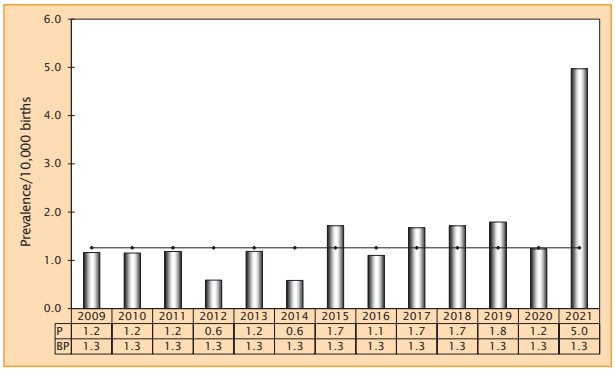
additional information:

pregnancy outcome	1 x live birth ,deceased until 7 days of live 7 x termination of pregnancy
sex	3 x male 4 x female 1 x no indication
number of isolated malformations/MCA	6 x MCA 2 x isolated

In seven fetuses there were abnormal, mostly severe ultrasound results (6 x) or a positive result of a NIPT (3 x) which led to an invasive prenatal chromosome examination. The ultrasound screening took place between 12th and 22nd WOG, in which a Patau syndrome was diagnosed. In case of one live birth, the Patau syndrome was not known prenatally.

Malformation combinations (MCA) or superordinated syndromes detected:

- microcephaly, diaphragmatic hernia, dextrocardia
- 3 x holoprosencephaly (1 x with TGA, 1 x with cardi ac malformation, polydactyly)
- omphalocele, cardiac malformation
- accessory finger left



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.2	1.2	1.2	0.6	1.2	0.6	1.7	1.1	1.7	1.7	1.8	1.2	5.0
BP	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3	1.3

Fig. 41: Development of prevalence/10,000 births with a Patau syndrome in Saxony-Anhalt since 2009

In 2021, one Patau syndrome (trisomy 13) per 2.012 births was registered in Saxony-Anhalt.

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

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	6	3.73	↔
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	4.55	3.68 - 5.57	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	6.10	5.94 - 6.27	

Edwards syndrome is generally the second most common of the trisomies. Six births were affected by trisomy 18 in Saxony-Anhalt in 2021. This determines a **prevalence of 3.7 per 10,000 births**, which is still within the confidence range of the basis prevalence (2009-2020: 4.6 per 10,000 births), but close to the lower tolerance limit.

The basis prevalence of Saxony-Anhalt for Edward's Syndrome is not as high as the European-wide total prevalence provided by EUROCAT (2009-2020: 6.1 per 10,000 births). Thus, the current prevalence value (2021) of Saxony-Anhalt can be considered as very low compared to the European prevalence. Since the age of the pregnant woman influences the occurrence of an Edwards syndrome, the different prevalence levels probably reflect the average maternal age in Saxony-Anhalt in comparison to the European maternal age (2013-2020: 29.4 years vs. 30.6 years*).

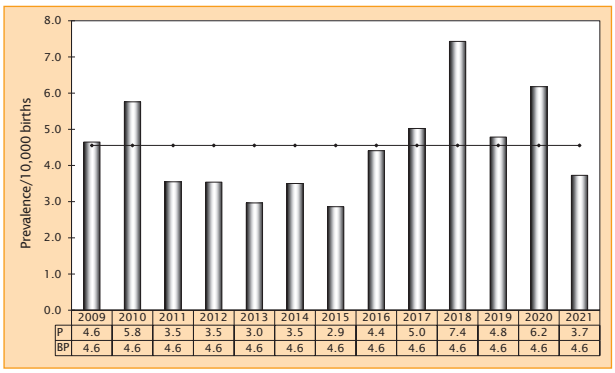
additional information:

pregnancy outcome	1 x live birth 5 x termination of pregnancy
sex	1 x male 3 x female 2 x no indication
number of isolated malformations/MCA	2 x MCA 4 x isolated

In all six children/fetuses with Edwards syndrome, the diagnosis was made prenatally. The earliest findings resulted from NIPT and ultrasound examination during the 12th/13th week of gestation. Between the 12th and the 22nd week of gestation, the diagnoses were then confirmed by invasive chromosome examination. In case of the live birth, the diaphragmatic hernia was operated and the infant survived for at least one year.

Malformation combinations (MCA) or superordinated syndromes detected:

- unilateral diaphracmatic hernia
- VSD



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	4.6	5.8	3.5	3.5	3.0	3.5	2.9	4.4	5.0	7.4	4.8	6.2	3.7
BP	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6	4.6

Fig. 42: Development of prevalence/10,000 births with Edwards syndrome in Saxony-Anhalt since 2009

In 2021, one Edwards syndrome per 2,683 births was registered in Saxony-Anhalt.

* Quelle: https://ec.europa.eu/eurostat/databrowser/view/DEMO_FORDAGEC__custom_3743023/default/table
Titel: Live births by mother's age and birth order
letzte Aktualisierung: 22.06.2022 23:00

10.36 Turner Syndrome (Q96.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	1	0.62	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.13	1.55 - 2.86	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	2.58	2.47 - 2.69	

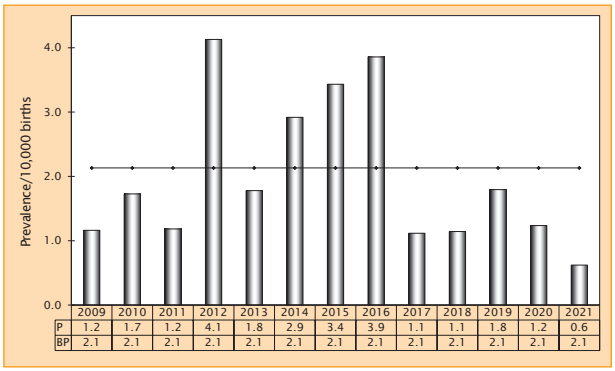
The rare indicator malformation Turner syndrome, also called monosomy X, was discovered only once in Saxony-Anhalt in 2021. Prenatal ultrasound screening of the fetus in the 11th week of gestation revealed a marked hydrops fetalis and a hygroma colli.

In the current year (2021), this results in an **annual prevalence of 0.6 per 10,000 births.** This annual prevalence is a minimum value in the reporting period and lies noticeably below the basis prevalence of Saxony-Anhalt (2009-2020: 2.1 per 10,000 births). At least three affected girls would have been expected. It can be assumed that not all Turner syndromes are detected pre- or neonatally.

The confidence limits of the basis prevalence of Saxony-Anhalt are wider than those of the confidence interval of the Europe-wide prevalence provided by EUROCAT (2009-2020: 2.6 per 10,000 births). While the Saxony-Anhalt basis prevalence and the European prevalence can be seen at about the same level, the annual prevalence of Saxony-Anhalt of 2021 lies well below the overall European prevalence.

additional information:

pregnancy outcome	1 x termination of pregnancy
sex	1 x female
number of isolated malformations/MCA	1 x isolated



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.2	1.7	1.2	4.1	1.8	2.9	3.4	3.9	1.1	1.1	1.8	1.2	0.6
BP	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1

Fig. 43: Development of prevalence/10,000 births with Turner syndrome in Saxony-Anhalt since 2009

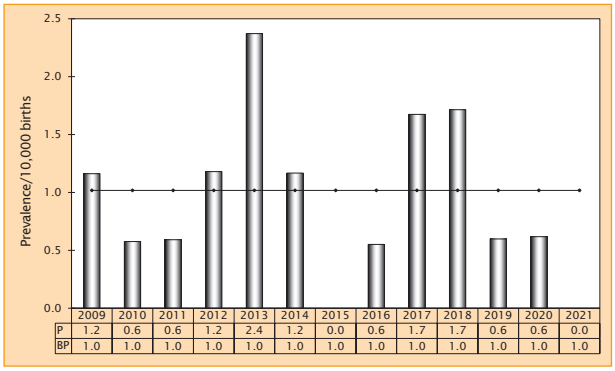
In 2021, one Turner syndrome per 16,096 births was registered in Saxony-Anhalt.

10.37 Klinefelter syndrome/male gonosome anomalies (Q98.)

	2021		
Saxony-Anhalt	Number	Prevalence/ 10,000 births	Comparison to basis prevalence
	0	0.0	↓
	Reporting period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence intrval (CI 95%)	
	1.02	0.63 - 1.56	
EUROCAT (Full members)	Period 2009-2020		
	Basis prevalence/ 10,000 births	Confidence interval (CI 95%)	
	no information	no information	

As already in 2015, no child/fet was born in Saxony-Anhalt in this year (2021) with Klinefelter syndrome or a male gonosome anomaly. The occurrence of the indicator malformation is rare. Between 2009 and 2020, there were only 21 affected individuals in total. From this, a basis prevalence for the indicator malformation Klinefelter syndrome/male gonosome anomalies of Saxony-Anhalt of 1.0 per 10,000 births (2009-2020) is calculated. The maximum prevalence (2.4 per 10,000 births) of the reporting period was reached in 2013.

Separately, the prevalence of Klinefelter syndrome (Q98.0-Q98.4) in Saxony-Anhalt during the reporting period lies at 0.87 per 10,000 births (2009-2020; CI 0.44-1.26). Since this year, no prevalence data is provided by EUROCAT for Klinefelter syndrome any more.



	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021
P	1.2	0.6	0.6	1.2	2.4	1.2	0.0	0.6	1.7	1.7	0.6	0.6	0.0
BP	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0

Fig. 44: Development of prevalence/10,000 births with Klinefelter syndrome/male gonosome anomalies in Saxony-Anhalt since 2009

In 2021, no Klinefelter syndrome/male gonosome anomalies was registered in Saxony-Anhalt.

10.38 Trend analysis of indicator malformations

The chapters 10.1 to 10.37 of the annual report show evaluations of the current frequency of indicator malformations in a long-term and international comparison. The definition of all indicator malformations (chapter 10.0) is based on the description of the ICBDSR (International Clearinghouse for Birth Defects Surveillance and Research). One of the tasks of the malformation monitoring center is to identify trends of malformations. The development of the incidence in the **time frame of 2008 to 2021** is evaluated separaely in chapter 10.38.

In total, 210 births with indicator malformations were registered in 2021 in Saxony-Anhalt, 23 of them with two indicator malformations and four with three indicator malformations. A total of 241 indicator malformations were diagnosed. Of the 210 children/fetuses with indicator malformations, 84 had multiple malformations. In 2009-2020, an average of 74.5% of children affected by an indicator malformation were live births, 2021 152 (72,4%). Of these, nine died in the first year of life. Indicator malformations were recorded in 0.9% of spontaneous abortions up to the 16th WOG (5 cases). The proportion of fetuses whose pregnancies were terminated was at 24.8% in 2021. This figure is slightly higher than in comparison to the value of the total reporting period (2009-2020: 23.52%).

In 1.30% of all children/fetuses in Saxony-Anhalt, one of the 37 indicator malformations was identified in 2021. The annual prevalence in 2021 is therefore significantly lower than the basis prevalence (2008-2019: 1.43%, CI 1,38-1,49).

The objective of the below presented trend analysis is to identify long-term trends in the occurrence of malformations. Therefore, the strength and orientation of the changes of indicator malformation prevalences over the period 2008-2021 is examined in the current annual report.

Trend estimation has been an integral part of the annual report for more than ten years. It is performed for indicator malformations that meet the basis requirement that, in the tested time period, the expected value for the malformation is at least five and the observed value is at least two. Indicator malformations belong, for the most part, to the rare diseases.

In order to fulfill the precondition for the test of change in case of small frequencies, two years are combined into one interval and the trend is analyzed. This procedure did not change during the last two years.

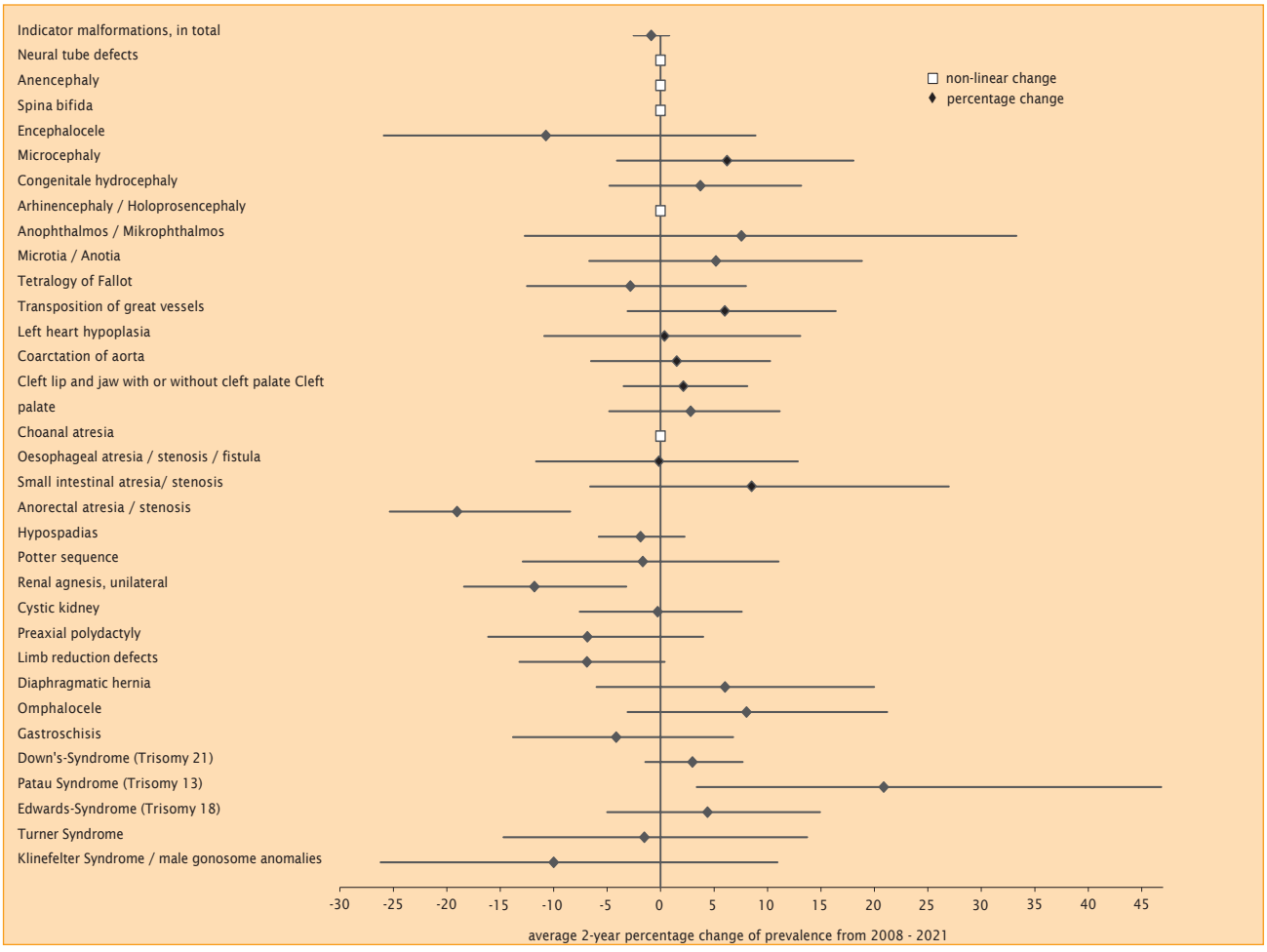


Fig. 45: Trend analysis 2008 to 2021 with average percentage change of two-year prevalence (95% CI)

Figure 45 on page 64 and the table on this page show the estimated average percentage changes in the two-year prevalence of the indicator malformations for which the above-mentioned initial conditions apply. The mathematical basis of the analysis is binary logistic regression based on the maximum likelihood method.

The measure of the strength and direction of the percentage annual change is the regression coefficient B. In the case of a significantly increasing trend characterised by a positive regression coefficient, this is entered into the diagram on the right side of the ordinate axis, including the CI of 95%. In case of a decreasing trend, the regression coefficient can be found on the left side of the axis (in the negative range). The shown trend is significant if the confidence interval does not cover the zero value.

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 identify a non-linear trend. This applies for neural tube defects, anencephaly, spina bifida, arhinencephaly/holoprosencephaly, and choanal atresia.

A probability value of $p < 0.05$ for the linear percentage and $p > 0.01$ for the non-linear percentage means that the linear percentage dominates, and the non-linear percentage can be neglected. The observed trend is significant, corresponding to the regression coefficient B. A **significant increasing trend** can be observed for Patau syndrome during the reporting period. A **significant decreasing trend**, according to a negative regression coefficient B and a non-effective non-linear component, is observed for rectal and anal atresia/stenosis and unilateral renal agenesis.

All other below illustrated 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, no decision regarding a more frequently increase or decrease can be made, even though the non-linear percentage is not decisive for a trend evaluation.

	regression coefficient B in% B in%	confidence interval (CI of 95%)
Indicator malformations, in total	-0.88	-2.54 to 0.81
Encephalocele	-10.72	-25.90 to 8.89
Microcephaly	6.21	-4.09 to 18.06
Congenital hydrocephaly	3.72	-4.79 to 13.15
Anopthalmia / Micropthalmia	7.57	-12.72 to 33.29
Microtia / Anotia	5.17	-6.68 to 18.84
Tetralogy of Fallot	-2.83	-12.50 to 8.00
Transposition of great vessels	6.02	-3.10 to 16.39
Left heart hypoplasia	0.37	-10.90 to 13.06
Coarctation of aorta	1.51	-6.52 to 10.26
Cleft lip with or without cleft palate	2.13	-3.48 to 8.12
Cleft palate	2.82	-4.82 to 11.15
Oesophageal atresia/stenosis/fistula	-0.15	-11.65 to 12.84
Small intestinal atresia	8.51	-6.61 to 26.95
Anorectal atresia/stenosis	-19.03	-25.34 to 8.45
Hypospadias	-1.87	-5.80 to 2.26
Potter sequence	-1.68	-12.91 to 11.04
Renal agenesis, unilateral	-11.80	-18.41 to -3.21
Cystic kidney	-0.28	-7.59 to 7.61
Preaxial polydactyly	-6.85	-16.14 to 3.99
Limb reduction defects	-6.89	-13.21 to 0.38
Diaphragmatic hernia	6.02	-5.99 to 19.97
Omphalocele	8.04	-3.09 to 21.20
Gastroschisis	-4.15	-13.81 to 6.80
Down‘s-Syndrome (Trisomy 21)	2.97	-1.45 to 7.68
Patau Syndrome (Trisomy 13)	20.86	3.37 to 46.83
Edwards Syndrome (Trisomy 18)	4.39	-5.00 to 14.91
Turner Syndrome	-1.53	-14.72 to 13.72
Klinefelter Syndrome/male gonosome anomalies	-10.00	-26.20 to 10.93

13 Summary

On the basis of the nationwide malformation data, which are provided to the monitoring of malformations from all over the Federal State of Saxony-Anhalt, and which are recorded by the monitoring of malformations, an anual report is compiled since 1995 about the incidence of congenital malformations and anomalies as well as genetically caused diseases. With the help of the official birth figures of the Statistical Office of Saxony-Anhalt data of the years 2009-2021 was statistically evaluated and presented in the annual report 2021. For the determined prevalences of the indicator malformations, European prevalences of EUROCAT are listed. Saxony-Anhalt is the only state in Germany that currently holds up-to-date data about malformations.

In **2021, 16,024** children were **live births** in Saxony-Anhalt. Since 2016, the number decreased monotonously. In the reporting period (2009-2020), the average number lies at a rounded value of 17,126 per year. According to the Federal Statistical Office (Destatis) 795,492 children were live births in Germany in 2021. The birth rate lies at 1.58 children per woman. 2.0% of all newborns in Germany originate from Saxony-Anhalt.

According to the State Statistical Office, **72 children were stillborn** in 2021 in Saxony-Anhalt. This corresponds to one stillbirth per 223 live births. In the reporting period (2009-2020), the ratio is one stillbirth per 240 live births.

Basis for the analyses of the annual report is a total number of **16,096 live births and stillbirths in the year 2021** (chapter 1). In addition to the data about children, data from **58 terminations of pregnancy** and **26 spontaneous abortions** from the 16th WOG was collected.

In case of **588 children/fetuses** (3.65% of births) **major malformations** were reported in 2021. This results in a malformation rate significantly below the basis prevalence (2009-2020: 3.83%, CI 3.74-3.91%) in 2021. 522 children with major malformations were live births. Of these, 506 reached the first year of life (96.93%). In 58 fetuses (9.86% of children/fetuses with major malformations) the pregnancy was terminated prematurely (chapter 6).

As usual, ASD and VSD cardiac malformations are the two **most common single diagnoses** (0.96%; 0.50% of births) in 2021. These are followed in the frequency list (chapter 9), also with a standard value, by dilated uropathy II-IV. grade/ ureterocele (0.25% of the births) and Down`s syndrome (0.22% of births).

In 2021, 210 children/fetuses were diagnosed with one of the 37 clearly defined **indicator malformations** (chapter 10). The indicator malformations anencephaly, arhincephaly/holoprosencephaly, anophthalmia/microphthalmia, transposition of the great vessels, preaxial polydactyly, diaphragmatic hernia, and Patau's syndrome have a **higher annual prevalence** than the basis prevalence (2009-2020). A lower annual prevalence was seen for spina bifida, encephalocele, microtia/anotia, aortic valve stenosis, cleft lip and palate, choanal atresia, rectum and anal atresia/stenosis, epispadias, indifferent sex, Potter sequence, unilateral renal agenesis, reduction malformations of the extremities, gastroschisis, Turner syndrome and Klinefelter syndrome.

For the **58 malformation** caused termiantions of pregnancy, which were reported to the malformation monitoring in 2021, the pregnancies were terminated at Ø 17.2 WOG. The timing of abruptio differs depending on the type of malformation. In fetuses with a chromosomal aberration (58.6%) the pregnancies were terminated earliest at Ø 16.7 WOG, in the presence of multiple anomalies and other malformations (19.0%) at Ø 17,4 WOG and for fetuses with CNS malformation (22.4%) the latest at Ø 19.1 WOG (chapter 12).

Syndromes, multiple or complex malformations are topic of chapter 11. **Genetic/co-caused diseases or microdeletions affected** 39 children/fetuses in 2021. Ten children/fetuses were found to have a **sequence, association or a complex**. An **embryopathy or fetopathy** was present in eleven children, and five children/fetuses had a **congenital infection**. 57 children/fetuses were registered with a **chromosomal aberration**, most of them (35) suffered from Down`s syndrome.

The special topic in chapter 14.1 deals with the most common malformations, the congenital heart defects, their prevalence and outcome between 1980 and 2021. In comparison with other epidemiological evaluations, it is clear how important it is to define cardiac malformations as well as their classification by severity statements. In chapter 14.2, the effects of a COVID-19 infection during pregnancy, births and post partum are analysed once again. Additionally, the post-COVID syndrome and the value of COVID-19 vaccination is part of the analysis.

For the 2021 birth cohort, the malformation monitoring system received **1,982 reports** (chapter 4) about 1,733 children/fetuses. 588 children/fetuses had at least one major malformation, in 249 children/fetuses only minor malformations were reported. Furthermore, the data of children without malformations is essential as well, because only in the comparison (case-control-study-design) malformation risks can be evaluated.

With the help of many colleagues from different medical institutions who have been reporting congenital malformations for many years, a solid database has been created, which also served as basis for the 2021 annual report. **We would therefore like to express our sincere thanks to all our „senders", in the confidence that we will continue to work successfully together, and we are looking forward to go ahead .**

14. Focus theme

14.1 Congenital heart defects

Benefits of an epidemiological registration

Congenital Heart Defects (CHD) are the most frequent organ malformations in newborns in Europe [1]. Due to the pediatric cardiological therapie offers, combined with cardiac surgery and intensive care, currently more than 90% of children with a congenital heart defect reach adulthood. Despite all progress made in the treatment of CHD, it would be wrong to speak of a „cure of the heart defect". In almost all CHD patients, residual and secondary conditions are found in the course of morbidity and mortality of the patients. This led to the emergence of a new group of patients: Adults with congenital heart defects. Meanwhile more adults than children with congenital heart defects live in western Europe [2].

Questions from affected individuals or their parents about the prognosis of CHD in various forms present a challenge to caring physicians or even public health workers. The most significant question parents ask themselves after learning that their child has a serious heart defect: „What will happen to my child?" (consequences, implications), „Why did this happen?" (cause), and at some point, „What can we do to prevent it from happening again?" (prevention). Remarkably, our present answers are better than they were in the past, but they are still fragmentary and often based on data that is old and not population-based. Also the integration of the different strands of evidence into a life-long, person-centered progression remains a goal that is far from being achieved.

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The epidemiologic evaluation of data about CHD can help to fill these gaps. With its
focus on the methodologically founded analysis of health data in human populations, epidemiological studies can complement the wealth of clinical data from descriptive case series and reports, and can illuminate the multitude of current clinical studies about the „burden of disease associated with CHD", causes and prevention of CHD.

How common are congenital heart defects in Saxony-Anhalt?

The monitoring of malformation in Saxony-Anhalt analysed data of the birth cohorts 1980 to 2021 with focus on the incidence, the importance of prenatal diagnostics and the survival rate of Congenital Heart Defects (CHD).

For a better classification, data of the years 1980-2021 was divided into three groups and presented in table A and B on pages 76 and 77.

Overall, the prevalence of CHD at birth is approximately at one percent [3]. The summarized estimation of this figure is the subject of reviews and useful for public health purposes. However, for most clinical purposes, it is nearly useless and potentially misleading. Because of the causal heterogenity, the assessment of individual types of CHD (grouped by anatomy, severity, or embryology, depending on the goal of the analysis) is much more useful and more informative.

For example, the prevalence, temporal trends, and variability between studies vary considerably depending on the severity, as well as the burden of disease and costs do. Therefore, in table A, the various subgroups are listed in different columns (grouping is based on the groups defined by the EUROCAT network: without minor cardiac defects (CHD under exclusion of „Minors") and severe heart defects („Severe
CHD")) [1].

Severe CHD are less common, their burden of disease is greater and their reported prevalences are more consistent across studies. Accordingly, well-defined individual heart defects are presented in Table B.

Table A: Overview of children/fetuses with congenital heart defects 1980-2021 in Saxony-Anhalt

categories evaluated	Q20-Q26 heart defects, in total[1]		Q20-Q26 without minor heart defects[1,2]		Q20-Q26 severe heart defects[3,4]	
year of birth	number	%	number	%	number	%
1980-1999[5]	1,426	17.7	1,097	26.7		
2000-2010[6]	2,882	35.7	1,362	33.2	499	46.9
2011-2021[7]	3,766	46.6	1,644	40.1	566	53.1
total	8,074	100.0	4,103	100.0	1,065	100.0
relation to the total number of births in the coverage region[8]	%		%		%	
1980-2021[9]	1.25		0.63			
2000-2021[10]	1.75		0.79		0.28	
relation to the total number of live births (LB) in the coverage region[8]	%		%		%	
1980-2021[11]	1.18		0.57			
2000-2021[12]	1.66		0.70		0.23	
pregnancy outcome	number	%	number	%	number	%
live births (LB)	7,601	94.1	3,666	89.3	880	82.6
of which LB deceased	*549*	*6.8*	*402*	*9.8*	*101*	*9.5*
stillbirth (SB)	69	0.9	56	1.4	13	1.2
spontaneous abortions from 16 WOG	48	0.6	44	1.1	10	0.9
termination of pregnancy	356	4.4	337	8.2	162	15.2
gestational age live births (LB)	number	%	number	%	number	%
premature births (< 37th WOG)	2,236	29.4	705	19.2	198	22.5
full term births (37+ WOG)	4,716	62.0	2,407	65.7	651	74.0
no indication	649	8.5	554	15.1	31	3.5
live births, in total	7,601	100.0	3,666	100.0	880	100.0
maternal age	number	%	number	%	number	%
under 20	267	3.3	124	3.0	32	3.0
20 to 24	1,270	15.7	635	15.5	176	16.5
25 to 29	2,103	26.0	1,006	24.5	281	26.4
30 to 34	2,120	26.3	950	23.2	321	30.1
35 to 39	1,115	13.8	507	12.4	169	15.9
over 40	294	3.6	160	3.9	59	5.5
no indication	905	11.2	721	17.6	27	2.5
sex	number	%	number	%	number	%
male	4,231	52.4	2,129	51.9	616	57.8
female	3,774	46.7	1,909	46.5	420	39.4
no indication	69	0.9	65	1.6	29	2.7
chromosomal/ genetic	number	%[13]	number	%[13]	number	%[13]
1980-1999	190	13.3	152	10.7		
2000-2010	323	11.2	200	6.9	108	3.7
2011-2021	348	9.2	230	6.1	120	3.2
in total	861	10.7	582	7.2	228	3.4

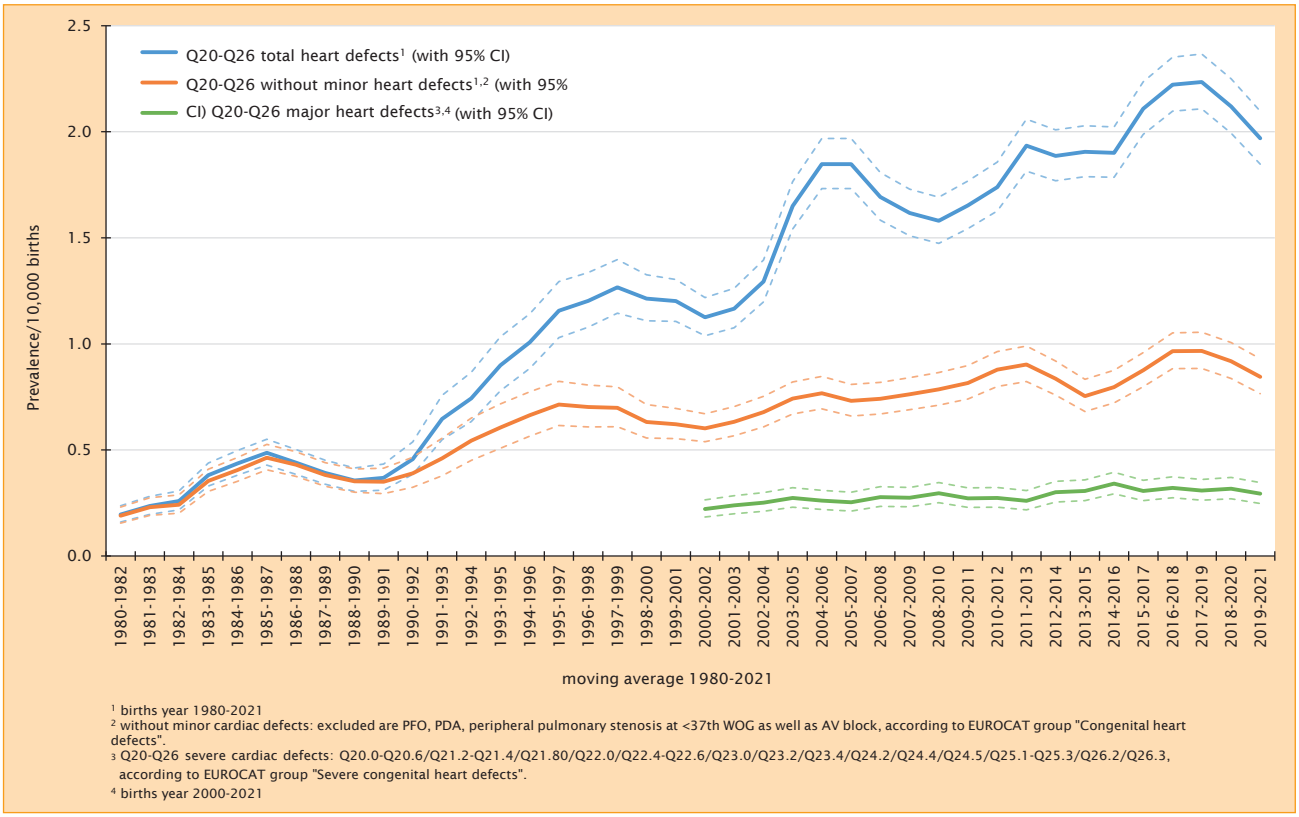
Table B: Overview of children/fetuses with congenital heart defects 1980-2021 in Saxony-Anhalt - defined individual heart defects

categories evaluated	Q23.4 Hypoplastic Left Heart Syndrome (HLHS)[1]		Q21.3/Q21.80 Tetralogy of Fallot[1]		Q20.1-Q20.3 Transposition of the great vessels (TGV)[1]		Q25.1 Aortic isthmus stenosis[1]		Q26.2-Q26.4 Malocclusion of pulmonary veins[4]	
year of birth	number	%	number	%	number	%	number	%	number	%
1980-1999[5]	90	44.6	31	18.5	73	29.0	64	24.2		
2000-2010[6]	59	29.2	71	42.3	82	32.5	92	34.7	15	34.9
2011-2021[7]	53	26.2	66	39.3	97	38.5	109	41.1	28	65.1
total	202	100.0	168	100.0	252	100.0	265	100.0	43	100.0
pregnancy outcome	number	%	number	%	number	%	number	%	number	%
live births (LB)	152	75.2	152	90.5	229	90.9	232	87.5	38	88.4
of which LB deceased	*99*	*49.0*	*14*	*8.3*	*33*	*13.1*	*45*	*17.0*	*11*	*25.6*
stillbirth (SB)	6	3.0	2	1.2	4	1.6	8	3.0	0	-
spontaneous abortions from 16 WOG	1	0.5	0	-	1	0.4	6	2.3	0	-
termination of pregnancy	43	21.3	14	8.3	18	7.1	19	7.2	5	11.6
gestational age live births (LB)	number	%	number	%	number	%	number	%	number	%
premature births (< 37th WOG)	17	11.2	35	23.0	35	15.3	58	25.0	8	21.1
full term births (37+ WOG)	91	59.9	102	67.1	164	71.6	141	60.8	30	78.9
no indication	44	28.9	15	9.9	30	13.1	33	14.2	0	-
live births, in total	152	100.0	152	100.0	229	100.0	232	100.0	38	100.0
maternal age	number	%	number	%	number	%	number	%	number	%
under 20	6	3.0	4	2.4	6	2.4	6	2.3	3	7.0
20 to 24	23	11.4	27	16.1	37	14.7	41	15.5	9	20.9
25 to 29	46	22.8	41	24.4	71	28.2	51	19.2	9	20.9
30 to 34	34	16.8	48	28.6	62	24.6	70	26.4	10	23.3
35 to 39	15	7.4	26	15.5	29	11.5	33	12.5	4	9.3
over 40	5	2.5	7	4.2	9	3.6	7	2.6	5	11.6
no indication	73	36.1	15	8.9	38	15.1	57	21.5	3	7.0
sex	number	%	number	%	number	%	number	%	number	%
male	126	62.4	98	58.3	171	67.9	150	56.6	23	53.5
female	71	35.1	68	40.5	77	30.6	110	41.5	20	46.5
no indication	5	2.5	2	1.2	4	1.6	5	1.9	0	-

[1] birth year 1980-2021
[2] without minor heart defects: excluded are PFO, PDA, peripheral pulmonary stenosis at <37th WOG, and AV block, according to EUROCAT group „Congenital heart defects".
[3] Q20-Q26 severe heart defects: Q20.0-Q20.6/Q21.2-Q21.4/Q21.80/Q22.0/Q22.4-Q22.6/Q23.0/Q23.2/Q23.4/Q24.2/Q24.4/Q24.5/Q25.1-Q25.3/Q26.2/Q26.3, corresponding to EUROCAT group „Severe congenital heart defects".
[4] birth years 2000-2021
[5] LB + SB in the period 1980-1999: 265,387
[6] LB + SB in the period 2000-2010: 193,050
[7] LB + SB in the coverage period 2011-2021: 187,891
[8] coverage region: starting in 1980 with 20 counties of the Magdeburg district, in 1990 the entire Magdeburg district, from 1993 to 1999 the administrative district of Magdeburg and increasingly other states of the administrative districts of Dessau and Halle, since 2000 all of Saxony-Anhalt
[9] LB + SB in the coverage period 1980-2021: 646,328
[10] LB + SB in the period 2000-2021: 380,941
[11] LB in the coverage period 1980-2021: 643,250
[12] LB in the coverage period 2000-2021: 379,355
[13] proportion of heart defects, in total Q20-Q26

The definition of a „severe“ cardiac defect varies to a certain extent from study to study, but the overall result remains the same: This relatively small group of CHD contributes to a disproportionately high share of the burden of disease associated with CHD. The remaining group - primarily septal defects, pulmonary and aortic stenoses - is comparatively milder and more common, occurring in 4 to 8 of every 1,000 births. Its prevalence at birth is much more variable in different studies, which reflects variations in reporting and in the recording process. Because they are so common, these diseases are responsible for most part of the fluctuation reported in the studies of the overall frequency of cardiac defects. International surveys and comprehensive meta-analyses reach the same general conclusions [3].

This variability would be even greater if some milder diseases were included - e.g. small muscular ventricular septal defects, which are clinically almost always benign and often regress spontaneously. They are found in one percent or more of newborns when they are systematically echocardiographed at birth. The differences in various classifications are shown in figure 49. It can be seen very clearly, that if all malformations (including the „minors“) are considered, the prevalence seems to increase, whereas the severe heart defects do not follow this temporal trend.



[1] births year 1980-2021
[2] without minor cardiac defects: excluded are PFO, PDA, peripheral pulmonary stenosis at <37th WOG as well as AV block, according to EUROCAT group "Congenital heart defects".
[3] Q20-Q26 severe cardiac defects: Q20.0-Q20.6/Q21.2-Q21.4/Q21.80/Q22.0/Q22.4-Q22.6/Q23.0/Q23.2/Q23.4/Q24.2/Q24.4/Q24.5/Q25.1-Q25.3/Q26.2/Q26.3, according to EUROCAT group "Severe congenital heart defects".
[4] births year 2000-2021

Fig. 49: Moving average of children/fetuses with heart defects 1980-2021 in Saxony-Anhalt

The geographic and temporal variations in the prevalence of milder CHD at birth (ASD, VSD, PDA, peripheral pulmonary stenosis), as also shown in figure 49, which contribute significantly to the overall rate of CHD, have never been convincingly demonstrated. The increase in recent decades is associated with the spread and continuous improvement of echocardiography, which may suggest, that improved detection, rather than biology, may be the main cause of these changes. These and many other data underscore the importance of evaluating carefully the different methodologic factors that may increase or decrease the reported rates.

A more important aspect is the recording of cases regardless of pregnancy outcome (live births, stillbirths, spontaneous abortions from the 16th week of gestation, terminations of pregnancy after prenatal diagnosis (TOPFA)), so that fetal deaths are also included.
The example of hypoplastic left heart syndrome (see table B) is indicative of this: the proportion of TOPFA cases varies widely from country to country and can be as high as 50% [1, 4, 5].
Although much of the reported variation is likely related to methodology, small differences in birth prevalence by sex or ethnic are likely real, such as the slightly higher rates of d-transposition of the great arteries (d-TGA) and left-sided defects in boys compared with girls and in non-Hispanic Whites compared with non-Hispanic Blacks. There is not yet a satisfactory explanation of these differences.

How critical are congenital heart malformations?

Similar to the costs of medical care outcome parameters - such as mortality, morbidity, disability, quality of life - are most useful when they relate to the specific setting and health care system. Local assessments can help to identify specific problems, inequalities and influencing factors. Despite massive global differences, it can be said that wherever outcome studies have been conducted, whether in low-, middle-, or high-income countries congenital heart defects contribute significantly to the costs and permanent health limitations.

Worldwide, congenital heart defects are the leading cause of infant death due to congenital anomalies - they are responsible for about one out of three infant deaths. The proportion in deaths in the neonatal period is also significant - in the United States and in several European countries, one out of four neonatal deaths is estimated to be due to a congenital heart defect. In high-income countries, congenital heart defects are estimated to be responsible for about one out of ten infant deaths from any cause. Global data about infant deaths clearly show, that congenital anomalies, and therefore also congenital heart defects are among the leading causes.They are thus in urgent need of effective measures to contain them through global improvements in prevention and care. Among infants and young children, a disproportionate share of the deaths is caused by the relatively small group of severe congenital heart defects (see also EUROCAT study on classification), in particular by hypoplastic left heart syndrome, conotruncal defects and atrioventricular septal defects. As documented in Denmark and in the United States, the excess mortality extends over many decades into adulthood. How does it compare in Europe? In a recently published trend analysis of data about nonsyndromic heart defects in the European malformation registry EUROCAT, the overall prevalence and the live birth prevalence were examined. The basis of the study is formed by the number of 36,685 cases which were reported between January 1, 2008, and December 31, 2015 by 25 population-based malformation registries from 14 European countries. For this study, cases with ICD-10- codes 20-Q26, excluding small heart defects were included. Cases that occurred in multiple pregnancies were excluded from the analysis, because twins have an increased risk of heart defects, particularly monochorial twins. An evaluation was also performed according to severity (categorized into severity I to III). The most severely affected group (severity I) is the univentricular heart, the hypoplastic left heart syndrome, the hypoplastic right heart syndrome, Ebstein anomaly and tricuspid atresia.

The overall prevalence amounts to 57.1 per 10,000 births for the 8-year period and is stable across the three degrees of severity levels, whereas the live birth prevalence amounts to 60.2 per 10,000 births. The reported overall prevalence of heart defects and the direction of the trends varied considerably according to the different malformation register. Among the registries Norway and England/Wales, a decreasing prevalence was observed, whereas the prevalence of congenital heart defects increased in the registries in Italy and Croatia.

The overall prevalence remained stable between 2008 and 2015 for all congenital heart defects and for the three severity groups. The declining trend which was observed in previous studies did not continue [6].

Survival in the course of time

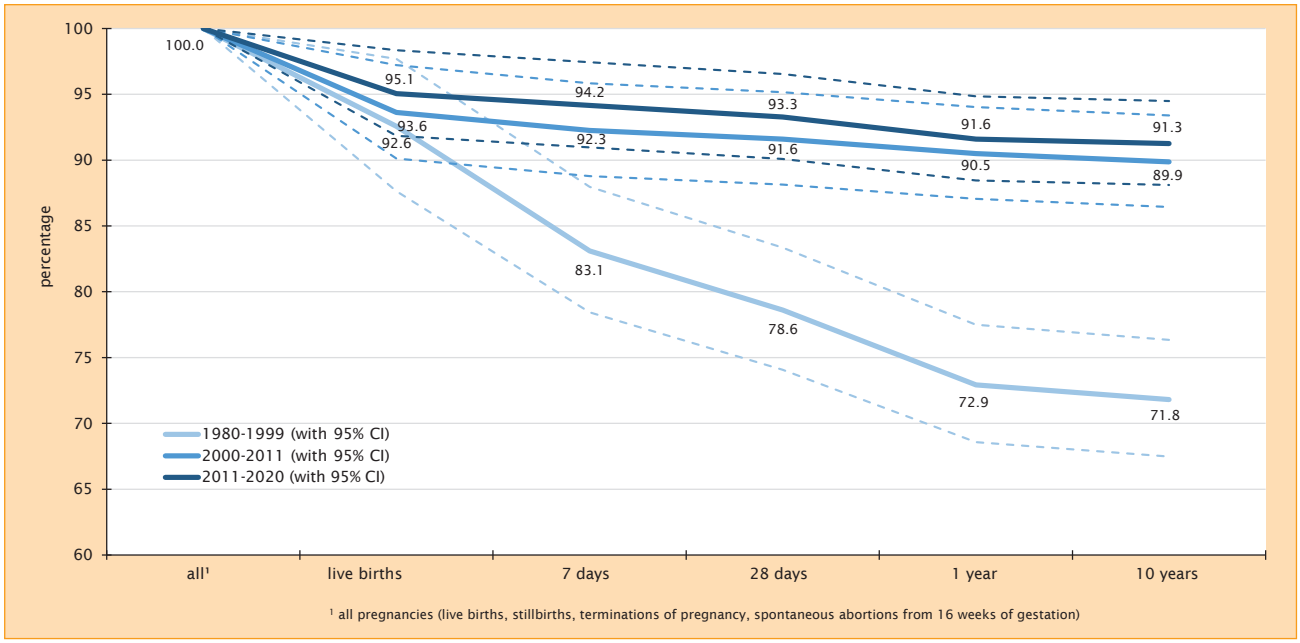


Fig. 50: Survival of children/fetuses with heart defects Q20-Q26 (grouped) 1980-2020 in Saxony-Anhalt

Figures 50 to 52 show the survival estimates from the malformation monitoring of Saxony-Anhalt for all cases registered during the of years of birth 1980 to 2020, for the groups of heart defects shown in table A and B in total (blue), without small heart defects (orange) and critical/severe heart defects (green). The cases with cardiac malformations originate from the population of a total of 630,232 live births and stillbirths in the coverage region between 1980 and 2020.

The proportion of fetal deaths is not significantly different across the three time groupings (probability of survival at birth between 82% and 95%). For the total number of all heart defects (blue illustration, fig. 50) and the group without small cardiac defects (orange illustration, fig. 51), there is a great difference for the 1-year survival probability with 73% vs. 68% for the birth cohorts 1980-1999 compared to the births from the year 2000 onward. A possible factor is the increased proportion of prenatally diagnosed cases with congenital heart defects.

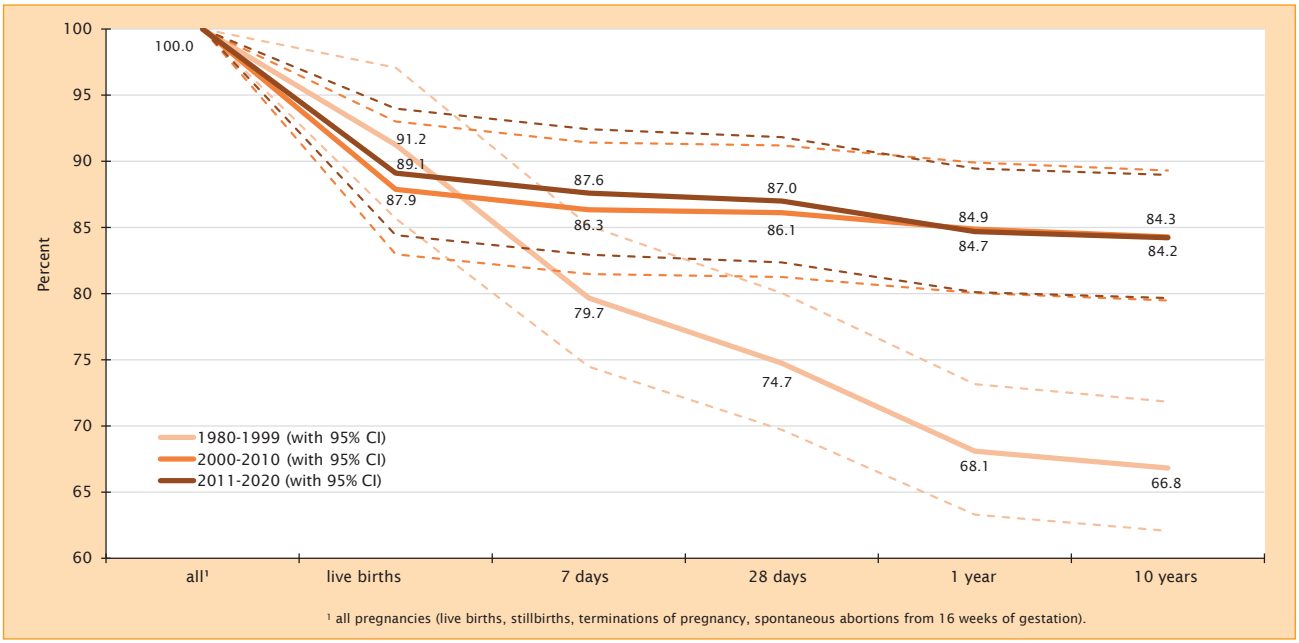


Fig. 51: Survival of children/fetuses with heart defects Q20-Q26 without minor heart defects (grouped) 1980-2020 in Saxony (excludes PFO, PDA, peripheral pulmonary stenosis at <37th WOG, and AV block, corresponding to EUROCAT group „Congenital heart defects“)

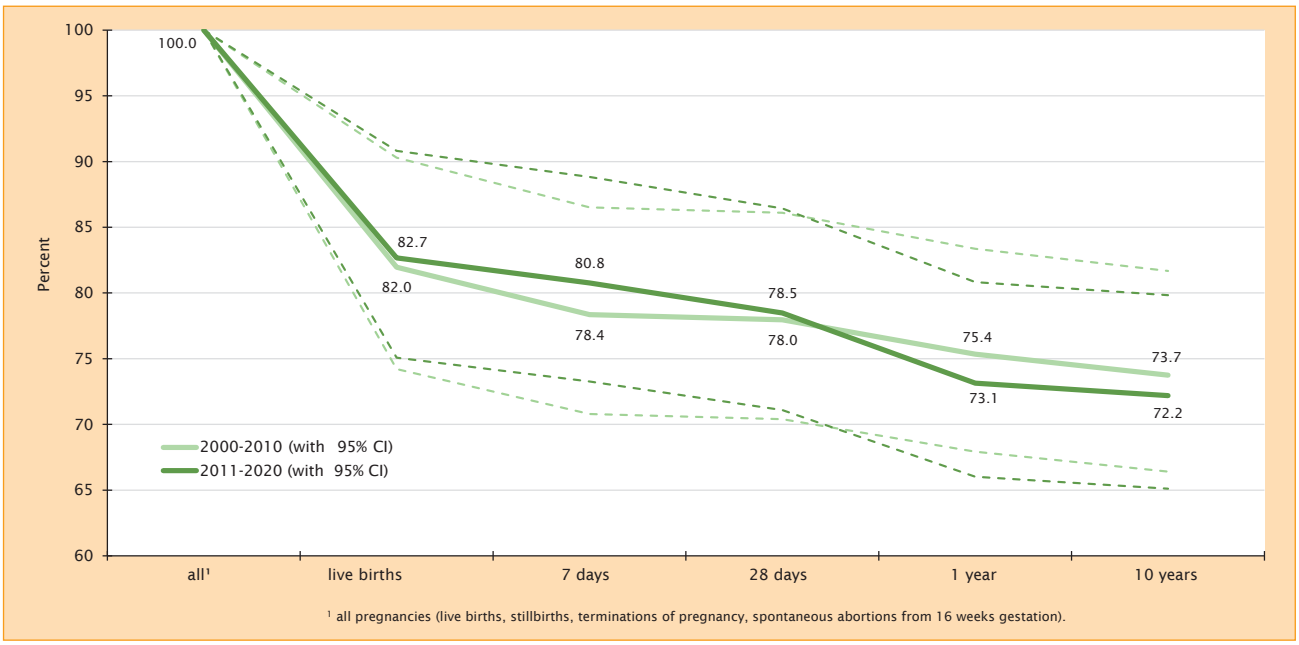


Fig. 52: Survival of children/fetuses with critical/severe heart defects Q20-Q26 (grouped) 1980-2020 in Saxony-Anhalt (Q20.0-Q20.6/Q21.2-Q21.4/Q21.80/Q22.0/Q22.4-Q22.6/Q23.0/Q23.2/Q23.4/Q24.2/Q24.4/Q24.5/Q25.1-Q25.3/Q26.2/Q26.3, according to EUROCAT group „Severe congenital heart defects“)

Predictors for survival known from the international literature are birth as a full term infant, correspondingly high gestational age and birth weight, as well as absence of concomitant malformations (especially genetic or chromosomal disorders) [4, 5].

Figure 53 shows the percentage of chromosomal aberrations and microdeletion syndromes of the cases with cardiac defects from the malformation monitoring Saxony-Anhalt as of birth year 2011. The largest proportion with 43% is trisomy 21 (Down`s syndrome), followed by trisomy 18 (Edwards syndrome) and the 22q11 deletion syndrome (CATCH-22 syndrome) with 8% each.

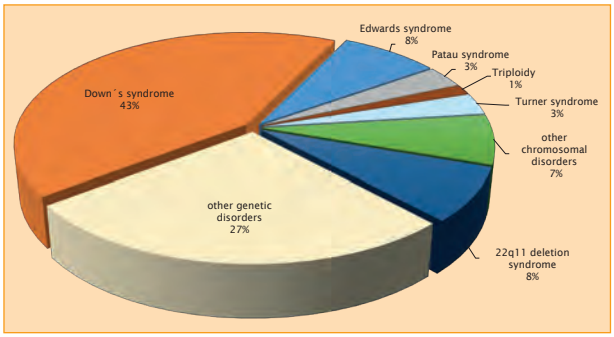


Fig. 53: Distribution of chromosomal aberrations and microdeletion syndromes among heart defects Q20-Q26 in the period 2011-2021 (N=348)

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14.2 Current aspects of SARS-CoV-2/COVID-19 during pregnancy, childbirth and post-partum period

Pregnancy and childbirth generally do not increase the risk of infection with „severe acute respiratory syndrome coronavirus 2“ (SARS-CoV-2), but appear to increase the clinical course of COVID-19 compared to non-pregnant individuals of the same sex and age. However, most (>90 percent) of infected individuals recover without delivery [1]. Furthermore, published data show that infected women, especially those who develop pneumonia, are more likely to have a preterm delivery and possibly undergo a cesarean section, which is probably related to more severe maternal illness. Most preterm births are iatrogenic (i.e., caused by induced labor or planned cesarean delivery) [2].
We would like to refer to the scientific recommendations for action of the DGPM, which were published in May 2022 with the S2k-guideline about SARS-CoV-2 during pregnancy, childbirth and post-partum period [3].

Most of the data about pregnancy outcomes originate from systematic reviews and large case series, published prior to the appearance of the Omicron variant at the end of 2021. Omicron has been associated with a lower risk of severe disease than the previous delta variant. Preliminary data about pregnancy effects suggest that infection with the delta variant during pregnancy is associated with a higher risk of placental dysfunction and, therefore, possible impairment of the fetus than with earlier variants and the subsequent omicron variant [4].

The German Medical Association has dealt extensively with the post-COVID syndrome in a statement published in September 2022. According to definition of the WHO, a post-COVID syndrome (synonymous Long-COVID) exists if three months after a SARS-CoV-2 infection for at least two months otherwise unexplained symptoms such as fatigue, dyspnea or cognitive impairment are present. According to current estimates in the literature, up to 15% of SARS-CoV-2 infected persons may develop post-COVID syndrome. For Germany, this would mean several hundred thousand affected [5, 6]. In this case pregnancy, birth and post partum period are not excluded.

The September 2022 publication of the CRONOS registry („COVID-19 Related Obstetric and Neonatal Outcome Study in Germany“) of the German Society for Perinatal Medicine (DGPM), which evaluated data about 3,481 women, with comparison of survey periods (1st period 03/2020 to 08/2021, 2nd period 01/2022 to 06/2022) confirmed the reduced risk of hospitalization due to COVID-19. Compared to period 1, there were fewer severe courses with the omicron variant. Relevant data underscored the preventive impact of vaccination [7].

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16 Newborn Hearing Screening 2021

Introduction

Every newborn is entitled to receive a general newborn hearing screening which belongs as from 1st January 2009 to the recommended early detection examinations after birth of a child. **Aim** of the newborn hearing screening (NHS) is to detect **congenital hearing disorders** at an **early stage (up to the 3rd month of life)** and to **initiate** the corresponding **therapies (up to the 6th month of life**).

Basis for this screening examination is the **Children's Directive of the Joint Federal Committee about the early detection of diseases at infants (Children's Directive)** with section **IV. Early detection of hearing disorders at newborns.**

The Children`s Directive determines the **process of the newborn hearing screening** in the following way:

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

According to the Children`s Directive **performance and results of the newborn hearing screening as well as** 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 specific 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 2008):

- - positive family history regarding hearing disorders
- - clinical suspicion of hearing disorder/ deafness
- - premature birth, birth weight under 1500 g
- - neonatal intensive care (> 2 days)
- - hyperbilirubinemia (exchange transfusion)
- - pre-, peri- or postnatal hypoxia (pH < 7.20)
- - peri- and postnatal cerebral haemorrhage, 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 0-6 after 5 minutes

Literature:
Joint Committee on Infant Hearing: Year 2008 position statement: Principles and guidelines for early hearing detection and intervention programs. PEDIATRICS 2008; 120: 898–921

Participating institutions

21 maternity clinics existed in Saxony-Anhalt in 2021. All these clinics offer a newborn hearing screening already for several years by TEOAE or AABR. These maternity clinics all participated in the newborn hearing screening in 2021.
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 are 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 86 gives an overview about the single maternity clinics and number of births with a screening ID.

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

Maternity Clinic	Tracking period 2021	Live births with screening ID in this period
AMEOS Klinikum Aschersleben	01.01.-31.12.2021	449
Helios Klinik Jerichower Land Burg	01.01.-31.12.2021	410
Städtisches Klinikum Dessau	01.01.-31.12.2021	958
Altmark-Klinikum Krankenhaus Gardelegen	01.01.-31.12.2021	273
AMEOS Klinikum Halberstadt	01.01.-31.12.2021	458
Krankenhaus St. Elisabeth und St. Barbara Halle (Saale)	01.01.-31.12.2021	1,932
Universitätsklinikum Halle (Saale)	01.01.-31.12.2021	1,273
Helios Klinik Köthen	01.01.-31.12.2021	467
Krankenhaus St. Marienstift Magdeburg	01.01.-31.12.2021	998
Klinikum Magdeburg	01.01.-31.12.2021	1,387
Universitätsklinikum Magdeburg	01.01.-31.12.2021	1,278
Carl-von-Basedow-Klinikum Saalekreis Merseburg	01.01.-31.12.2021	892
SRH Klinikum Naumburg	01.01.-31.12.2021	413
Harzklinikum Dorothea Christiane Erxleben, Klinikum Quedlinburg	01.01.-31.12.2021	505
Altmark-Klinikum Krankenhaus Salzwedel	01.01.-31.12.2021	418
Helios Klinik Sangerhausen	01.01.-31.12.2021	590
AMEOS Klinikum Schönebeck	01.01.-31.12.2021	178
Johanniter-Krankenhaus Stendal	01.01.-31.12.2021	706
Harzklinikum Dorothea Christiane Erxleben, Klinikum Wernigerode	01.01.-31.12.2021	772
Evangelisches Krankenhaus Paul Gerhardt Stift Wittenberg	01.01.-31.12.2021	732
SRH Klinikum Zeitz	01.01.-31.12.2021	319
Total number of live births with Screening-ID in Saxony-Anhalt		**15,408**
Further live births with Screening-ID: e.g. home births / births in a birthing centre resp., infants not born in Saxony-Anhalt	01.01.-31.12.2021	160
Tracked infants, in total		**15,568**

In total, **15.408 births** received a screening ID in their maternity clinic in Saxony-Anhalt in 2021. In this way, these infants could participate in the hearing screening tracking. Furthermore, **160 data records of infants** which were delivered at home or born in a birthing centre are included in our analyses. These infants received also a screening ID after birth, e.g. by their corresponding midwife.

Tracking Effort

Tracking of the newborn hearing screening requires an ample organising and personnel effort. It starts with recording the results of the hearing test in the maternity clinic and forwarding them by mail or fax to the Monitoring of Congenital Malformations. The results are entered here in a special tracking database. In total, we received results of **95 senders** in 2021.

Births with screening-ID and number of incoming results

2021	Infants with screening ID	Numer of incoming results
January	1,315	1,933
February	1,195	1,439
March	1,268	1,796
April	1,212	1,632
May	1,340	1,507
June	1,234	1,824
July	1,413	1,720
August	1,448	1,565
September	1,367	1,937
October	1,268	1,844
November	1,264	1,313
December	1,244	1,166
total	**15,568**	**19,676**

The previous table shows how many newborns received a screening ID per month and how many results were forwarded to the Monitoring of Congenital Malformations per month.
It becomes apparent that currently per month an average of approx. 1,640 reports can be expected, however in some cases we received multiple reports for one child (e.g. from the maternity clinic, paediatric clinic, ENT clinic, ENT physician, paediatrist and from the parents).

To carry out the tracking thoroughly, **3015 letters resp. faxes** were forwarded in 2021 (one up to nine letters per infant). With reference to all infants with screening ID this corresponds to an average of 0.19 letters per infant. Additionally, the parents and attending physicians of the infants born in 2021 were contacted by telephone as well as processing notes logged. For the children born in 2021 with screening ID, a total of **1,521 telephone calls or log notes** were documented as part of the tracking measures (average 0.10 phone calls/log notes per infant).

Results (date October 2022)

All results that were reported to the hearing screening tracking centre about infants that were born in 2021 are included in our analyses 2021 of the newborn hearing screening:

12.944 infants out of **15,568 infants** with screening ID had an **unsuspicious newborn hearing screening result**. In **2,624 cases** the **first hearing test had to be followed-up**, resp. no newborn hearing screening took place in the maternity clinic (these cases are regarded also as follow-up cases). There are numerous reasons why a hearing test did not take place, e.g. ambulant delivery, early discharge from maternity clinic, transfer of the child to another clinic or a defective hearing screening device.

The **follow-up examination** of the 2,624 infants showed in **1,894 cases** an **unsuspicious result**. The remaining **730 infants** had again a **suspicious result**.
248 of these 730 infants received a **complete paediatric audiological confirmation diagnostic**.
According to our knowledge, **222 infants** did **not receive a confirmation diagnostic** and therefore are considered as **lost to follow-up**. In **11 cases**, the **further examinations** were **were refused** by the parents.

190 infants did **not participate in the screening** (no reaction of parents to reminder letters or refusal of examination) and in **11 cases** the **status** is still **pending**, i.e. the examinations were not finished in October 2021 or the tracking process still requires more time.
In **48 cases** the **tracking** was closed from our side **without any result**, because the parents could not be contacted, or the infant had died.

In total, the **follow up-examinations** of **271 infants** who were born in 2021 could be **completed (confirmations diagnostics)**. Among 248 infants with a suspicious result, 23 infants had an unsuspicious first screening. Maybe these infants received a follow-up-examination due to present risk factors.
Within the follow-up examination, a **hearing disorder** could be **excluded** in **238 cases**. In **33 cases** a **hearing disorder was diagnosed** (27 x bilateral and 6 x unilateral hearing disorder) and the corresponding therapy was initiated. For instance, **23 infants** received a **hearing aid** (19

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according to §13 to § 42 inclusive attachments of the valid Children Directive of the Federal Joint Committee about early detection of diseases at infants

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Kompetenznetz Neugeborenen-Screening
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Introduction

The Newborn screening is a population-based preventive measure with the aim of a complete and early detection as well as quality-assured therapy of all newborns with severe, congenital metabolic disorders (Tab. 1).
The Directive of the Joint Federal Committee about the early detection of childhood diseases (Children's Directive) stipulates the details of the newborn screening (NGS) and screening for cystic fibrosis (CF) in paragraphs 13 to 42.
The German Society of newborn screening (DGNS) compiles annually a national screening report in cooperation with the German screening laboratories (http://screening-dgns.de/reports.php). The statistical processing of the screening data is based on the quality criteria defined in the Directive for the implementation of NGS and CF screening in Germany.

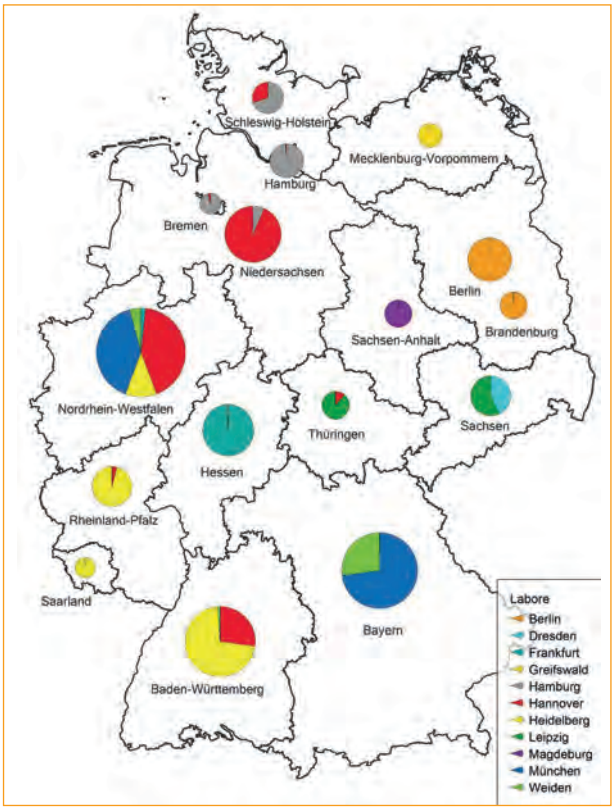

Fig. 1: Sample distribution of the screening centers in Germany[1]

The report only refers to congenital metabolic and endocrinologic diseases which are defined as „target" diseases by the Directive. Furthermore, it gives a complete statistical compilation of related screening figures, recall rates and confirmed diagnoses for the current year. Additionally, data about process quality for whole Germany is presented.
Screening samples from the single Federal States are distributed to the laboratories as it is presented in figure 1 1. The screening laboratory in Magdeburg handles the dry blood samples of all infants born in Saxony-Anhalt.
Table 1 shows the frequencies 2020 of the screening target diseases in Germany1 for a total number of 773,144 screened births.

Tab. 1: Frequency of diesase detected in screening in Germany 2020[1] (including mild forms)

Diease	Confirmed cases	Prevalence
Congenital hypothyroidism (CH)	265	1 : 2,918
Congenital adrenal hypoplasia (CAH)	60	1 : 12,886
Biotinidase deficiency (incl. partial defects)	23	1 : 33,615
Galactosemia (classical)	19	1 : 40,692
Hyperphenylalaninemia (HPA) [of which phenylketonuria (PKU)]	149 [79]	1 : 5,189 [1 : 9,787]
Maple syrup urine disease (MSUD)	2	1 : 386,572
Medium-Chain-Acyl-CoA-Dehydrogenase deficiency (MCAD)	84	1 : 9,204
Long-Chain 3-OH-Acyl-CoA-dehydrogenase deficiency (LCHAD)	11	1 : 70,286
(Very-)Long-Chain-Acyl-CoA-dehydrogenase deficiency (VLCAD)	12	1 : 64,429
Carnitin-Palmitoyl-CoA-Transferase I deficiency (CPTI)	3	1 : 257,715
Carnitin-Palmitoyl-CoA-Transferase II deficiency (CPTII)	-	
Carnitin-Acylcarnitin-Translocase deficiency (CACT)	-	
Glutaric aciduria type I (GA I)	7	1 : 110,449
Isovaleric acidaemia (IVA)	6	1 : 128,857
Tyrosinemia type I	7	1 : 110,449
Cystic Fibrosis (CF) / CFSPID	146	1 : 5,296
Severe combined immunodeficiency (SCID)	32 [5]	1 : 24,161 [1 : 154,629]
Total	**826**	**1 : 936**

Screening data 2021 of Saxony-Anhalt is outlined in the following:

Process quality

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

- complete coverage of target population
  - coverage method and rate
  - blank card systems
- completeness of control (recall)- and follow up examinations
- registration of examination parameter and standard values / 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 results of newborns, which must be examined further on
- confirmation diagnostics
  - -diagnostics type
  - -diagnostics period
- final diagnosis
- start of therapy

Registration rates

Since according to §15 and §31 of the Children's Directive each newborn has a right of participation in the extended newborn screening and cystic fibrosis screening, a tracking for completeness is necessary. This can be realised for infants which are delivered in obstetric clinics by control of the respective consecutive number in the birth register and by means of a so-called blank card system in the screening laboratory. According to the Children`s Directive the obstetric clinics have to document on a blank test card the total refusal of screening, the refusal of an early blood taking within the screening, the transfer to specialised institutions or death of the newborn. These blank cards should be sent to the laboratory to support the tracking process.

The coverage rates in Saxony-Anhalt were as following for the year 2021:
According to the Federal Statistical Office 16,024 children were live births in Saxony-Anhalt
(data according to the place of maternal residence).

Tab. 2: Initial examinations according to the place of maternal residence

	Number
First screening in Magdeburg, in total	15,450
Non-resident in Saxony-Anhalt	705
Screening of children living in Saxony-Anhalt	**14,745**

The discrepancy between the number of live births and screened infants with residence in Saxony-Anhalt amounts to 1279.

Basis for the data of the State Statistical Office are the births that are reported by the birth centres to the registry offices, sorted according to the place of maternal residence. However, the number of mothers with residence in Saxony-Anhalt but who delivered their infant in another Federal State can not be recorded in our screening statistics if the screening of the infant also took place in another Federal State.

Tab.3: Registration rates by blank cards

Blank cards in total	**524**
Blank card: infant deceased/ stillbirth	20
Blank card: refusal of early taking	441
Blank card: transfer to another hospital	43
Blank card: screening refused by parents	16
Blank card: without response	4
Screening took place	414

As result of follow-up (telephone calls, faxes, letters), only 1% of the blank cards sent in remained without result. All other live births participated later successfully in the newborn screening and the CF screening in our or in a neighbouring screening laboratory. Furthermore, the tracking of missing screening examinations is performed successfully according to the reasons mentioned in table 4.

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

Reason for second screening	**Suspicious first screening**	**First screening < 36h or < 32 WOG**
Requested	97	426
Received at own laboratory	92	372

WOG = weeks of gestation

Examination numbers, recall rates and assured cases

Table 5 shows recall rates of the single parameter and assured cases. A total of 159 control examinations had to be carried out in 2021.

Tab. 5: Recall-rate 2021 and diagnosed patients with a metabolic disease in reference to 15.450 screening examinations (includes also early withdrawal < 36 h and preterm births < 32 WOG), prevalence 1999-2021

Target disease incl. all forms of disease	Number of recalls* 2021	Assured cases 2021	Prevalence in Saxony-Anhalt 1999-2021
Hypothyroidism (CH)	64	3	1 : 4,061
Phenylketonuria (PKU/ HPA)	2	1	1 : 5,399
Galactosemia (classical)	2	0	1 : 122,831
Biotinidase deficiency	4	0	1 : 92,269
Adrenogenital syndrome (AGS)[I]	53	4	1 : 15,841[I]
Medium-Chain-Acyl-CoA-Dehydrogenase deficiency[II] (MCAD)	1	0	1 : 11,184[II]
Long-Chain 3-OH-Acyl-CoA-dehydrogenase deficiency[II] (LCHAD)	-	-	1 : 73,815[II]
(Very-)Long-Chain-Acyl-CoA-dehydrogenase deficiency[II] (VLCAD)	2	0	1 : 184,539[II]
Maple syrup urine disease [II] (MSUD)	-	-	
Carnitin-Palmitoyl-CoA-Transferase I and II deficiency[II] (CPTI)	-	-	
Carnitin-Acylcarnitin-Translocase deficiency[II] (CACT)	-	-	
Glutaric aciduria type I (GA I)[II]	1	-	
Isovaleric acidaemia (IVA)[II]	9	0	
Mucoviscidosis[III]	12	3	1 : 5,895[III]
Tyrosinemia type I[IV]	1	0	1 : 64,807[IV]
Severe combined immunodeficiencies (SCID)[V]	-	-	
5q-associated spinal muscular atrophy (SMA)[VI]	1	1	
Sickle cell disease (SCD)[VI]	-	-	
Other[II]	8	0	

* Recall: Request of a new blood sample at suspicious screening result at first examination..
Shown here the number inclusive early blood withdrawal (< 36h) or premature infant (< 32 WOG)
I Screening to detect adrenogenital syndrome (AGS) since 1997
II Enlarged screening (TMS) since 05/2001
III Screening for mucoviscidosis since 09/2016
IV Screening for tyrosinemia since 04/2017
V SCID since 08/2019
VI 5q-SMA and SCD since 10/2021

Process times

Point of taking blood samples

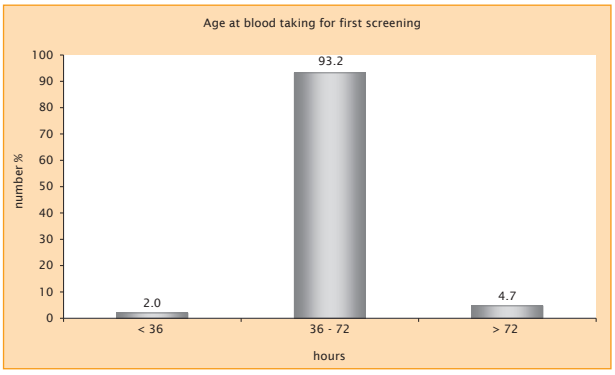

Fig. 2: Age at point of blood taking for first screening

The optimal point of taking blood samples for the newborn screening (36 –72 hours of life, §20 Children`s Directive) took place within the required period of time at 93.2% (2019: 92.1%) of all cases. At a total number of 6.7% the taking of blood samples took not place within the required period of time (2020: 7.9%).

Note: : Only newborns were included in the analysis if all required information was available (date and time of birth and blood collection date and time).

Transmission Time

According to §21 of the Children‘s Directive, the date of dispatch of the blood sample shall be equal to the date of blood collection. The aim is to ensure that the postal route does not exceed 72 hours. Figure 3 shows that 20,6% (2020: 20,8%) of all transmittals reached the laboratory more than three days after the blood taking. On average, samples from 21 clinics reach the laboratory in the required time window (table 6). Postal transport times are longer than they were ten years ago, but they have not deteriorated further in the last three years.

Athough there were dry blood cards that took more than 10 days to arrive at the laboratory, the average transport time for 19 of the 21 clinics are within the required range. Only two clinics continued to have significantly too high shipping times (<72 hrs, in 2020 it was only the case at one clinic). Since every delayed blood collection or every prolonged postal route means a potential (lfe) risk for the concerned infants, the laboratory tries to improve the quality of the blood collection by means of training events (letters, training events) to sensitize hospitals about th this important issue. The main cause is certainly the sending of dried blood samples via private mail carriers. We urgently recommend sending the samples directly to the screening laboratory mailbox by Deutsche Post. The following instructions should also be observed:

- send blood samples on the day of collection, i.e. do not collect over several days, the letter should leave the hospital as soon as possible
- do not send to the hearing screening tracking center

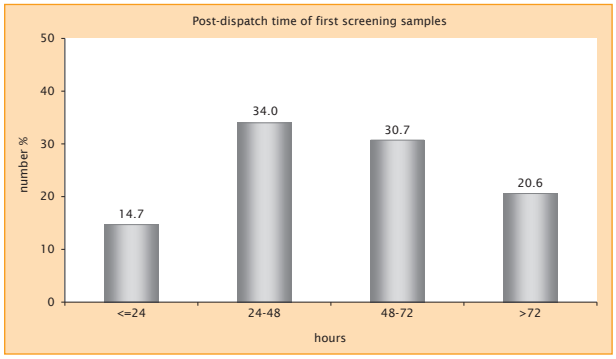

Fig. 3: Post-dispatch time of the dry blood (first screening)
Time from blood collection to arrival at the laboratory

Transmission of Results

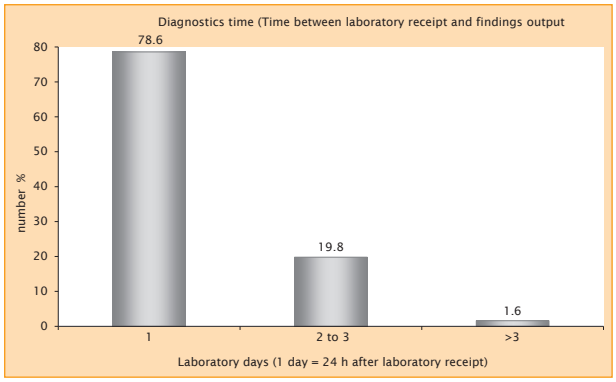

Fig.4: Duration of findings transmission

Cystic fibrosis screening

Tab.7: CF-Screening, participation and confirmed cases

	2021	2019
Screening, in total	15,450	15,951
CF screening included	99.7%	99.7%
CF screening positive	12	8
sweat test performed	12	8
CF confirmed	3	2

The screening for cystic fibrosis (CF) is offered since 09/2016 for all children throughout Germany. During the course of the 3-step laboratory analysis no control card is requested in case of a suspicious finding, but the children have to attend a CF outpatient clinic in order to exclude CF by means of a sweat test.

There is an increasing participation in the CF screening and a good acceptance of the program. In the year 2021 no parent or guardian rejected the participation in the CF screening. 0.3% of CF analyses were not carried out due to the special fact that midwives are not allowed to take blood samples for this screening without permission from a doctor. Usually, the cooperation between midwifes and paediatricians works well. All children received a sweat test after a positive CF screening. A sweat test showed highly abnormal findings in 3 children. A genetic analysis subsequently confirmed the diagnosis of severe cystic fibrosis.

Tab. 6: Post-dispatch time of dry blood cards per sending hospital (average value of all wards of a hospital), comparison 2021 to 2015

Maternity clinic	Average shipping time (h)	
	2020	2015
Magdeburg St. Marienstift*	21	12
Magdeburg Universitätsklinikum*	27	29
Magdeburg Klinikum*	38	25
Gardelegen	42	41
Schönebeck	45	41
Zeitz	47	49
Quedlinburg	48	44
Salzwedel	50	45
Halle St. Elisabeth und St. Barbara	52	50
Stendal	54	46
Aschersleben	55	50
Naumburg	55	41
Merseburg	58	51
Burg	58	44
Dessau-Roßlau	59	44
Lutherstadt Wittenberg	60	56
Sangerhausen	60	50
Köthen	60	49
Wernigerode	63	50
Halberstadt	86	62
Halle Universitätsklinikum	90	53

* Clinic with a courier service

Figure 4 shows the duration of laboratory analysis of all initial screening examinations. 19,8% of all findings, that leave the laboratory after more than 24 hours, essentially reflect the prolonged duration of the findings due to the cystic fibrosis screening (3-stage screening including mutation analysis), internal repetition of analyses in case of implausibility and disruptions in the laboratory process (equipment maintenance, repairs, etc.). A slight increase compared to 2020 is due to the introduction of the new target diseases SCD and 5q-SMA, as there are more internal repeats necessary in qPCR analysis
In case of a highly suspicious finding, the information is immediately transmitted by telephone to the attending physician as partial finding. Due to the urgency, we do not wait for completion of all laboratory analyses in such cases.

Confirmation diagnostics and therapy of screening-positive patients

12 suspected screening cases could be confirmed by confirmation diagnostics and provided with a therapy:

Tab. 8: Diagnosis, confirmation diagnostics and therapy starting

Diagnosis	Confirmation diagnostics	Age at start of therapy
3 x Hypothyroidism	Serum TSH, fT3, fT4, sonography, thyroid antibodies	8-10 days
1 x Phenylketonuria	Serum Phe, BH4 test, DHPR activity, pterins, partial mutation analysis	10 days
1 x 5q-associated spinal muscular atrophy	Mutation analysis:3 copies of the SMN2 gene	No feedbak
4 x Adrenogenital syndrome 2 x salt wasting syndrome 1 x without salt wasting syndrome	Mutation analysis, steroid analysis	5-11 days
3 x Mucoviscidosis 2 x classical homocygotic mutation 1 x compound heterozygous mutation	Sweat test Mutation analysis	19-44 days

Summary

On March 2021, a new version of the Children's Directive came into force. The target diseases 5q-associated spinal muscular atrophy (SMA) and sickle cell disease (SCD) were added to the extended newborn screening. Since October 2021, every child born in Germany will be screened for SMA and SCD. Accordingly, new information flyers were provided and senders were informed about this innovation. As before, parents have the option to have the screening for cystic fibrosis performed independently from the extended newborn screening or to decline it (checkbox on the dry blood card). CF screening can take place up to the 4th week of life of the newborn. The analysis of all target diseases of the Extended Newborn and Cystic Fibrosis Screening can be performed from one blood sample, provided that sufficient blood has been dripped. Here, new pre-analytical problems arose due to the introduction of the new laboratory method for the analysis of the SMN1 gene for SMA and haemoglobin S for SCD. The SMN1 gene is analysed by means of qPCR and tolerates no additives such as heparin or EDTA. The senders have been trained to fulfil the required criteria for the collection of dry blood samples from the heel strictly:

- Do not use EDTA, heparin or coated capillaries.
- Recommendation: use lancets with cutting blades, they provide optimal blood flow (e.g. Safety-Lancet Neonatal Blade or Safty-Heel Neonatal by Sarstedt, BD QuikHeel™ safety incision lancet)
- Disinfect heel with 70-80% alcohol and allow to dry thoroughly before puncture. Do not use hand sanitizers or similar, as they will interfere with the analysis
- Soak all 4 circles completely
- The analysis of haemoglobin variants for SCD led to the following findings:
- Children with previous transfusion are in most cases not reported to the screening centre in most cases and only become apparent during Hb analysis
- Sample manipulation through e.g. application of foreign blood (adult blood) was discovered in one clinic and led to a report and police investigation

The Gene Diagnostics Act also applies to cystic fibrosis screening and is the overarching law with penalty paragraphs. Midwives are only allowed to take blood from newborns for the cystic fibrosis screening after permission by a paediatrician. Forms can be found on our homepage (www.stwz.ovug.de).

The Newborn Screening and Metabolism Laboratory belongs to the Institute of Clinical Chemistry and Pathobiochemistry since October 2015 (central laboratory of the University Hospital Magdeburg A.ö.R.). Nevertheless, the intensive cooperation with pediatricians for endocrinology and metabolism continues and is strongly encouraged.

The process quality of the newborn screening of Saxony-Anhalt remains very good, similar to the previous years and lies in the middle of the national average of all German screening laboratories (national screening report of the German society of newborn screening[1]).

We thank all materny clinics/ ambulances and midwifes for the good and smooth collaboration.

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

www.stwz.ovgu.de

We would like to inform senders, parents and interested people here about the Newborn Screening and about special metabolic diagnostics and provide downloads/ forms.
The national screening report of the DGNS1 is available on the Society's own website (http://screening-dgns.de) two years after the respective period of time.

[1] Source: Deutsche Gesellschaft für Neugeborenenscreening e.V. (DGNS) (German Society of newborn screening): National screening report Germany 2019 http://www.screening-dgns.de/Pdf/Screeningreports/DGNS-Screeningreport-d_2019.pdf