International Clearinghouse for Birth Defects
Surveillance and Research

# 49th Annual Meeting and Scientific Session of the International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

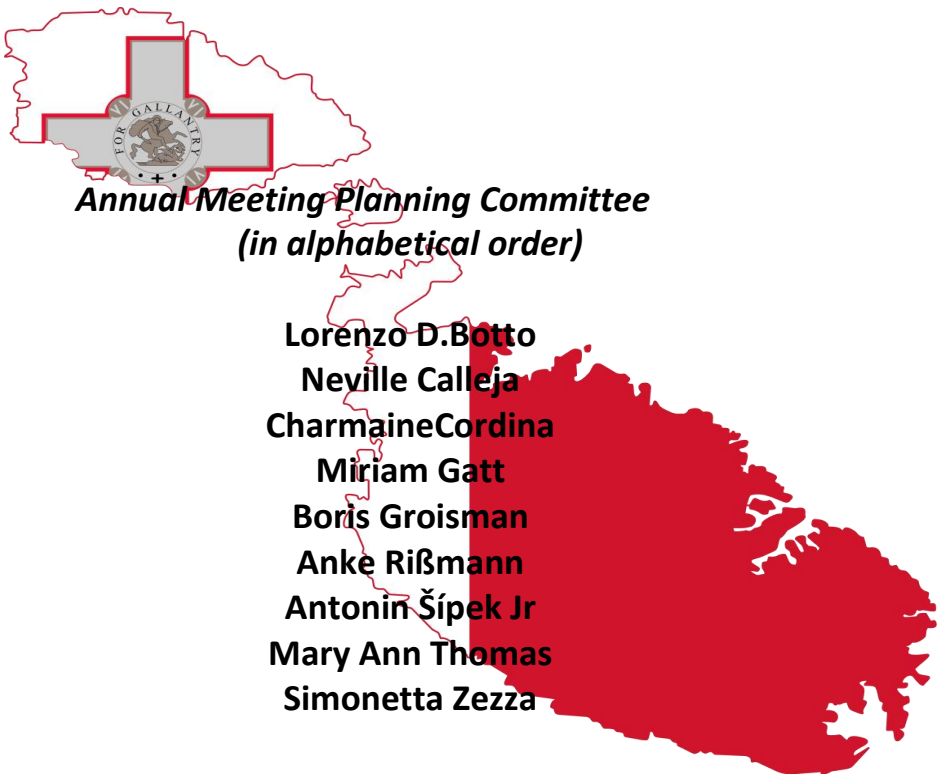
# Primary Prevention, Surveillance and Management of Birth Defects

## November 5th- 8th, 2023

## Malta

## *Cavalieri Art Hotel, St Julians*

**Organized by**
**ICBDSR**
**In collaboration with the Malta Congenital Anomalies Registry (MCAR), Directorate for Health Information and Research, Malta**



***Annual Meeting Planning Committee***
***(in alphabetical order)***

**Lorenzo D.Botto**
**Neville Calleja**
**CharmaineCordina**
**Miriam Gatt**
**Boris Groisman**
**Anke Rißmann**
**Antonin Šípek Jr**
**Mary Ann Thomas**
**Simonetta Zezza**

ICBDSR website: www.icbdsr.org

The ICBDSR Executive Committee and ICBD Staff thank the **Program Director and the Staff of the Malta Congenital Anomalies Registry (MCAR) of the Directorate for Health Information and Research (DHIR),** and **all ICBDSR members** who work in birth defects surveillance and research, individually as well as in the ICBDSR, to achieve our common goal of primary prevention of birth defects to help ensure that infants worldwide are born healthy.

International Clearinghouse for Birth Defects
Surveillance and Research

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## The ICBDSR is a Promoting Organization of


www.worldbirthdefectsday.org

# *PROGRAM*

| | **Sunday, November5th, 2023** |
|---|---|
| 14:00-16:00 | **Executive Committee Meeting** *(Executive Committee members and ICBD staff only)* |
| 18:00-19:30 | **Registration** ICBDSR Annual Meeting |
| 19:30 | **Welcome Reception** *at Cavalieri Art Hotel, offered by ICBDSR with the support of Visit Malta Incentives & Meetings* |

| | **Monday, November 6th, 2023**<br>**Meeting Room Babylon** |
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| 8:30-9:00 | **Registration** |
| 9:00-9:15 | **Welcome – Walter Busuttil, Chief Medical Officer, Malta and Boris Groisman, Chair ICBDSR** |
| 9:15-9:30 | **ICBDSR Executive Committee Talk**<br>*Boris Groisman, ICBDSR Chair and Lorenzo D Botto, ICBD Director* |
| 9:30-10:10 | **J. David Erickson Lecture** – *Pablo Duran, Pan American Health Organization (PAHO)* |
| 10:10-10:30 | **Keynote Lecture** Surveillance research and NTDs prevalence estimates around the world: the importance of the WHA67.19 Resolution<br>*Sylvia Roozen, Secretary General, International Federation for Spina Bifida and Hydrocephalus* |
| | **Updates from Partner Organizations: EUROCAT, NBDPN, ConcePtion Project**<br>**Moderators:**<br>*Salimah R Walani - Global Policy & Advocacy Advisor, MiracleFeet, USA*<br>*Helen Malherbe - Director of Research and Epidemiology, Rare Diseases South Africa* |
| 10:30-10:45 | **EUROCAT Updates**<br>*David Tucker, President EUROCAT Association, CARIS, Swansea University, Wales, UK* |
| 10:45-11:00 | **NBDPN Updates**<br>*Wendy A Nembhard, Chair NBDPN, University of Arkansas for Medical Sciences, USA* |
| *11:00-11:15* | *Coffee break* |
| 11:15-11:30 | **From ConcePTION project to sustainable solution for medicines safety assessment during pregnancy and breastfeeding in Europe and beyond**<br>*Miriam Sturkenboom, Department of Data Science & Biostastistics, University Medical Center Utrecht, Netherlands* |
| 11:30-13:00 | **Session I – Oral Presentations**<br>**Moderators:**<br>*Yves Muscat Baron* - Clinical Chairperson, Department of Obstetrics & Gynaecology, University of Malta<br>*Dieuwke Broekstra* - Head Eurocat NL, Research group Congenital Anomalies, Department of Genetics, University Medical Center Groningen, The Netherlands<br>**Birth defects surveillance – Methodology I**<br>Global burden of birth defects estimation: methods, progress and selected results<br>*Kathleen L Strong*<br>Estimating the contribution of different disease groups to the global rare diseases burden using data from the Veneto region RD registry, 2002 through 2019<br>*Monica Mazzucato* |

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| | MALFOVAR Registry / Repository Update<br>*Tidhar Steiner*<br><br>Using population-level, real world data to establish cytogenetic testing patterns and evaluate genotype-phenotype correlations in congenital anomalies in England<br>*Corinne R Mallinson*<br><br>Current activities of the JRC-EUROCAT Central Registry<br>*AgnieszkaKinsner-Ovaskainen*<br><br>Validating routinely collected data to improve ascertainment of congenital anomalies to support national registration in England<br>*Jennifer M Broughan*<br><br>An update on the status of global prevention of folic acid-preventable spina bifida and anencephaly, Year 2022.<br>*Vijaya Kancherla* |
| *13:15-14:15* | *Lunch* |
| 14:15-15:45 | **Session II – Oral Presentations**<br><br>**Moderators:**<br>*Juliana Lores Espinosa* - Cali Birth Defects Surveillance Program, Department Health Sciences, Javeriana University, Cali, Colombia<br>*Anke Rißmann*, Medical Director of Malformation Monitoring, Saxony-Anhalt, Germany<br><br>**Birth defects surveillance - Descriptive epidemiology**<br><br>Prenatal findings in craniofacial microsomia using the Alberta Congenital Anomalies Surveillance System, 1997-2019<br>*Mary Ann Thomas*<br><br>Prevalence of skeletal dysplasia in Emilia Romagna, Italy<br>*Elisa Ballardini*<br><br>Monitoring an emerging maternal and infant health threat: expanding a birth defects surveillance program to include infants with congenital cytomegalovirus infections<br>*Paul A Romitti*<br><br>Diaphragmatic hernia in the Czech Republic. Incidence, prenatal diagnosis and sex ratio<br>*Antonin Šípek, Jr*<br><br>Population-based study on epidemiology and outcomes of Congenital Tracheo-Oesophageal Anomalies in South Wales over a 21-year period<br>*Margery Morgan*<br><br>Years of potential life lost for children and adults with Congenital Heart Defects, United States, 2007-2017<br>*Wendy N Nembhard* |
| *15:45-16:00* | *Coffee break* |

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| 16:00-16:45 | **Poster session** *(meeting room Olympia)* |
| 16:45–18:15 | **Session III – Oral Presentations**<br><br>**Moderators:**<br>*Elisa Ballardini* - Emilia Romagna Registry of Birth Defects-IMER, Neonatal Intensive Care Unit, University of Ferrara, Italy<br>*Csaba Siffel* - College of Allied Health Sciences, Augusta University, Augusta, GA, USA<br><br>**Risk factors and health outcomes of birth defects**<br><br>A brief overview of the current state of knowledge: pregnancy outcome after first trimester exposure to statins<br>*Katarina Dathe*<br><br>Analysis of medication consumption during pregnancy in newborns with birth defects in Bogotá, and Cali, 2002-2019<br>*Karen Sarmiento*<br><br>Profile of live births with birth defects in Brazil, their risk factors and associated infant mortality, 2011 to 2020<br>*Julia A Gomes*<br><br>Health outcomes of children born with genetic syndromes in Europe: an undergoing EUROlinkCAT study<br>*Alessio Coi*<br><br>Factors associated with the survival of isolated cardiovascular and digestive congenital defects, in the first year of life, in Cuba 2011-2020<br>*Yudelkis Benitez Cordero*<br><br>Radionuclides – Neural Tube Defects – Developmental anomalies – Chornobyl<br>*Wladimir Wertelecki* |
| *19:30* | *Dinner at Cavalieri Art Hotel (included in the registration fee of delegates staying at the hotel)* |

| | Tuesday, November 7th,2023<br>**Scientific session: Surveillance, management, care and transition to adulthood**<br>**Meeting room Babylon** |
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| 8:00-8:30 | **Registration** |
| 8.30–10:30 | **Scientific Session I - Surveillance and management**<br><br>**Moderators:**<br>*Neville Calleja*, Director, Directorate for Health Information & Research, Ministry for Health, Malta<br>*Charmaine Cordina*, Directorate for Health Information & Research, Ministry for Health, Malta<br><br>Surveillance of Congenital Anomalies in Malta - Setting the scene<br>*Miriam Gatt*<br><br>Neonatal mortality due to congenital anomalies in Malta and beyond<br>*Merle Wilhelm*<br><br>Evolution of Screening in Malta<br>*Mark Cordina*<br><br>The accuracy of antenatal ultrasound screening in Malta: a population-based study<br>*Jeremy Borg Myatt*<br><br>Fetal Cardiac Screening in Malta<br>*Sarah Darmanin*<br><br>Prenatal Orofacial screening in Malta<br>*Maria Christina Tabone*<br><br>Orofacial Clefts in Malta: Prevalence, Impact & Public Health Implications – A 20-Year Analysis<br>*Terence Micallef*<br><br>The epidemiology of congenital heart disease in Malta<br>*Victor Grech*<br><br>Maternal and Gestational Risk Factors of Congenital Diaphragmatic Hernia<br>*Sophie Hackenbruch* |
| 10:30-10.50 | *Coffee break* |
| 10.5013:15 | **Scientific Session II - Care, transition to adulthood and personal experiences**<br><br>**Moderators:**<br>*Victor Grech*, Paediatric Department, Mater Dei Hospital, Tal-Qroqq, Malta<br>*Miriam Gatt,* Directorate for Health Information & Research, Ministry for Health, Malta<br><br>Breaking the news<br>*Ryan Farrugia*<br><br>Several decades later - a look at long-term outcomes of congenital heart defects in Malta<br>*Maryanne Caruana* |

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| | The European Reference Networks - Raising the bar for patients with rare diseases and their healthcare providers across Europe<br>*James Clark*<br><br>Rare Diseases in Paediatrics: Outsourcing the specialized paediatric services into the Community Resource Centres<br>*Christopher Sciberras*<br><br>Adult Down Syndrome Clinic<br>*Maria Callus*<br><br>Carer experiences<br><br>**Closing** – *Yves Muscat Baron* – Clinical Chairperson, Department of Obstetrics and Gynaecology |
| *13:15-14:15* | *Lunch* |
| *Afternoon* | *Tour-personal payment, optional (afternoon)* |
| | *Social dinner offered to ICBDSR delegates and invited speakers by Ministry for Health (accompanying persons and others - personal payment)* |

| | **Wednesday, November 8th, 2023**<br>**Meeting Room Babylon** |
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| 9:00-11:30 | **ICBDSR Annual Business Meeting** *(ICBDSR members only)* |
| *11:30-11:45* | *Coffee break* |
| *11:45 – 12.45* | **Session IV– Oral Presentations**<br><br>**Moderators:**<br>*Florence Rouget* - Brittany Registry of congenital anomalies, Rennes University Hospital, France<br>*Yudelkis Benitez Cordero* - National Center of Medical Genetics, RECUMAC, Cuba<br><br>**Birth defects surveillance – Methodology II**<br><br>The JRC-EUROCAT Information System<br>*Annie Perraud*<br><br>A patient-initiated rare disease registry for South Africa<br>*Helen L Malherbe*<br><br>National Congenital Anomaly and Rare Disease Registration Service: how the Congenital Anomaly Official Statistics Report can influence and improve care<br>*Kathryn Johnson*<br><br>Semi-automated identification of ventricular septal defects from a clinical data warehouse<br>*Julie Thomas-Chabaneix* |
| *12:45 – 13:30* | **Session on ICBDSR Report and collaborative projects** |

## Posters

*(Alphabetical order by corresponding author's last name)*

**The posters will be shown on Monday 6th November**
**Meeting room "Olympia"**

Using national congenital anomaly registration to evaluate the roll out of the non-invasive prenatal testing (NIPT) in England - *Jennifer M Broughan*

Infants with Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) in Malta - *Gabrielle de Gray*

Congenital anomalies as rare diseases: the importance of genomic linkage for congenital anomaly registries - *Kathryn Johnson*

The unexplored effects of social and health inequality on adverse outcomes to children born with Spina Bifida: 2010-2020 -*Kathryn Johnson*

Sibling birth defects recurrence in Florida, 2000 to 2019 - *Russell S Kirby*

Prenatal detection of birth defects: pathway of care in obstetric ultrasound services in Bogotá, Colombia - *Maria Camila León-Sanabria*

Echocardiography evaluation of congenital heart disease with its outcome in a Medical University Hospital of Dhaka, Bangladesh - *M Abdul Mannan*

Prevention of neural tube defects in Chile: more than two decades of folic acid fortification - *Cecilia Mellado*

WHO's Resolution calls for micronutrient fortification to prevent spina bifida and other Neural Tube Defects - *Rosa Pardo*

Epidemiology and risk ractors concerning transposition of the great vessels: A population-based case-control study in Bogotá and Cali, Colombia- *Pablo Pineda-Sanabria*

Characterization of risk factors for Clubfoot in Bogotá and Cali, between 2002-2020 - *Esteban Portilla*

Polydactyly risk factors in Bogotá and Cali, Colombia between 2002-2020: A case-control study
*Lina María Ramírez*

Severe congenital protein C deficiency: epidemiology, diagnosis and long-term management - *Csaba Siffel*

Sex ratio and congenital anomalies in children born after assisted reproduction - *Antonin Šípek Sr*

Application of Photon counting CT in the diagnostics of Post mortem fetal malformations for the assessment of skeletal , external skin surface and vasculature anomalies - *Tidhar Steiner*

Characterization of environmental exposures in the French ATENA registry - *Julie Thomas-Chabaneix*

Multidisciplinary consultation in fetuses with malformations: prenatal exome experience in a tertiary public hospital - *Eduardo Tizzano*

Prevalence of Congenital Heart Defects Among Boys with Hypospadias in England - *Lee T Watson*

Can be viewed at: www.icbdsrtraining.org

# Monday, November 6th, 2023

## Session I – Oral Presentations

**Moderators:**
***Yves Muscat Baron*** - Clinical Chairperson, Department of Obstetrics and Gynaecology, University of Malta
***Dieuwke Broekstra*** - Research group Congenital Anomalies, Department of Genetics, University Medical Center Groningen, The Netherlands

### Birth defect surveillance and descriptive epidemiology

Global burden of birth defects estimation: methods, progress and selected results
*Kathleen L Strong*

Estimating the contribution of different disease groups to the global rare diseases burden using data from the Veneto region RD registry, 2002 through 2019
*Monica Mazzucato*

MALFOVAR Registry / Repository Update
*Tidhar Steiner*

Using population-level, real world data to establish cytogenetic testing patterns and evaluate genotype-phenotype correlations in congenital anomalies in England
*Corinne R Mallinson*

Current activities of the JRC-EUROCAT Central Registry
*Agnieszka Kinsner-Ovaskainen*

Validating routinely collected data to improve ascertainment of congenital anomalies to support national registration in England
*Jennifer M Broughan*

An update on the status of global prevention of folic acid-preventable spina bifida and anencephaly, Year 2022
*Vijaya Kancherla*

**Global burden of Birth Defects Estimation: Methods, progress and selected results**

KL Strong[1], H Blencowe[2], H Malherbe[3], J Perin[4], Burden of Birth Defects Technical Working Group
*[1] Department of Maternal, Newborn, Child and Adolescent Health and Aging, World Health Organization, Geneva Switzerland; [2] London School of Hygiene and Tropical Medicine, London, UK; [3] Rare Diseases South Africa, Cape Town, South Africa; [4] Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA*

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Birth Defects Program on which the work is based: Global Burden of Birth Defect Estimates

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**Background and Objectives:** Globally, birth defects are associated with substantial morbidity and mortality, accounting for 8% of under-5 child deaths in 2019, with the highest mortality found in low- and middle-income countries (LMICs). Global estimates for major birth defects for all countries were first published in 2006 by the March of Dimes in collaboration with the WHO . The 2006 estimates were made for single gene disorders, chromosomal disorders, and malformations combining demographic data with data sourced from the literature and surveillance systems. These have since been updated as part of the Modell Global Database (MGDb) but not published. Estimates are also published by the Institute for Health Metrics and Evaluation (IHME) since 2012. However, these include a different range of conditions and methods and results have not been readily accessible. We present the process that WHO and partners are using to revise estimates of the global burden of birth defects.

**Methods:** In 2022, WHO formed a Burden of Birth Defects Technical Working Group (BBD-TWG) to review the previous estimation work, identify available data and advise on optimal approaches to estimation. First, priority conditions were defined. Next, available prevalence and case-fatality data for these conditions were identified through registry review supplemented with literature reviews of specific conditions. Finally, the MGDb is being updated to include revised demographic, birth prevalence, mortality and case-fatality data. A repository for the MGDb that is on-line and open access will document: data inputs and methods; results by country, region and globally; and limitations of the results. Prevalence and mortality estimates of birth defects are being incorporated into the Born Healthy Toolkit for use in countries. Additionally, work is on-going with the IHME team to detail methods and results for birth prevalence of birth defects in the Global Burden of Disease (GBD) 2024.

**Results:** Five priority conditions of immediate relevance to policy makers and clinicians, were identified by the BBD-TWG for which prevention and care strategies exist, including: Structural anomalies that can be seen at birth or in uteri, including NTDs, orofacial clefts, abdominal wall anomalies; Trisomies and syndromic conditions; Congenital heart defects; Congenital hypothyroidism and congenital syphilis; Haemoglobinopathies. Preliminary results will be presented for selected birth defects. These results will be compared with other estimates of congenital disorder burden and similarities and differences will be discussed.

**Discussion and Conclusions:** National, regional and global health estimates can play an important role in raising visibility of specific health conditions and advocating for commensurate allocation of resources for implementing policies and programmes to tackle these conditions. Birth defects as a group have been neglected in many national child health strategies and policies, especially in LMICs where they are thought to be less prevalent than in high income countries. Our work shows that this is not the case and in fact, as child under-5 survival improves, the proportion of mortality due to birth defects increases. To capitalize on this finding, we focus on including available data from registries and studies in LMICs to close the data gap. Data improvement is the next step and this is being done by the development of congenital disorder registries in LMICs. We hope to generate consensus on how to take global estimates further for advocacy.

**Analysis of long-term survival of patients diagnosed with different rare disease groups-including selected congenital anomalies - using data from the Veneto region RD registry, 2002 through 2019**

M Mazzucato[1,2] L Visonà Dalla Pozza[1,2] C Minichiello[2], E Toto[1,2] A Vianello[2,3],P Facchin[1,2,3]
*[1] Congenital Malformations Registry Veneto region, Italy; [2] Rare Diseases Coordinating Centre, Veneto region, Padua University Hospital, Italy; [3] Padua University-Italy"*

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Birth Defects Program on which the work is based: Veneto region -Italy Congenital Malformations Registry, Italy

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**Background and Objectives:** Rare diseases (RD) surveillance is critical to understanding their impact both at individual and at population level. A number of studies have estimated the mortality attributable to selected groups of RD, among them major congenital anomalies (CA). More limited information is available regarding the contribution of CA burden on older age groups, as a long observation period is needed to obtain accurate estimates. A further area requiring investigation is the specific contribution of different nosological subgroups with the RD category on mortality figures. These data can only be derived using data from population-based registries monitoring CA together with other RDs. The aim of this study is to provide a descriptive analysis of mortality and survival in a cohort of patients diagnosed with RDs, including CA, using data from a population-based registry ongoing in the Veneto region, Italy, and referred to the period 2002-2019.

**Methods:** The study population included all Veneto region residents (4,905,854 inh). The data sources used are the Veneto region RD registry (VRRDR) and the Veneto region administrative health database (AHD). The VRRDR is a web-based registry collecting data on patients diagnosed with a RD since 2002. The Veneto AHD is an archive of healthcare beneficiaries and includes demographic information and the vital status of each resident. The two data sources are fully interoperable. In the VRRDR each disease entity is assigned ICD, OMIM and ORPHA codes. Each patient included in the VRRDR was followed from the date of first diagnosis until 31 December 2019 or the date of death. Cases with rare congenital anomalies were included only if a diagnosis was reported after the first month of life. Gender-specific standardized mortality ratios (SMR) (with 95% CIs), considering as reference the Veneto region population data, fatality rates per year and per group of diseases, Kaplan-Meyer survival curves (with 95% CIs) per sex and per Orphanet classification were calculated.
**Results:** In the study area there were 30,879 patients alive as of 31 December 2019; 53.8% were females. 19.9% were pediatric patients (<18 years). The overall prevalence of RD was 62.93 per 10,000 inhabitants (95% CI 62.23-63.63). 15.8% of the patients alive as of December 31, 2019 were diagnosed with a congenital anomaly. A total of 3,367 patients died during the study period. The overall crude mortality rate in RD patients was 8.87 per 100,000 inhabitants (95% CI 8.03-9.70), 0.26 per 100,000 inhabitants in patients with CA. Patients with a diagnosis of a rare neurologic disease, rare skin disease and rare systemic or rheumatologic disease had the lowest long-term survival rate, 58%, 68% and 81%, respectively, after 15 years of observation. Patients with chromosomal anomalies present higher survival rates compared to these groups: 94%, after a 15-year follow-up period.

**Discussion and Conclusions:** This study followed a consistent group of patients diagnosed with different RD. As the enrolment in the VRRDR is the prerequisite to obtain exemption from healthcare costs we believe the population coverage to be high. Other strengths of the study are the long observation period, diagnosis accuracy performed by Centres of expertise, the availability of real-time information on patients' vital status. CA are one of the most represented groups in terms of prevalence. A greater number of deaths is observed within other RD groups. CA present higher survival rates, especially in the long-term period. Finally, we explored the possible use of a RD-specific coding resource as the Orphanet classification to investigate the distinct contribution of different nosological groups when providing epidemiological figures derived from an RD population-based registry monitoring CA within the broader RD category.

**MALFOVAR Registry / Repository Update**

T Steiner [1,2] ,G Rudas[4] , M Csáky-Szunyogh[3]
*[1]Semmelweis University Medical Imaging Center , Budapest; [2] Semmelweis University Obstetrics and Gynecology Department, Budapes; [3] NNK National Public Health Center , VRONY, Budapest; [4] Mind Clinic Budapest*

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Birth Defects Program on which the work is based: VRONY MALFOVAR / Hungary

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**Background and Objectives:** MALFOVAR is a multi disciplinary, multi modality registry / repository. The repository is collecting information in a multicentric manner, between 3 centers in Budapest. The aim of the register is to collect Human malformations and variable anatomy changes (VAC) in fetuses, children and adults. The core of the registry is of fetal anomalies that have been analyzed by the MALFOVAR centers with MRI and Ultrasound as a comparative imaging modality using Multi Modality Harmonization (MMH) technique. The registry activity is supported by IRG: The foundation for living children with Central Nervous system anomalies.

**Methods:** MALFOVAR Malformations and variable anatomy register is an email based register of Semmelweis University and NNK / VRONY / NNMR (Hungarian Institute of Public Health fetal malformations register) in Hungary .The source of the register is medical imaging (IMPACS) and its interpretation documentation (MEDSOL) . Follow up projects of MALFOVAR: 1. Post Mortem Multi-modality imaging;
2. Adult and neonate screening and follow up (incidental findings);
3. Reverse engineering scanning/ search: Brain malformation cases associated with Epilepsy;
4. Summary of data in Multiple Pregnancies;
5. Summary of data in Liver Malformations and ventriculomegaly;
6. MAN (MRI Assisted Neurosonography);
7. Establishment of Digital MALFOVAR Museum in the Semmelweis University Anatomy department Museum;
8. AI applications and algorithms: BBR: BOD/BOD Ratio , FTR: Fluid Tissue Ratio algorithms in the brain malformations; 8. IT solutions/ Tools : MALFOVAR App , internet site.

**Results:** The total amount of cases analyzed 475 cases .We present case collections and surveys according to specific subjects of interest (eg: Summary of data in Multiple Pregnancies, ,Summary of data in Liver Malformation and ventriculomegaly). In the lecture we will present importance of VAC (variable anatomical changes ) and adult data detection and collecting system .

**Discussion and Conclusions:** There are 2 principles that guided us to the development of this register.

1. Importance of VAC variable anatomical changes. ( with similarities to VUS in genetics) Malformations and variable anatomical changes are part of same biological spectrum. Until today we did not have interest in variable anatomical changes (VAC) because we do not consider them as disease and therefore collecting them may be burden on the system. Since VAC represent the mild type malformation spectrum they may teach us on the developmental biological mechanisms of serious malformations and hint for possible mechanisms of development and future prevention.
2. Broad base population detection and collection / missed cases .Today we collect usually the malformation and not the VAC, Therefore the main population of interest is fetal and pediatrics.

**Using population-level, real world data to establish cytogenetic testing patterns and evaluate genotype-phenotype correlations in congenital anomalies in England**

CR Mallinson[1], D Williams[1,2], K Johson[1,3], S Stevens[1], S Hardy[1]
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Birth Defects Program on which the work is based: National Congenital Anomaly and Rare Disease Registration Service, National Disease Registration Service, NHS England

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**Background and Objectives:** Congenital anomalies are a complex and heterogeneous group of conditions which are present at birth and are a frequent cause of morbidity and mortality. Structural congenital anomalies are known to be frequently associated with an underlying chromosomal anomaly. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) collects national data relating to structural and chromosomal anomalies across England from a variety of sources, providing a unique and powerful resource to evaluate genotype-phenotype correlations at population-level. Linkage between NCRADRS registration data and cytogenetic testing also allows for insights into the impact of prenatal testing on pregnancy outcome at a national level.

**Methods:** We collected cytogenetic testing data performed between 2018-2020 from all English NHS Genomic Laboratory Hubs and matched this to national congenital anomaly records within NCARDRS which includes patient demographics, pregnancy details, including fetal outcome and ICD10-coded structural and chromosomal anomalies. Patterns of cytogenetic testing and correlations between registered genotype and phenotype were explored

**Results:** 35,970 cytogenetic tests were performed in 23,389 individuals between 2018-2020, of these 18,132 were prenatal tests. Chromosomal anomalies were identified in 57% of cases. Trisomy 21 was the most identified anomaly (n=5761); however, chromosomal anomalies were frequently identified alongside other major congenital anomaly subgroups including abdominal wall defects (56%) and cardiac anomalies (47%). Rates and types of chromosomal anomalies varied within subgroups; for example, 75.2% of atrioventricular septal defects had an associated chromosomal anomaly compared to 12% of transposition of the great arteries. The prenatal identification of chromosomal anomalies was shown to have an impact on pregnancy outcomes, with higher rates of terminations of pregnancy seen (79.4% versus 29.4% with no chromosomal anomaly). A smaller increase in spontaneous losses was also seen (5.0% versus 2.5%).

**Discussion and Conclusions:** Population-level data held within NCARDRS can be used to establish correlations between chromosomal and structural congenital anomalies, allowing for a greater understanding of the associations between these complex anomaly groups. We present for the first time a comprehensive evaluation of cytogenetic testing and outcomes in congenital anomalies for the population of England.This information can be used to inform decisions making and improve knowledge of associations of genotype-phenotype correlations.

**Current activities of the JRC-EUROCAT Central Registry**

A Kinsner-Ovaskainen[1], A Perraud[1], S Martin[1]
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Birth Defects Program on which the work is based: EUROCAT

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**Background and Objectives:** The Central Registry of EUROCAT, the European network of population-based registries for the epidemiological surveillance of congenital anomalies, is part of the European Platform on Rare Diseases Registration since 2015. The Central Database contains at present about 500,000 individual cases among livebirths, stillbirths and terminations of pregnancy, and covers around 1/4 of the European birth population.

**Methods:** The JRC-EUROCAT Central Registry collects data from member registries twice a year using a secure and complex information system. The data are used for epidemiological surveillance of congenital anomalies. For this purpose, EUROCAT developed internationally recognised standards of classification: (i) the EUROCAT subgroups, gathering anomalies that share etiological mechanisms or clinical characteristics and (ii) the EUROCAT multiple congenital anomaly (MCA) algorithm, which classifies cases as syndromic, potential MCA or isolated anomalies. The results of surveillance, including prevalence, prenatal detection rates and the evaluation of clusters and pan-European trends in major congenital anomalies across Europe, are publicly available on the EUROCAT website (https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en).

**Results:** Several major changes occurred in the past three years. The Central Registry put in place a renewed secure information system to ensure data protection and high data quality. This solution includes an improved, secure data submission portal, a revised website and a novel EUROCAT Data Management Software that assists member registries in the collection, management, reporting and analysis of their data. The EUROCAT subgroups and the MCA algorithm have been reviewed and updated, based on developments in clinical genetic diagnostics, literature reviews, data extracts from the JRC-EUROCAT Central Database and expertise from the EUROCAT Coding and Classification Committee. This methodology is described in the newly issued EUROCAT Guide 1.5 available on the website. Finally, EUROCAT is a dynamic network continuously attracting new member registries, which contributes to its increase the coverage. The EUROCAT accession criteria have been formally described and are available on the website.

**Discussion and Conclusions:** With its high-quality, standardised, population-based data EUROCAT continues to be a valuable and principal source of epidemiological data on congenital anomalies in Europe. The EUROCAT standards and classification systems provide a clear methodology for research on congenital anomalies and we encourage their wider use by the international research community. The EUROCAT network is dynamic and new memberships will help increasing the geographical coverage and strengthening the activities and the value of the network at European level.

**Validating routinely collected data to improve ascertainment of congenital anomalies to support national registration in England**

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Birth Defects Program on which the work is based*:* National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

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**Background and Objectives:** NCARDRS was formed in 2015 from regional congenital anomaly registers and by 2018 had expanded geographically to cover all births in England (approximately 600K per year). Routinely collected healthcare datasets have the potential to be a valuable and efficient source of ascertainment for congenital anomaly registration on a national level. Hospital episode statistics (HES) are routinely recorded at every hospital admission within the National Health Service (NHS) in England. They record diagnoses (coded using ICD-10) and procedures and interventions, (classified using a custom coding system, OPCS4) for each episode of care. This study validates ICD-10 and procedure code combinations to develop algorithms to improve the ascertainment of postnatally identified conditions.

**Methods:** Candidate ICD-10 and associated procedure code combinations were identified according to their frequency within the routine data collection, the specificity of the procedure code and their degree of underrepresentation in NCARDRS data collection. Priority was assigned to those conditions that are more likely to be identified postnatally. Relevant disease/procedure code combinations for selected conditions were extracted from HES for babies born in 2016 to 2018 for the seven trusts for which remote access to clinical systems was available. These were assigned to registration officers who verified the disease coding using this remote access. The positive predictive value (PPV) of selected ICD-10 anomaly codes in combination with procedure codes in Hospital Episode statistics (HES) was estimated. Disease/procedure code combinations that exceeded a predetermined threshold of 95% PPV were registered using an automated process for birth cohorts from 2018.

**Results:** 971 individuals across 17 disease/procedure combinations representing 10 conditions in seven trusts where remote access to clinical systems was available were extracted from HES and these cases were validated using remote access. Seven conditions, reflecting 13 disease/procedure combinations, were identified where the PPV of each individual disease/procedure code combinations exceeded a predetermined threshold of 95%. These were: Choanal atresia (overall PPV 100%, 95% confidence interval 95.2%-100.0%), oesophageal atresia (96.7%, 91.9%-98.7%), polydactyly (98.7%, 95.3%-99.6%), accessory kidney (100%, 86.7%-100.0%), congenital posterior urethral valves (97.5%, 91.3%-99.3%), talipes equinovarus (100.0%, 92.0%-100.0%) and congenital cataract (100.0%, 92.0%-100.0%).

**Discussion and Conclusions:** Routinely collected data sources are a useful tool in the ascertainment of postnatally treated congenital anomalies for national registrations. Disease/procedure code combinations from HES in England reflect a scalable and accurate method of ascertainment, maximising the potential of routinely collected healthcare data.

**An update on the status of global prevention of folic acid-preventable spina bifida and anencephaly, Year 2022**

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Birth Defects Program on which the work is based*:* NA

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**Background and Objectives:** Mandatory folic acid fortification of staple foods is an effective public health intervention to prevent a large proportion of spina bifida and anencephaly globally. In May 2023, the World Health Assembly passed a resolution promoting large-scale fortification of staple foods with folic acid in an effort to prevent spina bifida and other neural tube defects. As of year 2020, only around 60 countries implemented mandatory food fortification policy using WHO recommended concentrations of folic acid added to wheat flour, maize flour, and/or rice. Our objective was to estimate the global proportion of folic acid-preventable spina bifida and anencephaly (FAP SBA) prevented through mandatory folic acid fortification of staples (wheat flour, maize flour, and rice) during the year 2022.

**Methods:** The Food Fortification Initiative database was used to identify countries that implemented mandatory fortification policies with folic acid added to cereal grains (wheat flour, maize flour, and/or rice). We built FAP SBA prevention models assuming mandatory folic acid fortification at 200 mcg/day of folic acid fully protects against FAP SBA and reduces their prevalence to a minimum achievable 0.5 / 1,000 live births.

**Results:** We will present results from our analysis showing country-specific number and global proportion of FAP SBA cases prevented through mandatory food fortification in year 2022. Countries and regions with and without folic acid fortification will be identified.

**Discussion and Conclusions:** The knowledge of the status of global prevention of FAP SBA helps in policy advocacy. Findings from this study can be used in parallel with the WHA76.19 resolution on food fortification to promote neural tube defects prevention in over 100 countries that can benefit from equitable large-scale food fortification interventions.

## Session II – Oral Presentations

**Moderators:**

***Juliana Lores Espinosa*** - Cali Birth Defects Surveillance Program, Department Health Sciences, Javeriana University, Cali, Colombia

***Anke Rißmann***, Medical Director of Malformation Monitoring, Saxony-Anhalt, Germany

### Birth defects surveillance - Descriptive epidemiology

Prenatal findings in craniofacial microsomia using the Alberta Congenital Anomalies Surveillance System, 1997-2019
*Mary Ann Thomas*

Prevalence of skeletal dysplasia in Emilia Romagna, Italy
*Elisa Ballardini*

Monitoring an emerging maternal and infant health threat: expanding a birth defects surveillance program to include infants with congenital cytomegalovirus infections
*Paul A Romitti*

Diaphragmatic hernia in the Czech Republic. Incidence, prenatal diagnosis and sex ratio
*Antonin Šípek, Jr*

Population-based study on epidemiology and outcomes of Congenital Tracheo-Oesophageal Anomalies in South Wales over a 21-year period
*Margery Morgan*

Years of potential life lost for children and adults with Congenital Heart Defects, United States, 2007-2017
*Wendy N Nembhard*

**Prenatal findings in craniofacial microsomia using the Alberta Congenital Anomalies Surveillance System, 1997-2019**

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Birth Defects Program on which the work is based: Alberta Congenital Anomalies Surveillance System (ACASS)

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**Background and Objectives:** Craniofacial microsomia (CFM) primarily includes specific craniofacial and vertebral anomalies that co-occur more frequently than expected. Other terms such as oculo-auriculo-vertebral (OAVS) spectrum, Goldenhar syndrome and hemifacial microsomia are also used to describe this heterogeneous disorder. The anomalies are usually asymmetric and primarily affect the face, ear, mouth, eye, and vertebrae. Severity is variable as are the associated congenital anomalies outside of the head and neck. Published prenatal findings for OAVS is limited. Castori et al., (2006) summarized 21 cases which included most published cases for that time. There is one population-based study using data from the European network of congenital anomalies registries (EUROCAT) that includes limited details on prenatal findings (Barisic et al. 2014).The current study contributes 11 cases with CFM and anomalies identified prenatally.

**Methods:** Cases born between January 1, 1997 and December 31, 2019 with CFM were abstracted from the Alberta Congenital Anomalies Surveillance System (ACASS). This provincial, population-based program ascertains congenital anomalies for livebirths, stillbirths and termination of pregnancies (ToPs) and thus, ascertains all birth outcomes and includes cases along the full spectrum of this condition.

**Results:** There were 63 cases with CFM and 11 (17%) were identified with prenatal findings. Nine were live births (82%) and 2 were ToPs (18%). Three cases (27%) had facial anomalies, one each with left cleft lip, right microtia and bilateral micropthalmia. Two cases (18%) had vertebral anomalies (thoracic and sacrococcygeal). Other anomalies included: 4 (36%) with brain anomalies, 4 (36%) with congenital heart anomalies, 5 (45%) with renal anomalies and 2 (18%) with radial ray anomalies. Five (45%) were SGA (<10%ile), 6 (55%) had a single umbilical artery and 3 (27%) were from a twin pregnancy, discordant for anomalies.

**Discussion and Conclusions:** This study identified 11 cases with CFM and prenatal findings. The anomalies detected prenatally were heterogenous and relatively severe. Comparable to prior published cases, there were recurring anomalies on prenatal imaging, including anomalies of the brain, eye, heart, kidneys, and radial ray which may aid in the prenatal diagnosis of OAVS.

## Prevalence of skeletal dysplasia in Emilia Romagna, Italy

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Birth Defects Program on which the work is based: IMER Registry, Italy

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**Background and Objectives:** Skeletal dysplasia (SD) is a heterogeneous group of over 700 disorders characterised by abnormality of growth and structure of the skeleton. More than 500 genes are involved and more than 40 disease groups have recently been defined (Unger 2023). Although each condition is relatively rare, the overall birth incidence is almost 1/5000 (EUROCAT syndrome guideline) and depends on the capacity to recognize and correctly define skeletal dysplasia. Congenital anomaly registries that integrate cases with rare disease and clinical registries are therefore important in order to properly define SD epidemiology. Our aim is to present prevalence of SD in Emilia Romagna, Italy.

**Methods:** Data were extracted from IMER registry, a population-based congenital anomaly database covering the first year of life, active since 1978. IMER uses multisource ascertainment, including hospital discharge records (HDR) from 2009, through a validated algorithm to recognize CA not communicated to the registry by clinicians. Cases are notified to the registry also from the rare disease registry. Live birth, stillbirth and TOPFA (termination of pregnancy for fetal anomalies) are included. IMER follows EUROCAT coding guidelines and CA definitions, where SD are referred as ICD 10 codes Q 74.02, Q77, Q 78.0-78.9.Analyzed period: 2011-2020 included.

**Results:** During the study period of ten years, 98 cases of SD were reported in the IMER registry.
The overall prevalence was stable at 2.54 per 10 000 (2.06 – 3.07), and is comparable to EUROCAT prevalence, 2.25 per 10 000 (2.15 – 2.35).Of the 98 cases, 78% were obtained from clinicians, 9% from the rare diseases registry, 8% from HDR, 4% from clinicians but required a change in definition thanks to the collaboration with rare disease registry. Particularly relevant is the collaboration with the rare disease registry for this specific group of disease (9%) whilst cases from the rare diseases represent only the 1.5% in the whole IMER database. Of the 98 cases, 45% were TOPFA cases (the same as EUROCAT, 47%). Prenatal diagnosis occurred in 66% of cases. For live birth cases prenatal diagnosis was present only in 39% of cases. The group was heterogeneous as expected, even if the most used code was related to a unspecific code used in a prenatal diagnosis of severe SD, typically lethal conditions.

**Discussion and Conclusions:** During the study period, the IMER registry prevalence of skeletal dysplasia was stable, around 2.54 per 10 000. The characteristics of the disease group shows the usefulness of the sources used by the IMER registry.

**Monitoring an emerging maternal and infant health threat: expanding a birth defects surveillance program to include infants with congenital cytomegalovirus infection**

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Birth Defects Program on which the work is based: Iowa Registry for Congenital and Inherited Disorders

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**Background and Objectives:** Cytomegalovirus (CMV) is a highly prevalent human herpes virus infection, which typically presents with mild, non-specific symptoms. Transmission of CMV typically occurs via direct contact with virus-containing secretions such as saliva, urine, genital secretions, and blood. Infected persons retain latent infection for life and regularly shed the virus. Congenital CMV (cCMV) is the most common congenital viral infection, with 90% of infected infants being asymptomatic. It is the leading non genetic cause of sensorineural hearing loss and contributes to neurodevelopmental disabilities, ophthalmological disorders, and other chronic conditions. As most infected people are asymptomatic, the prevalence of CMV and cCMV is substantially underestimated. In the US, universal prenatal screening for CMV is not conducted. Moreover, only one state conducts newborn screening for cCMV. As such, active, multisource population-based surveillance is needed to generate informed cCMV prevalence estimates.

**Methods:** The Iowa Department of Health and Human Services (Iowa HHS) and Iowa Registry for Congenital and Inherited Disorders (IRCID) are funded by the US Centers for Disease Control and Prevention (CDC) to develop a cCMV surveillance program using a two-tier approach. Tier 1 (T1) includes developing and testing surveillance methods at a sentinel hospital (University of Iowa Hospitals and Clinics [UIHC]), under institutional review board approval. Tier 2 (T2) expands T1 methods statewide via a CMV reporting mandate issued by the Iowa HHS Director. Data collection will use linkage to prenatal care, delivery, and infant birth records at UIHC (T1) and similar records at birthing facilities statewide (T2) to document cCMV infection within 21 days following birth. T2 will also facilitate access to statewide vital, hospital discharge, birth defect surveillance, early hearing detection and intervention, and electronic laboratory reporting data, along with medical record abstraction.

**Results:** For T1 and T2, IRCID and Iowa HHS investigators participated in a national workgroup to develop and submit a position statement for a standardized case definition for cCMV surveillance to the US Council for State and Territorial Epidemiologists. These investigators also collaborated with CDC investigators on development of a cCMV surveillance data dictionary. For T2, Iowa HHS investigators developed a reporting order to mandate CMV infection reporting in Iowa; the order is pending signature by the Iowa HHS Director. Also for T2, IRCID investigators are developing an electronic surveillance application for medical record abstraction. A future task to enhance cCMV surveillance efforts, including tracking and follow-up of affected live births, will be to develop a partnership with the Iowa e-health system, CyncHealth Iowa. This partnership will increase statewide access to outpatient prenatal care records and pediatric care records for case finding and record abstraction.

**Discussion and Conclusions:** IRCID has a successful history of establishing surveillance programs for infectious diseases during pregnancy, including our work for Zika virus infection and SARS-CoV-2 infection. Building on our success with those programs, we are now developing a two-tier approach for surveillance of cCMV infection. This presentation will describe our challenges and successes with our proposed approach and provide tools to expand this approach to include life course surveillance of affected infants and opportunities for collaboration by International Clearinghouse member programs.

## Diaphragmatic hernia in the Czech Republic. Incidence, prenatal diagnosis and sex ratio

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Birth Defects Program on which the work is based: National Registry of Congenital Anomalies of the Czech Republic

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**Background and Objectives:** Retrospective analysis of the frequency and sex ratio of children born with diaphragmatic hernia in the Czech Republic in the period 1961–2020.

**Methods:** In the work, we used data from the National Registry of Congenital Anomalies maintained by the Institute of Health Information and Statistics of the Czech Republic (ÚZIS ČR). The analyzed period covers the years 1961 to 2020.

**Results:** More than 7.5 million children were born in the period we monitored. Among those 1,742 of children were born with diaphragmatic hernia (973 boys, 758 girls,11 cases of unknown/undetermined sex). Of the total number of children born without a diaphragmatic hernia, 51.22% were boys, and 48.78% were girls. In the case of children born with a diaphragmatic hernia, there were statistically significantly more boys, 56.21% versus 43.79% of girls ($p<0.001$). The representation of boys and girls changes over time, in the first twenty years the predominance of boys over girls was not so pronounced and statistically significant compared to the group without the anomaly. The total incidence of the anomaly does not have a clear and distinct trend of continuous decrease or increase in incidence during the observed period.

**Discussion and Conclusions:** The overall incidence of diaphragmatic hernia does not change significantly during the observed period. However, the share of prenatal diagnosis is increasing. It was proven that there were statistically significantly more affected boys compared to girls.

The study is Supported by the Ministry of Health of the Czech Republic, (RVO project: “Thomayerovanemocnice – TN, 00064190)"

**Population-based study on epidemiology and outcomes of Congenital Tracheo-Oesophageal Anomalies in South Wales over a 21-year period**

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Birth Defects Program on which the work is based: CARIS - Congenital Anomaly Register & Information Service,

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**Background and Objectives:** Oesophageal atresia (OA) is a congenital anomaly of the upper gastro-intestinal tract characterised by interruption of oesophagus continuity, with or without a persistent communication with the trachea, termed trachea-oesophageal fistula (TOF). The aetiology is multifactorial. This population-based study aims to determine the prevalence, demographics, trends and outcomes of babies diagnosed with congenital trachea-oesophageal anomalies over a 21-year period in Wales, UK.

**Methods:** All cases with trachea-oesophageal anomalies (ICD10 code Q39.0-Q39.2, Q32.0-Q32.4) reported to CARIS (Congenital Anomaly Register and Information Service) in Wales, UK, between 1st January 2001 and 31st December 2021 were identified. Cases with ICD-10 code of Q39.0 [OA without TOF], 39.1 [TOF with OA] and 39.2 [TOF without OA] were analysed in further detail. Standard statistical tests were used including means with 95% confidence intervals (CI) and medians with inter-quartile ranges (IQR), where applicable. Deprivation quintiles were calculated according to the Welsh Index of Multiple Deprivation (WIMD) scale relative deprivation. This WIMD is place based according to postcode of residency and considers a number of indicators such as employment and health.

**Results:** 227 cases were analysed:- 25 were OA without TOF; 172 were TOF with OA and 30 were TOF without OA. Mean prevalence was 3.29 (95%CI 2.9-3.6) /10000 total births. Mean prevalence among live-born with OA without TOF was 0.27 (95%CI 0.1-0.4); for TOF with OA, it was 2.06 (95%CI 1.8-2.3) /10000 live births (LB). 14% mothers were > 35 years and 10% were <20 years old. Of the 227 cases, 186 (82%) were LB, 15 (6.6%) still births and 26 (11.4%) terminations. 70 (30%) were isolated anomalies, 24 (10%) associated with chromosomal anomalies, remaining 60% associated with multiple anomalies. For OA without TOF, median birth weight was 1850 gm (IQR 1230-2274) and median gestational age (GA) 33 weeks (IQR 30-36); 64% were diagnosed antenatally. For TOF with OA, median birth weight was 2312 gm (IQR 1462-2897) and median GA 37 weeks (IQR 31-39); 62% were diagnosed after birth. 172/227 cases (75%) cases had surgery. Among the LB, 23(12.3%) died, mostly had low birth weight and/or had multiple anomalies.

**Discussion and Conclusions:** This population-based study provides an epidemiological insight into trachea-oesophageal anomalies over a period of two decades in a nation of the UK. Pure OA without TOF had prevalence of 1/40,000 live births as compared to 2/10,000 for OA with TOF. No annual trends in prevalence of cases were observed over the study period. There was no significant difference in the deprivation quintiles as per the birth address. The majority were live born and with other associated anomalies. OA without TOF was more likely to be diagnosed antenatally as compared to TOF with OA. Mortality was high among babies with multiple anomalies and low birth weight. The remaining live born babies had a successful surgical outcome.

**Years of Potential Life Lost for Children and Adults with Congenital Heart Defects, United States, 2007-2017**

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Birth Defects Program on which the work is based*:* NA

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**Background and Objectives:** Congenital heart defects (CHD) are the most prevalent birth defects; recent improvements in medical treatment have resulted in most children surviving into adulthood. However, many children and adults with CHDs still experience premature death. Understanding the impact of potential years lost due to premature death associated with CHDs is limited. Our study estimated years of potential life lost (YPLL) among individuals with CHDs in the United States (US).

**Methods:** We used death records from the US National Center for Health Statistics, 2007-2017 to identify all deaths where a CHD was listed as the underlying or contributing cause of death. We calculated the YPLL for each age-group (per 100,000 population) overall and by sex, and race/ethnicity. The average percent change (APC) in YPLL was estimated for the time period.

**Results:** Between 2007 and 2017, 28.35 million deaths occurred to US residents, of which 42,158 were CHD related. Of those experiencing death related to a CHD, the total YPLL for individuals <65 years old was nearly 2.1 million years, and 1.13 million- and 941,115-years for males and females, respectively. The age standardized YPLL (per 100,000) was highest for NH-Blacks (95.5, 95%CI: 93.2-97.7) followed by the males (74.1, 95%CI: 73-75.1)) During the study period, the overall APC in YPLL declined by 17.8%. The APC in YPLL declined among all groups but had the greatest decrease for children aged 1-4 years (-31.6%) and adults aged 35-49 years (-24.3%). NH-Blacks experienced the greatest decrease in APC for adults aged 35-49 years (-38.2%) and infants (-25.4%), followed by adults aged 18-34 years (-24.4%).

**Discussion and Conclusions:** Although the overall YPLL declined during the study period, racial/ethnic- and sex-specific disparities were observed. Both NH-Blacks and males experienced higher burden of premature death from CHDs than their counterparts. Further research is required to elucidate the underlying dynamics contributing to these disparities.

## Session III – Oral Presentations

**Moderators:**
***Elisa Ballardini*** - Emilia Romagna Registry of Birth Defects (IMER), University of Ferrara, Italy
***Csaba Siffel*** - College of Allied Health Sciences, Augusta University, Augusta, GA, USA

### Risk factors and health outcomes of birth defects

A brief overview of the current state of knowledge: pregnancy outcome after first trimester exposure to statins
*Katarina Dathe*

Analysis of medication consumption during pregnancy in newborns with birth defects in Bogotá, and Cali, 2002-2019
*Karen Sarmiento*

Profile of live births with birth defects in Brazil, their risk factors and associated infant mortality, 2011 to 2020
*Julia A Gomes*

Health outcomes of children born with genetic syndromes in Europe: an undergoing EUROlinkCAT study
*Alessio Coi*

Factors associated with the survival of isolated cardiovascular and digestive congenital defects, in the first year of life, in Cuba 2011-2020
*Yudelkis Benitez Cordero*

Radionuclides – Neural Tube Defects – Developmental anomalies – Chornobyl
*Wladimir Wertelecki (video-recorded)*

## A brief overview of the current state of knowledge: pregnancy outcome after first trimester exposure to statins

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Birth Defects Program on which the work is based: Not applicable

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**Background and Objectives:** The management of therapy in young women of childbearing age and pregnant patients with increased risk for adverse cardiovascular events, i.e. raised lipid levels, metabolic disorders, chronic kidney disease or after adverse cardiovascular events, challenges clinicians. Patients may be treated with statins as secondary prophylaxis. Statins, in addition, are used to treat familial hypercholesterolemia. There is data inconsistency on the safety of statin therapy during pregnancy, especially after treatment in the first trimester.

**Methods:** A structured search based on a defined search strategy for relevant studies and aggregated evidence was performed in PubMed. We focused on human studies reporting on first trimester statin exposure and outcome of pregnancy, in particular birth defects and spontaneous abortions. We selected the identified publications in a two-step-process according to predefined inclusion criteria. In addition, we performed an observational cohort study based on the Embryotox cohort. The Embryotox cohort comprises systematically recorded datasets obtainedby counselling activities of the Embryotox Center of Clinical Teratology and Drug Safety. Embryotox offers risk assessment on drug use in pregnancyto health care providers and patients for decades. Through structured collection and electronic documentation of related pregnancy follow-up data, the Embryotox cohort was established. Using an observational cohort study approach, we screened the Embryotox cohort for datasets between 2000 and 2021 with first trimester statin exposure and known pregnancy outcome. For further evaluations, the study cohort of statin exposed pregnancies (n=188) was compared to an appropriate control cohort (n=564) obtained from the Embryotox database.

**Results:** The risk of adverse pregnancy outcomes after exposure to statins in early pregnancy has been evaluated in several studies and meta-analyses. In the majority of these publications, however, subgroup analyses for different statin-drugs are missing. Taken together, the published study results do not indicate a significantly increased teratogenic risk for statins. However, a slightly elevated spontaneous abortion risk might be present in women treated with statins in the first trimester. These findings are in line with the preliminary results of the Embryotox observational cohort study on statins.

**Discussion and Conclusions:** This presentation aims to provide an overview of the available evidence on adverse pregnancy outcomes after statin therapy in early pregnancy. Current data speak against a substantial risk for major birth defects. An increased risk for spontaneous abortions cannot be excluded; underlying maternal disease and other confounders may act as contributing factors. The use of statins in pregnancy requires a careful risk-benefit assessment.

**Analysis of medication consumption during pregnancy in newborns with birth defects in Bogotá and Cali, 2002-2019**

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Birth Defects Program on which the work is based: PREVERDEC Bogotá – Cali

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**Background and Objectives:** Teratogens can cause functional or morphological alterations in the embryo, fetus, or even in the individual after birth. However, the impact can vary based on factors like dosage used, duration of exposure, genetic susceptibility, and the timing of medication use during pregnancy. Data on teratogenic effects mostly come from animal studies due to ethical restrictions on human research, consequently, this limited information leaves certain medications with unknown safety profiles during pregnancy. In Colombia, folic acid, calcium, and iron supplementation are mandatory by law for all pregnant women. This study aims to describe and analyze medication consumption during pregnancy, including multivitamins (MV), of the reported cases with birth defects (BD).

**Methods:** Retrospective cross-sectional study that analyzed cases with BD registered in the Program for the Prevention and Surveillance of Birth Defects and Rare Diseases (PREVERDEC) in the cities of Bogotá and Cali during 2002-2019. Case-control methodology by ECLAMC was used. BD were coded by ICD-10 and analyzed by affected system using EUROCAT classification; clinical presentation as isolated, polymalformed or syndromic; and categorized as major (involves a life-threatening risk, requires surgery, or involves severe aesthetic sequelae) or minor (none of the above). Medications recalled by the mothers were analyzed based on the group of medication as multivitamins (MV), antimicrobials (ATB), cardiovascular, neuropsychiatric, gastrointestinal, anti-inflammatory (NSAIDS), endocrinological drugs, anticoagulants, others, and combinations. Timing of consumption was analyzed by trimesters. Microsoft Excel was used for dynamic tables and frequency distribution analysis for BD and medication groups.

**Results:** From 2002-2019, 558,057 births were registered in both cities, with 10,948 cases of BD, resulting in a prevalence rate of 196.18 per 10,000 live births (LB). Among BD cases, 33.0% had no reported medication use during pregnancy, while 67% did. The most reported medications were MV (40.5%), ATB (35.5%), NSAIDS (10.5%), endocrinological drugs (4.1%), and 9.3% used combinations of different groups. Medication use varied across trimesters: 26.2% in first, 21.5% throughout gestation and 14.4% in the first and second trimesters. Excluding MV, ATB was most used in first trimester (64.8%), while NSAIDS were most used in second trimester (40.1%). The most prevalent BD system was limb malformations (10.2%), with 37.2% reporting no medication, 25% MV and 21.3% ATB use. Urinary system defects accounted for 9.7%, 27.6% reported no medication, 27.5% ATB and 27.4% MV use. Heart defects accounted 9.0%, 38.1% reported no medication, 25.3% MV and 21.5% ATB use.

**Discussion and Conclusions:** The status of micronutrients varies widely during pregnancy and among different populations, demands of gestation can exacerbate deficiencies with consequences for fetal health. Despite the mandatory recommendation of MV supplementation, we found that 33.0% of mothers did not report taking MV during pregnancy. In addition to the proven benefits of MV for maternal-fetal health, there may be other positive perinatal outcomes, such as reduced risks of low birth weight, that justify the use of MV in prenatal care. When analyzing cases by affected system, most cases did not report medication use, followed by cases that reported MV intake. Therefore, there may be factors influencing the presentation of BD in patients who consumed MV. These findings emphasize the importance of monitoring and follow-up of medication consumption before, during, and after pregnancy to identify potential risks and associations for effective prevention of outcomes.

**Profile of live births with birth defects in Brazil, their risk factors and associated infant mortality, 2011 to 2020**

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Birth Defects Program on which the work is based: Ministry of Health, Brazil

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**Background and Objectives:** In Brazil, less than 1% of live births (LB) are registered with some birth defects (BD). BD represent an important cause of morbidity and the main cause of infant mortality in the country. The Information Systems on Live Births (Sinasc) and Mortality (SIM) collect information about the occurrence, risk factors associated with these conditions and mortality associated with them in the country. The aim of this study was to describe the profile of LB with BD in Brazil between 2011-2020, as well as possible maternal risk factors and the fetal and infant mortality (under 1 year old) associated with BD.

**Methods:** Descriptive cross-sectional study, carried out from the Brazilian databases of Sinasc and SIM, publicly available (https://datasus.saude.gov.br/transferencia-de-arquivos/), from 2011 to 2020. The prevalence of BD in LB was calculated considering the number of LB with BD divided by the total number of LB registered in Brazil at Sinasc, in the analyzed period, multiplied by 10,000 LB.

**Results:** It was observed that between 2011-2020, 240,994 LB presented some BD in Brazil (0.8% of all LB). On average, 24,099 per year (83 cases to each 10,000 LB). Congenital malformations and deformations of the musculoskeletal system (Q65 to Q79) were the most prevalent anomalies in the country (41/10,000 LB), followed by congenital malformations of the nervous system (Q00 to Q07) (11/10,000 LB) and congenital malformations of the circulatory system (Q20 to Q28) (11/10,000 LB). Considering possible risk factors for BD, it was observed that mothers aged equal or above 35 years were more frequent among LBs with chromosomal abnormalities (Q90 to Q99) (54%) and congenital malformations of the circulatory system (26%) (versus 13 % for all NV). Among LBs with congenital malformations of the circulatory system and chromosomal abnormalities, a higher frequency of white mothers (50% and 45%, respectively) and with ≥12 years of schooling (25%) was observed compared to all LBs. During the evaluated period, 18,404 fetal deaths (6% of the total) and 81,136 infant deaths (22%) due to BD were registered. Other congenital malformations (Q80 – Q89) (40%) and congenital malformations of the nervous system (24%) were the main causes of fetal deaths, and congenital malformations of the circulatory system (39%) and congenital malformations of the nervous system (15%) were those of infant deaths.

**Discussion and Conclusions:** Considering the importance of BD as a public health problem and an important cause of child morbidity and mortality in Brazil, it is important to maintain active the surveillance of these conditions, as well as to reinforce its prevention and assistance to individuals affected by them.

**Health outcomes of children born with genetic syndromes in Europe: an ongoing EUROlinkCAT study**

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Birth Defects Program on which the work is based*:* EUROCAT

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**Background and Objectives:** Children with Genetic syndromes (GS) may suffer repeated hospital admissions, long stays in hospital and may undergo multiple surgeries which represent a significant burden for their families and carers. The overall aim of this ongoing EUROlinkCAT study is to evaluate the burden of disease in terms of survival, hospital admissions, surgeries undergone, and medications prescribed in children up to the age of 10 years, born with one of the following GS: Angelman syndrome, Prader Willi syndrome, Williams syndrome, Beckwith Wiedemann syndrome, Noonan syndrome, Cornelia de Lange syndrome, Di George syndrome, Oculoauriculovertebral spectrum (Goldenhar syndrome).

**Methods:** The EUROlinkCAT project enabled population-based congenital anomaly registries in different European countries to link their data on children born with anomalies to healthcare databases to determine their health in the first ten years of life. Data from the participating registries were registered according to the EUROCAT Guidelines. Data were locally linked to the healthcare databases according to the methods and quality controls defined by EUROlinkCAT. All the data were standardised to a common format, as the healthcare systems across Europe use different native languages and coding classification schemes. A common data model (CDM) containing all variables was developed. The use of the CDM enabled the development of common scripts for the data quality checks and the statistical data analysis to provide results on several health outcomes. All health outcomes were calculated at registry level and then pooled to calculate overall estimates using a meta-analytical approach.

**Results:** For each of the above-listed GS, the following estimates on survival, hospitalisation, surgeries and prescriptions were produced: probability of survival by age and conditional survival; number and proportion of children admitted to hospital by age, number and proportion of children admitted to hospital staying longer than 10 days by age and median length of stay in hospital by age; number and proportion of children undergoing surgery by age, median number of surgical procedures by age, median age at first surgery, number and proportion of children admitted to an intensive care unit by age and number and proportion of children put on ventilation by age; prevalence of use of medications and mean number of prescriptions per 100 children per year.

**Discussion and Conclusions:** This study can provide information for the families of children and their healthcare teams. The results could also be used in counselling parents following a diagnosis of one of the investigated GS and also support policy making. Additionally, variations across the different European areas could highlight differences in terms of therapeutic approaches that might stimulate discussions useful to improve the clinical management of children.

**Factors associated with the Survival of Isolated Cardiovascular and Digestive Congenital Defects, in the first year of life, in Cuba 2011-2020**

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Birth Defects Program on which the work is based: Registro Cubano de Malformaciones Congenitas (RECUMAC)

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**Background and objectives:** Congenital defects are the second cause of neonatal and infant mortality worldwide and it is Congenital Cardiopathies (CC) and Major Anomalies of the Digestive System that have a greater impact. The objective is to analyze the factors associated with survival during the first year of life in children with isolated cardiovascular and digestive anomalies in Cuba, born between 2011 and 2020.

**Methods:** A retrospective cohort of 2,706 live births registered in the Cuban Registry of Congenital Malformations with anomalies of the cardiovascular system and 1,134 of the Digestive System was analyzed. The probability and average survival time during the first year of life were estimated, taking into account the most frequent defects of both systems. The Kaplan Meier methods were applied and a set of explanatory variables or prognostic factors in the rate of occurrence of mortality were simultaneously evaluated by applying Cox Regression to identify relationships between the explored factors and survival.

**Results:** The survival of newborns with isolated CC was 79.8% with an average survival time of 238.6 days (95% CI: 226.7-250.1). 82% of CC in live births corresponded to the acyanotic group, with a probability of survival during the first year of life of 85-91%. The presence of cyanotic CHD (HR:3.24) and preterm delivery (HR:2.15) increased the risk of death in these birth defects. Non-surgical correction (HR:0.34) and the absence of complications (HR:0.569) were associated with a decreased risk of dying during the first year of life. For congenital defects of the digestive system, a cumulative survival rate was 82.99%, with an average survival time of 108.4 days. A higher survival rate was observed for duodenal and jejunalatresias, greater than 86%, and the lowest rate was for esophageal atresias, between 31 and 58%. The highest probability of survival was for those born at term (78.30%), weighing more than 2500g and without complications (95%). The presence of complications had a negative effect on the survival of the patients under study with only 41.50% probability of survival and a mean time of 86.90 days (95% CI: 78.173-95.635).

**Discussion and Conclusions:** Many therapeutic and patient care decisions depend on the estimate of their survival. The quality of prenatal care and therefore the personalization of genetic counseling is strengthened with these estimates, while offering more precise elements for the estimation of postnatal prognoses.

**Radionuclides – Neural Tube Defects – Developmental anomalies – Chornobyl**

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Birth Defects Program on which the work is based*:* OMNI-Net Ukraine Birth Defects Program

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**Background and Objectives:** To determine to what extent if any, Chornobyl ionizing radiation impacted population prevalence rates of visually detectable developmental anomalies. The implementations were in the Rivne province of Ukraine. The northern half of the province known as Polissia is polluted by Chornobyl radionuclides. We compared observations in Polissia with those in the rest of the province.

**Methods:** We recorded levels of incorporated cesium-137 (Cs-137) by pregnant women and concurrently determined population-based prevalence rates of neural tube defects (NTD), microcephaly (MIC), microphthalmia (MOPH), among other developmental anomalies (DA). DA were categorized with adherence to the methodology of ICBDSR. During the 2011-2019 time period, incorporated levels of cesium-137 were measured in 6650 and 4309 pregnant women residing in Polissia (POL) or in not Polissia (not-POL). During the 2000-2019 time period, rates of developmental anomalies among 133,433 and 153,485 births in POL and not-POL were registered.

**Results:** The incorporated Cs-137 levels and rates of NTD as a group, and AN, craniorachischisis (CRA), spina bifida (SB), MIC, and MOPH, were statistically significantly higher in POL than in not-POL. The population prevalence of AN, CRA, iniencephaly (INIEN) and SB in POL was 5.6, 2.4, 0.7, and 12.7, respectively. In the rest of Rivne the corresponding prevalence rates were 4.2, 1.3, 0.5, and 8.6. We compared the combined rates of AN, CRA and INIEN observed during 2000-2019 reported to ICBDSR by 10 registries across Europe. The 8.7 rate observed in POL was the highest followed by those France: Paris (4.8), Netherlands (3.5), Finland (3.5) and France: Remera (3.5). Also observed was a concurrent temporal decrement of incorporated levels of Cs-137 and NTD rates solely in Polissia. In a zone proximal to a nuclear power plant complex, we observed negligible incorporated levels of Cs-137 by pregnant women and high prevalence rates of NTD.

**Discussion and Conclusions:** This report confirms and amplifies observations of POL vs not-POL contrasts in terms of incorporated levels of Cs-137 by pregnant women and population-based prevalence rates of NTD, MIC, MOPH and associations with female prevalence, DA associations, and pregnancy outcomes. In addition to Cs-137, POL is polluted by Sr-90, among other Chornobyl radionuclides. Incorporated levels by pregnant women of Sr-90 remain unknown although we did measure incorporated levels of Cs-137 concurrently with Sr-90 in potato plants grown in POL. The Sr-90 Bq/Kg ranged from 41 to 327 and the range of Cs-137 was 24-88 Bq/Kg. The ratio Sr-90/Cs-137 among 20 specimens measured was 1:2. The radioactivity half-life of Chornobyl Cs-137 is 30 years and was reached in 2016. A cause-effect association is suggested by the observed temporal decrement of incorporated levels of Cs-137 and prevalence of NTD in POL. We conclude that further investigations with an emphasis on cause-effect are indicated.

# Tuesday, November7th, 2023

## Scientific session: Surveillance, management, care and transition to adulthood

### Scientific Session I - Surveillance and management

**Moderators:**
***Neville Calleja***, Directorate for Health Information & Research, Ministry for Health, Malta
***Charmaine Cordina***, Directorate for Health Information & Research, Ministry for Health, Malta

Surveillance of Congenital Anomalies in Malta - Setting the scene
*Miriam Gatt*

Neonatal mortality due to congenital anomalies in Malta and beyond
*Merle Wilhelm*

Evolution of Screening in Malta
*Mark Cordina*

The accuracy of antenatal ultrasound screening in Malta: a population-based study
*Jeremy Borg Myatt*

Fetal Cardiac Screening in Malta
*Sarah Darmanin*

Prenatal Orofacial screening in Malta
*Maria Christina Tabone*

Orofacial Clefts in Malta: Prevalence, Impact & Public Health Implications – A 20-Year Analysis
*Terence Micallef*

The epidemiology of congenital heart disease in Malta
*Victor Grech*

Maternal and Gestational Risk Factors of Congenital Diaphragmatic Hernia
*Sophie Hackenbruch*

**Surveillance of Congenital Anomalies in Malta – setting the scene**

M Gatt
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Birth defects program on which the work is based: Malta Congenital Anomalies Register

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Data on congenital anomalies in Malta was originally collected through the University of Malta as part of a research project between 1985 and 1996. At this time data was only collected from the main public hospital in Malta – St Luke's Hospital. Data collection was taken over by the then Department of Health Information in 1996 and a population-based Malta Congenital Anomalies Register was established as of January 1997. This register now covers births from all hospitals on the Maltese Islands and includes all cases suspected or diagnosed with a congenital anomaly until one year of age. The register became a member of EUROCAT (European Surveillance of Congenital Anomalies) in 1986 and a member of the ICBDSR (International Clearinghouse of Birth Defects Surveillance and Research) in 2000.

The register is population based and covers all births on the islands of Malta and Gozo which amount to around 4300 births per year. The small size and population of the islands (area: 316 km2; population: 540,000); the well-defined boundaries, and illegality of termination of pregnancy make the islands ideal for epidemiological studies. Several sources of active data collection and verification are used to ensure as complete and accurate a coverage as possible. The main sources of information are obstetric records, neonatal and paediatric intensive care unit records, Echocardiography Lab. records, Hospital Activity Analysis Register, Mortality Register, Pathology Autopsy reports. All cases are confirmed by reviewing patient hospital records.

Data collection and registration follows EUROCAT guidelines, registering only major congenital anomalies. The Register now includes over 4800 infants and currently registers an average of 140 babies with one or more major congenital anomalies every year. The overall congenital anomaly prevalence rate over the past 25 years is 32.7/1000 births. The most commonly registered anomalies in this time period were: Congenital heart defects with a prevalence rate of 15.2/1000 births followed by limb anomalies (4.6/1000 births), genetic and chromosomal disorders (3.9/1000 births) and genital anomalies (3.5/1000 births).

The Malta Congenital Anomalies Registry provides data for surveillance, policy development, research studies and media requests. Through its continued membership with EUROCAT and ICBDSR data from Malta is included in several international collaborative studies.

**Understanding Neonatal Mortality in Malta: Exploring the Impact of Congenital Anomalies and comparing to other European Countries**

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Birth defects program on which the work is based: Malta Congenital Anomalies Registry

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**Background and Objectives:** Worldwide, around 240,000 babies die in the neonatal period every year due to congenital anomalies (CA), contributing significantly to neonatal mortality. This study examines the neonatal mortality rate (NMR) in Malta, focusing on the contribution of CA to neonatal deaths. Maltese data are then compared with other EU countries.

**Methods:** Anonymous data for neonatal deaths in Malta from 2006-2020 were obtained from the National Obstetrics Information System (NOIS). NMRs reported by EUROSTAT and the Malta National Mortality Register were compared for Malta and other EU countries between 2011- 2020. Maltese data was analysed using Poisson and Logistic regression adjusting for maternal age, nationality, and education.

**Results:** From 2006-2020, there were 63890 livebirths with 283 neonatal deaths registered in Malta, with an NMR of 4·4 per 1000 livebirths. CA accounted for 39·6% of neonatal deaths. No significant time-trends were observed both in total NMR (odds ratio 0·997; 95% CI 0·97- 1·02; p= 0·81), and neonatal mortality attributed to CA (odds ratio 0·97; 95% CI 0·93-1·01; p= 0·19) or non-congenital anomaly causes (odds ratio 1·01; 95% CI 0·98- 1·05; p= 0·44). When comparing Malta with other EU countries, Malta had a comparatively high NMR, most marked for neonatal deaths due to CA. For Maltese data, adjusted variables revealed significant associations for women hailing from non-EU, low-income countries (odds ratio 2·23; 95% CI 1·34 - 3·71; p< 0·001).

**Discussion and Conclusions:** Between 2006-2020, Malta's NMR remained stable, with 39·6% of neonatal deaths attributed to CA. Malta consistently reported the highest NMR in the EU, primarily driven by early neonatal deaths. This was mainly apparent in the proportionately higher contribution of neonatal mortality attributed to congenital anomaly causes, which in turn is significantly influenced by termination of pregnancy being illegal. Maternal nationality, especially among women from non-EU low-income countries, was significantly associated with neonatal mortality.

**Evolution of Screening in Malta**

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Birth defects program on which the work is based: NA

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The local antenatal screening options and their introduction will be compared to international scenario. A description of the evolution of the screening process being currently offered in Malta both under NHS care and privately will be provided.

Screening in Malta is still in its infancy compared to other EU countries, highlighting the investment required to introduce more screening options to the rapidly increasing population.

**The accuracy of antenatal ultrasound screening in Malta: a population-based study**

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Birth defects program on which the work is based: Malta Congenital Anomalies Registry

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**Background and Objectives:** To analyse the accuracy of antenatal ultrasound screening in Malta, comparing detection rates within the private and public sectors, and with the rest of Europe. To assess local trends in accuracy for each organ system

**Methods:** Ethics approval was obtained to gather routinely collected data from the national congenital anomalies registry between 2016 and 2018. This was analysed to determine local antenatal ultrasound accuracy rates and trends. Electronic medical appointment record data was also used to indirectly determine whether a significant difference existed in the detection of antenatal anomalies in mothers scanned privately and those scanned within the public sector. χ2-for-trend was used to analyse changes in the accuracy rates. European Surveillance of Congenital Anomalies (EUROCAT) data was used to compare scanning accuracy in Malta and other EUROCAT centres.

**Results:** The local rate of undetected congenital anomalies was 62.0% for public scans and 83.9% for private scans. Local trends over the three-year period showed an improvement in accuracy rates in detecting isolated syndromes (p=0.05), anomalies of the renal system (p=0.02) and craniofacial anomalies (p=0.05). Malta's overall performance was similar to other EUROCAT centres.

**Discussion and Conclusions:** Scans carried out within the public sector may be more accurate than private scans, and Malta's overall performance was similar to other EUROCAT centres.

**Fetal Cardiac Screening in Malta**

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Birth defects program on which the work is based: NA

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This presentation describes the techniques used for cardiac screening at the main maternity hospital in Malta. Fetal medicine services in Malta are still at their early stages, and at present the focus is to recruit and adequately train, a number of professionals in performing high quality screening in order to improve detection rates, antenatal counselling and neonatal management.

The presentation will include the detection rates of different cardiac conditions in the Maltese population, a brief overview of their management in the local setting, as well as a discussion about methods to improve the current service.

**Prenatal Orofacial Screening in Malta**

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Birth defects program on which the work is based: NA

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A comparison of the local practice with international guidelines of prenatal orofacial screening.

Description of the current local practices in detection of orofacial anomalies in the second trimester as compared to the international guidelines. A comparison of local detection rates with other international centres and their associated management.

Prenatal screening in Malta is still evolving and although it has come a long way since its introduction; the current services are still focused on the formation of the fetal medicine services by providing training of health care professionals to offer a better service.

There is room for improvement by investing in more screening programmes across the national health service and more training to achieve the optimum skills to run such services.

**Orofacial Clefts in Malta: Prevalence, Impact & Public Health Implications – A 20-Year Analysis**

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Birth defects program on which the work is based: Malta Congenital Anomalies Registry

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**Background and Objectives:** Orofacial Clefts, comprised of cleft lip and cleft palate, pose a significant Public Health challenge due to their widespread prevalence, the physical and emotional toll on patients and their immediate relatives, as well as the financial burden associated with its complex treatment and rehabilitation. Our presentation gives a brief overview of the aetiology and management of Orofacial Clefts, reviews the existing literature on the effects of folic acid supplementation and explores the local prevalence trends in Malta over a 20-year period. Comparisons between Malta and other members of the EUROCAT network are also presented.

**Methods:** Data on orofacial cleft cases in Malta was obtained from the Malta Congenital Anomalies Register, housed within the Directorate of Health Information & Research (DHIR). The analysis focused on the period between January 2000 up to December 2020. Data related to the number and prevalence of cases, the type of cleft (cleft lip, cleft palate or cleft lip with cleft palate) and the presence of a genetic syndrome was collected. Data from EUROCAT was obtained from their website in order to make comparisons between Malta and other EUROCAT member registries. A comprehensive literature review was also carried out to examine the effects of folic acid supplementation on both cleft lip and cleft palate.

**Results:** 172 cases of orofacial clefts were registered in Malta between 2000-2020, accounting for 5% of all major birth defects in the Maltese Islands during this period. Most cases of orofacial clefts (85.5%) were non-syndromic, with the remaining 14.5% associated with a genetic syndrome. Pierre-Robin Sequence was the most commonly occurring genetic syndrome diagnosed. In terms of type of orofacial cleft, cleft palate alone was the subtype diagnosed in more than half of the total cases(55.8%), followed by cleft lip with cleft palate(24.4%) and cleft lip alone(19.8%).Comparisons between Malta and the other members of the EUROCAT network showed that Malta had the 5th highest prevalence rate for non-syndromic clefts in the study period.The literature review showed a beneficial association between folic acid supplementation in the periconceptional period and the rates of non-syndromic cleft lip with or without cleft palate, but no consistent association was seen for non-syndromic cleft palate.

**Discussion and Conclusions:** Orofacial clefts continue to be a significant public health concern in Malta. The prevalence rate of non-syndromic orofacial clefts, especially cleft palate, is higher than the EUROCAT average. Further research into understanding the factors behind the high rate of cleft palate in Malta, as well as the relationship between folic acid supplementation and non-syndromic cleft lip is warranted. Early diagnosis, timely surgical intervention and the involvement of a comprehensive multidisciplinary team are essential in improving outcomes for the affected children. Health Promotion campaigns aimed at both pre-conceptional women and expectant mothers that highlight the need for a healthy lifestyle and the targeting of specific modifiable risk factors for orofacial clefts play a crucial role in reducing their incidence.In conclusion, the burden posed by orofacial clefts can only be tackled by a multifaceted approach which includes research, prevention strategies and multidisciplinary care.

**The epidemiology of congenital heart disease in Malta**

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Birth defects program on which the work is based: Malta Congenital Anomalies Registry

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**Background and Objectives:** Congenital heart disease (CHD) refers to structural cardiac abnormalities which comprise the commonest group of congenital malformations. Malta is a small island in the central Mediterranean with excellent diagnostic and therapeutic facilities. It is unique in the European population as termination of pregnancy is illegal. This study was carried out to ascertain patterns in CHD prevalence in comparison with EUROCAT data (European Surveillance of Congenital Anomalies).

**Methods:** Anonymised data was obtained from the EUROCAT website for 1993-2020.

**Results:** There were a total of 22,833,032 births from all EUROCAT Registries, of which 121,697 were from Malta. The prevalence rate for Malta CHD was 32.38/10,000 births (at the higher end of the range). Malta had a significant excess of commoner, comparatively non-severe CHDs. For most of the severe lesions analysed rates reported were higher than EUROCAT average, however, apart from Ebstein's anomaly, they all fell within the ranges reported from the different Registries.

**Discussion and Conclusions:** Wide variations are reported in CHD prevalence. The Malta rates may be higher for milder defects due to pick up prior to spontaneous resolution. There may also be a higher pickup of milder forms of more severe conditions. For the more severe conditions, lack of termination may be the explanation. These factors may result in the higher neonatal mortality observed in Malta. Surgical cases are too few to permit a local surgical program, so all surgery is done in tertiary centres, mostly at Great Ormond Street in London. Antenatally diagnosed duct-dependent lesions are transferred in-utero for delivery and intervention in London. Catheter interventions are done here with the assistance of an interventional cardiologist. All follow-ups are done locally, with a well-established echocardiography service supplemented by excellent radiological backup for MR and CT imaging. Patients are transferred to the local Grown-Up Congenital Heart service at the age of 16 years for further follow-up.

**Maternal and Gestational Risk Factors of Congenital Diaphragmatic Hernia**

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Birth defects program on which the work is based: Malta Congenital Anomalies Register

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**Background and Objectives:** The incidence of congenital diaphragmatic hernias (CDHs) is high in the Maltese islands, but little is known about their association with maternal risk factors. A nationwide study in a country where abortion is still illegal allowed access to more data. This study was conducted to shed light on the possible risk factors in the development of CDH.

**Methods:** This population-based, retrospective study assessed the data of CDH cases from 1993 to 2016, which were collected from the Directorate of Health Information and Research (Malta). $\chi 2$ test was done to examine the associations between the cases and controls.

**Results:** Between 1993 and 2016, 55 cases of CDH were reported. The cases made up 0.0644% of the total births during that period. Advanced maternal age was more likely in CDH cases (P = .01). In 18.2% of the neonates with CDH, the birth weight was 1500 to 2499 g, while only 6.2% of the control group neonates had a birth weight in this range (P < .001). There was no statistically significant association between CDH (54.5%)and the neonates' sex (50.9%) (P = .404) and CDH (3.6%) and plural births (1.3%) (P = .333).

**Discussion and Conclusions:** CDH was found to be associated with advanced maternal age and low birth weight. Also, CDH increases the risk of other congenital anomalies.

## Scientific Session II - Care, transition to adulthood and personal experiences

**Moderators**
***Victor Grech***, Paediatric Department, Mater Dei Hospital, Tal-Qroqq, Malta
***Miriam Gatt***, Directorate for Health Information & Research, Ministry for Health, Malta

Breaking the news
*Ryan Farrugia*

Several decades later - a look at long-term outcomes of congenital heart defects in Malta
*Maryanne Caruana*

The European Reference Networks - Raising the bar for patients with rare diseases and their healthcare providers across Europe
*James Clark*

Rare Diseases in Paediatrics : Outsourcing the specialized paediatric services into the Community Resource Centres
*Christopher Sciberras*

Adult Down Syndrome Clinic
*Maria Callus*

Patient / Carer experiences
Luisa Soler and Katrina Aquilina

**Closing** – *Yves Muscat Baron*, Clinical Chairperson, Department of Obstetrics and Gynaecology, University of Malta

**Breaking the news**

R Farrugia
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Birth defects program on which the work is based: NA

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As healthcare professionals we are frequently called upon to deliver important news to prospective parents. This can be one of the most challenging aspects of our profession. We owe these parents a duty of care to deliver factually correct information in a manner that can be assimilated during stressful situations.

The establishment of a good doctor-parent relationship depends on the success of the initial encounter. In perinatal care, the 'breaking the news' meeting is usually the first opportunity for the neonatal team to be introduced by the obstetric team and to start building a rapport with the prospective parents. There are many factors that make these conversations uncomfortable for health-care professionals. Despite years of medical training, most have never received formal training in the delivery of bad news. Health-care providers also instinctively feel the need to shield parents and patients from grief and hardship. Such conversations also frequently elicit anxiety, sadness and a feeling of inadequacy in the providers themselves.

Appropriate preparation significantly influences the flow of information. A structured approach helps communicate the important points. While the perceptions of the prospective parents need to be explored, the main points should be communicated without delay. The use of silent pauses allows the information to sink in and also gives the healthcare provider the opportunity to gauge the response to the news, allowing some degree of judgment as to whether the important points have been understood. Such encounters require training and experience. They therefore lend themselves well to simulation training. Team debriefs are vital for the emotional wellbeing of the healthcare providers as they allow the facts to be reviewed, misconceptions corrected, as well as valid and fair observations taken on board.

**Several decades later - a look at long-term outcomes of congenital heart defects in Malta**

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Birth defects program on which the work is based: Congenital Heart Disease

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**Background and Objectives:** The majority of babies born with congenital heart defects are nowadays surviving into adulthood. However, these patients might still have increased morbidity and mortality compared to their peers. The main objective of this research was to investigate long-term outcomes of two specific congenital heart lesions - tetralogy of Fallot (ToF) and aortic coarctation (CoA) - in the Maltese population.

**Methods:** All 130 ToF patients born before end-1997 included in the local database were extracted. Surgical repair type, age at repair and operative survival were analyzed among the 103/130 repaired patients. Kaplan–Meier survival analyses were performed on the 75 repair survivors with complete follow-up data. All 72 aortic coarctation patients with any type of repair, born by end-1997 and logged in the local database were included. Trends in timing and type of repair were determined by comparing patients born before and after 1985. Kaplan-Meier analyses of survival and reintervention-free survival were performed on the 59 repair survivors with complete follow-up data. Cardiovascular mortality in repair survivors was compared with that in 438 age- and sex-matched general Maltese controls.

**Results:** Overall estimated mean survival among the 75 ToF repair survivors was 45.56 years with estimated survival rate of 77.5% at 40 years from repair. Estimated mean reintervention-free survival was 37.71 years with estimated reintervention-free survival rate of 59.2% at 40 years. Among the 59 CoA, estimated mean survival was 40.33 years with a survival rate of 67.5% at 40 years from repair. Estimated mean reintervention-free survival was 38.13 years with freedom from reintervention rate of 77% at 30 years. There was an excess of cardiovascular deaths among repaired coarctation subjects compared to the general population (11.9% vs 1.4%; $P < .001$) and survival in coarctation patients was significantly lower (67.90 years vs 85.78 years; $P < .001$).

**Discussion and Conclusions:** Although survival after ToF and CoA repair in contemporary patients is very good, these patients remain at increased risk of cardiovascular death and an important proportion need structural reintervention. Regular specialist clinical follow-up in dedicated clinics remains of utmost importance in all patients to improve long-term outcomes.

**The European Reference Networks - Raising the bar for patients with rare diseases and their healthcare providers across Europe**

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Birth defects program on which the work is based: NA

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Approximately 6,000 rare diseases affect the health of some 30 million EU citizens. Around 80% of these rare diseases have a genetic basis and about 50% of all rare diseases affect children. In addition, a significant number of rare diseases in children are actually congenital anomalies.

Many patients suffering from a rare or complex medical condition may not have access to the appropriate specialized care. This may be due to demographic factors related to the country of residence, but more often is due to the paucity of both the rare condition as well as the relevant centres of expertise. No country alone has the medical knowledge and institutional capacity to treat all rare and complex diseases, especially in children.

Over the last decade, the EU has taken a proactive approach to ensure access to expert knowledge and treatment for rare diseases to all its 447 million citizens, including Norway, through the launch of the European Reference Networks (ERNs) in 2017. The ERNs are virtual networks that link healthcare professionals from over 1000 centres of expertise located in over 300 hospitals across 26 European countries. This virtual network allows for timely cross-border travel of expert medical knowledge directly to the patient's caring physician.

Malta joined the ERNs as a National Coordination Hub in 2019 and this affiliation has proved to be a significant asset for our healthcare providers and patients alike to address the significant challenges posed by rare and complex medical conditions.

**Rare Genetic Diseases in Paediatrics : Outsourcing the Specialised Paediatric Services into the Community Resource Centres in Malta**

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Birth defects program on which the work is based: NA

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**Background and Objectives:** Students attending the four Resource Centres in Malta : San Miguel Centre in Pembroke, Guardian Angel Centre in Hamrun, Helen Keller Centre in Qrendi and Dun Manwel Attard Centre in Wardija, and having rare genetic diseases including HCFCF1 (Host Cell Factor C1 gene disease), ZTTK syndrome, 18p tetrasomy, CDK13, WWOX syndrome, SAT B2 syndrome, Di George syndrome, Interstitial Deletion of 9Q33, MECP2 Duplication Syndrome and Christianson Syndrome were assessed and managed through the outsourced specialized paediatric community services.

**Methods:** Participants : Malta currently has a total of 288 such students attending the 4 Resource Centres, with 58 in San Miguel primary Centre, 36 in Helen Keller secondary Centre, 79 in Guardian Angel secondary Centre and 115 in the post-secondary Wardija Centre, aged between 3 and 23 years. (Services in San Miguel, Pembroke are also offered as early as from 1 month of age).

**Results:** Outsourcing the paediatric services into the community involves the regular medical assessment though a sensitive and empathic approach towards the management of the needs of children with rare genetic diseases (and their carers), attending these Resource Centres in Malta. The service involves a holistic, multi - disciplinary format, including speech and language therapy, occupational therapy, physiotherapy, orthotist clinics, nutrition and dietician clinics together with the involvement of social workers, psychologists and other psychiatric services when needed. An educational approach towards understanding the issues of rare genetic diseases for parents is also considered and liaison with the Inspire Star 25 programme is also included in the list of services.

**Discussion and Conclusions:** The mission of our work is to serve as an advocate for children and their families through professional, academic and other channels. Outsourcing of specialized paediatric services has proved to be one effective way of achieving optimal levels of care in children with rare genetic diseases in the community.

**Adult Down Syndrome Clinic**

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Birth defects program on which the work is based: NA

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The Adult Down Syndrome Clinic is a clinic set through the collaboration of the Ministry for Health and the Malta Down Syndrome Association. It is offered free of charge and the clinic is intended for individuals with Down Syndrome aged 16 years and above. The clinic focuses on the needs of the adult with Down Syndrome. Management plans are based upon the individual needs and decisions, with the help of the individual's caregivers where appropriate.

People with Down syndrome are unique and differ from other people with intellectual disabilities and others with developmental disorders. They require specialised medical care and attention. They are more likely to suffer from congenital heart anomalies, endocrine conditions including thyroid disorders, gastrointestinal disorders, haematological disorders including different leukaemias, visual and auditory disorders, and early development of Alzeihmer's dementia. They are also more prone to respiratory tract infections.
The Adult Down Syndrome Clinicrecognises that some people with Down syndrome do not have any of these conditions. While some medical conditions may be evident during foetal development or early childhood, other comorbidities may not develop until later in adolescence or adulthood. Also, people with Down Syndrome are less likely to develop solid malignancies than those without Down Syndrome and may be less likely to suffer from atherosclerotic cardiovascular disease.
The Adult Down Syndrome Clinic provides an opportunity for screening and early detection of disease. People with Down syndrome are assessed using a questionnaire directed towards both people with Down Syndrome and their carers/relatives. Routine blood tests for most common disorders are taken on a yearly basis. The aim of such screening is to detect these conditions early and provide a biopsychosocial plan for the client and their carers.
People with Down Syndrome voiced their wishes for better education regarding body image, computer literacy, drama/singing/dancing, employment, socialisation and relationships including dating. Sexual health is an important topic which is often overlooked. Feedback gathered from older people with Down Syndrome highlights issues regarding residence, recreation, keeping and active lifestyle, health issues, legal and financial problems.
Most people with Down Syndrome experience cognitive and developmental delays, but the effect is usually mild to moderate and is not indicative of the many strengths and talents that each individual possesses. Guardianship arrangements and social stigmas are common problems and are often discussed. Despite the increased prevalence and longevity of adults with Down syndrome, relatively little is known regarding the optimal prevention and etiology of common diseases that occur more frequently in this population.

While many people with Down syndrome enjoy meaningful inclusion in their communities, as well as more physically active and longer lives, more needs to be accomplished in preventive healthcare to support healthier aging. The Adult Down's Syndrome clinic's holistic approach to patients forms the basis of good health care for adults with Down syndrome. Other than providing a medical follow-up, it provides an opportunity for diagnosing medical conditions at an early stage.

# Wednesday, November 8th, 2023

## Session IV – Oral Presentations

**Moderators**
***Florence Rouget*** - Brittany Registry of congenital anomalies, Rennes University Hospital, France
***Yudelkis Benitez Cordero*** - National Center of Medical Genetics, RECUMAC, Cuba

## Birth defects surveillance – Methodology II

The JRC-EUROCAT Information System
*Annie Perraud*

A patient-initiated rare disease registry for South Africa
*Helen L Malherbe*

National Congenital Anomaly and Rare Disease Registration Service: how the Congenital Anomaly Official Statistics Report can influence and improve care
*Kathryn Johnson*

Semi-automated identification of ventricular septal defects from a clinical data warehouse
*Julie Thomas-Chabaneix*

**The JRC-EUROCAT Information System**

A Perraud[1], A Brunetto[2], E Ben1, A Kinsner-Ovaskainen[1]
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Birth Defects Program on which the work is based: EUROCAT

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**Background and Objectives:** The European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT) was established in 1979. The Central Registry of this network, currently located at the European Commission Joint Research Centre (JRC), is part of the European Platform on Rare Disease Registration. Twice a year, individual cases with congenital anomalies among livebirths, stillbirths and terminations of pregnancy for fetal anomaly are collected from close to 40 registries covering about 25% of the European Union birth population.

**Methods:** The JRC developed a whole information system to handle the sensitive health data from all the member registries in a secure, reliable and standardised way, in line with the European data protection legislation. It consists of a secure web portal for data exchange, a software for data management (DMS), and a public website for the publication and dissemination of EUROCAT data.
The DMS is (i) modular: changes that concern only parts of the workflow can be implemented independently, (ii) universal: data collection and data management at local and central level are aligned, and (iii) automated: any change in the software specification is downloaded locally from a server through the internet and predefined procedures as well as EUROCAT standards are uniformly available throughout the network.

**Results:** The JRC-EUROCAT Information System is a costless solution to assist registries in the collection, management, reporting and analysis of their data. It significantly increases the efficiency of the JRC-EUROCAT Central Registry, by managing automatically and securely a complex workflow (data collection, transfer, validation, extraction, analysis and publication).
The modular design of DMS and the easy distribution of its updates allowed to implement smoothly three major changes during the elapsed year: (i) the new EUROCAT classification of congenital anomalies in homogeneous subgroups, (ii) the revised algorithm for the detection of potential multiple congenital anomalies, and (iii) the updated methodology for the detection of trends, including the possibility for multi-centre registries to run the analysis centrally. Finally, the system ensures that no errors occur in the data.

**Discussion and Conclusions:** The JRC-EUROCAT Information System goes beyond the historical EUROCAT system and offers a flexible, in-house developed solution provided to the registries free of charge to handle the network activities efficiently. The modularity of the software allows smooth implementation of new functionalities. The high quality data collected centrally in a standardised way enable epidemiological surveillance across Europe. Finally, the website facilitates the dissemination of the results and of key documentation developed by the network. It is used by researchers worldwide as a valuable source of epidemiological data and as the reference for congenital anomalies' data collection, analysis and interpretation.

## A patient-initiated rare disease registry for South Africa

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Birth Defects Program on which the work is based: NA

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**Background and Objectives:** An estimated 1 in 15 South Africans are impacted by rare diseases (RD), equating to 4.2 million people. The diagnosis/treatment of these conditions remains unprioritized, patient health records are largely paper-based, and surveillance of these conditions is not undertaken by government. This project aimed to develop an online system allowing patients to register, store and share their disease history data in a secure user-friendly way. It aimed to benefit multiple stakeholder groups: 1) Allows patients to document/share their patient journey, store diagnostic/health records and medical appointments, complete a daily 'journal' to improve disease management, and to participate in the National Rare Disease Biobank. 2) Enables clinicians to validate patient health records without inputting data. 3) Connects researchers with patient populations and anonymised, aggregated data. 4) To help quantify this burden of disease to assist policy makers in service planning and resource allocation.

**Methods:** From 2021-2022, RDSA collaborated with the MSD Richard T. Clark Fellowship for Global Health and the SA Rare Disease Biobank, Centre for Human Metabolomics, North-West University, South Africa. 1) A literature review was conducted to understand the definition and role of patient registries, explore registry-development lessons-learned elsewhere and identify global gold standards and best practice. 2) Landscape exploration and user interviews were conducted virtually with RDSA patients/caregivers to explore the SA landscape and identify the requirements of potential registry users. 3) Information from both the literature review and user interviews were used to develop a registry process flow and to identify if existing software (Salesforce) could be integrated into the registry. Different platforms were evaluated using the criteria of cost, maintenance, data storage, mode of patient data access, development (cost, effort), data sharing and clinical access.

**Results:** The RD patient journey in SA is complex and challenging due to lack of awareness and knowledge of clinicians, lack of holistic treatment, poor availability/access to diagnostics and care. Patients want to document their journey, record clinical visits, and optimise disease management. A daily personal journal would assist in appointment schedules, track disease flare-ups and record treatment regimens and side-effects. Patients/caregivers are often in close communication with treating clinicians electronically and the mental health and well-being of patients/caregivers is neglected. It was found that Salesforce provides a safe and secure environment at no cost for NPOs. The registry should be accessible both online (Salesforce integrated web-page) and via a mobile App to enable continuity of data across multiple platforms and Salesforce integration. Patients/caregivers should have their own individual login to add/access/share their own data via a safe and secure environment.

**Discussion and Conclusions:** Clinician-led registries are unsustainable and without an electronic health record system, patients are encouraged to keep track of their own health records - highlighting the need for a patient-initiated approach. Many NPO-led registries lack robust academic collaboration, preventing further utilisation of developed registries and associated data. This collaboration between RDSA and North-West-University highlights the benefits of connecting these stakeholders and associated communities (patients and researchers), providing a robust basis for registry development in association with the SA RD Biobank, with research ethics approval granted by North-West University. The registry website is under-development and aims to be operational by quarter 3 of 2023. Following evaluation of this pilot, follow-up phases are planned to enable treating clinicians to log-in/verify patient clinical data, for researchers to access anonymized data and for increased accessibility via App development.

**National Congenital Anomaly and Rare Disease Registration Service: how the Congenital Anomaly Official Statistics Report can influence and improve care**

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Birth Defects Program on which the work is based*:* National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

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**Background and Objectives:** The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) is a comprehensive registration service that collects and quality assures data on congenital anomalies and rare diseases in England. NCARDRS provides an annual congenital anomaly statistics report, recognised as English Government Official Statistics produced by NHSE. NCARDRS' sixth report, released at the end of 2022, contains information on congenital anomalies detected in babies delivered between 1 January and 31 December 2020 for the whole of England. The seventh annual report, containing information on congenital anomalies detected in 2021 will be published in late 2023.

**Methods:** Congenital anomalies are defined as being present at delivery, likely originating before birth, and include structural, chromosomal and genetic conditions. Congenital anomalies in live births, stillbirths, late miscarriages between 20-23 completed weeks of gestation and terminations at any gestation are included.

**Results:** Data from the latest annual report will be presented. This includes prevalence of congenital anomalies by region and by anomaly group, timing of detection, infant and neonatal mortality associated with congenital anomalies and the influence of maternal age and of deprivation on the prevalence.

**Discussion and Conclusions:** NCARDRS works closely with the English Fetal Anomaly Screening Programme (FASP) auditing detection rates for 11 physical conditions. These conditions are subject enhanced registration, resulting in higher data quality and ascertainment within the annual report. By quality assuring antenatal detection rates NCARDRS can ensure as many of affected infants as possible are diagnosed in the antenatal period thus allowing for appropriate counselling and planning. The NCARDRS annual report is a vital resource for commissioners and providers of healthcare involved in the diagnosis and management of babies with congenital anomalies. It also provides high quality data for researchers and those seeking detailed information about congenital anomaly prevalence in England. The NCARDRS annual report data can then feed in to EUROCAT and ICBDSR contributing valuable information for collaborative worldwide projects.

**Semi-automated identification of ventricular septal defects from a clinical data warehouse**

N Lagarigue[1,2], J Thomas-Chabaneix[3], R Griffier[1]
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Birth Defects Program on which the work is based*:* ATENA registry

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**Background and Objectives:** France's largest region, Nouvelle-Aquitaine covering an area of almost 80,000 km². With 5.8 million inhabitants, about 56,000 births take place here every year. The region's strong wine-growing and agricultural heritage make it the leading agricultural region in France and Europe, making it of undeniable interest for the creation of a register to support environmental etiological research. Under the impetus of Santé publique France (SpF), 7th registry in France, named ATENA, has been set up in the South West region in 2022 to ensure epidemiological surveillance of congenital anomalies in the Nouvelle-Aquitaine population. In addition to this surveillance aspects, the aim of the registry is to evaluate the feasibility of case identification and semi-automated data collection using new data sources, including hospital Clinical Data Warehouse (CDW) to identify cases of congenital anomalies, with an initial focus on interventricular septal defects (VSD).

**Methods:** The Bordeaux University Hospital has chosen i2b2, originally developed by Harvard DBMI, as its health data integration solution. The CDW includes all patients who have come to the hospital at least once, either for hospitalization or consultation, since 2010. For those patients, historical data since 2005 is available. This data includes, in particular, diagnosis and reimbursement data, drug prescriptions and administration data, movement data, as well as all free-text data (letters, examination reports, etc.). With the aim of evaluating the contribution of CDW to the phenotyping task for a surveillance registry, we used the Bordeaux University Hospital's CDW 1) to find the maximum population of interest for identifying congenital anomalies, i.e. pregnant women & children up to 1 year old on the basis of age at entry and 2) to identify cases of VSD on the basis of structured coded & free-text data. The study population consisted of patients coming to hospital.

**Results:** Between 2021 and 2023, from the CDW, we identified a total of 27,692 pregnant women. To identify them, we collected data from women who had been through the obstetrics department, those who had undergone a fetal ultrasound, as well as those who had undergone childbirth, medical termination of pregnancy or amniocentesis. Over the same period, we were able to identify 28,031 children who passed through the Bordeaux University Hospital under 1 year of age. Finally, we were able to identify 221 children under 1 year of age with VSD from structured reimbursement data. From free-text documents, 481 children with VSD were identified using the keywords "ventricular septal defect" and "VSD", filtering out negations such as "absence of", "no", "neither" of which 203 were common with those identified with the reimbursement data. The records are currently being examined to enable the creation of a gold standard for the evaluation of a machine learning model.

**Discussion and Conclusions:** This first work shows the interest of the use of CDW as new data sources for identifying cases within a healthcare facility. Identifying the maximum population (pregnant women and children under 1 year of age) enables us to reduce the scope of patients for whom anomalies should be detected. Within this sub-population, and by combining coded structured data with free-text data, it is possible to increase the detection sensitivity of VSD cases. The choice of these types of data, common to all French healthcare facilities, will make it easier to generalize the approach. The next stage of our work will be to create a gold standard based on these cases of suspected VSD to train a future machine learning model. We also want to generalize the approach within a more standard OMOP-CDM format, so that our work can be applied to other centers as well as other diseases.

## Posters

*(Alphabetical order by corresponding author's last name)*

**The posters will be shown on Monday 6th November**
**Meeting room "Olympia"**

Using national congenital anomaly registration to evaluate the roll out of the non-invasive prenatal testing (NIPT) in England - *Jennifer M Broughan*

Infants with Congenital Anomalies of the Kidneys and Urinary Tract (CAKUT) in Malta - *Gabrielle de Gray*

Congenital anomalies as rare diseases: the importance of genomic linkage for congenital anomaly registries - *Kathryn Johnson*

The unexplored effects of social and health inequality on adverse outcomes to children born with Spina Bifida: 2010-2020 - *Kathryn Johnson*

Sibling birth defects recurrence in Florida, 2000 to 2019 - *Russell S Kirby*

Prenatal detection of birth defects: pathway of care in obstetric ultrasound services in Bogotá, Colombia - *Maria Camila León-Sanabria*

Echocardiography evaluation of congenital heart disease with its outcome in a Medical University Hospital of Dhaka, Bangladesh - *M Abdul Mannan*

Prevention of neural tube defects in Chile: more than two decades of folic acid fortification - *Cecilia Mellado*

WHO's Resolution calls for micronutrient fortification to prevent spina bifida and other Neural Tube Defects - *Rosa Pardo*

Epidemiology and risk ractors concerning transposition of the great vessels: A population-based case-control study in Bogotá and Cali, Colombia- *Pablo Pineda-Sanabria*

Characterization of risk factors for Clubfoot in Bogotá and Cali, between 2002-2020 - *Esteban Portilla*

Polydactyly risk factors in Bogotá and Cali, Colombia between 2002-2020: A case-control study - *Lina María Ramírez*

Severe congenital protein C deficiency: epidemiology, diagnosis and long-term management - *Csaba Siffel*

Sex ratio and congenital anomalies in children born after assisted reproduction - *Antonin Šípek Sr*

Application of Photon counting CT in the diagnostics of Post mortem fetal malformations for the assessment of skeletal , external skin surface and vasculature anomalies - *Tidhar Steiner*

Characterization of environmental exposures in the French ATENA registry - *Julie Thomas-Chabaneix*

Multidisciplinary consultation in fetuses with malformations: prenatal exome experience in a tertiary public hospital - *Eduardo Tizzano*

Prevalence of Congenital Heart Defects Among Boys with Hypospadias in England - *Lee T Watson*

Can be viewed at: www.icbdsrtraining.org

**Using national congenital anomaly registration to evaluate the roll out of the non-invasive prenatal testing (NIPT) in England.**

JM Broughan[1], L Tempest[1], R Glover[1], N Permaloo[1], P Jones[1], G Brondel[1], S Stevens1, S Hardy[1]
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Birth Defects Program on which the work is based: National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

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**Background and Objectives:** In June 2021, non-invasive prenatal testing (NIPT) was added as an additional step to the existing English National Health Service (NHS) antenatal screening pathway for Down's syndrome (T21), Edwards' syndrome (T18) and Patau's syndrome (T13). The test is offered to those who receive a higher chance combined or quadruple screening test. The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), collects data on congenital anomalies across England and has been tasked with evaluating and quality assuring the NIPT testing roll out.

**Methods:** Data from clinical biochemistry screening laboratories in England were linked to NIPT test data from the three NIPT testing hubs using an algorithm based on NHS number and estimated date of delivery of the pregnancy. The characteristics of NIPT tests conducted between 1st June 2021 and 31st May 2022 were described including the test indication, NIPT outcome, result status and timing as well as maternal age and type of pregnancy (singleton/twin).This test data will be linked to congenital anomaly registration data containing detailed diagnostic, screening and birth outcomes in order to evaluate the performance of NIPT.

**Results:** In the first 12 months of the programme, 11,003 samples were taken of which a result was reported for 95.9%. 67.4% were referred for testing because of a higher chance T21 combined test, 4.5% for a higher chance T13/T18 combined test, 4.8% for a higher chance combined test for all three trisomies and 18.2% for a higher chance quadruple test for T21. Sample receipt and result reporting times are monitored, with 84.5% of results reported within 5 days of receipt. A higher chance NIPT result was reported for 6.7% of tests.

**Discussion and Conclusions:** On-going, timely surveillance of NIPT tests has been used to support the evaluative rollout of this valuable screening test and inform service delivery. Linkage and integration of laboratory data with national registration data provides an opportunity to evaluate the performance of a screening test in a real-world setting. The evolution of disease registries in supporting the evaluation and providing quality assurance of screening programmes and demonstrates their importance to both clinical practice and public health.

**Infants with congenital anomalies of the kidneys and urinary tract (CAKUT) in Malta**

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Birth defects program on which the work is based: Congenital Renal Anomalies

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**Background and Objectives:** Renal anomalies are one of the commonest anomalies picked up antenatally on ultrasonography scans (Angela Yulia, 2018). CAKUT are a group of anomalies comprising defects such as renal agenesis, multicystic dysplastic kidney (MCDK), unilateral or bilateral hydronephrosis (UL/BL HN), duplex kidney, ureteropelvic junction obstruction (PUJO), unilateral or bilateral vesico-ureteric reflux (UL/BL VUR) and posterior urethral valves (PUVs) (Rodriguez, 2014). Clinical Practice Guidelines were introduced (Mater Dei CPG, 2021) to guide antenatal and postnatal management. We aimed to assess diagnostic data of all children with CAKUT seen at Mater Dei Hospital Malta, from January to December 2021.

**Methods:** All children with CAKUT referred to the nephrology team between Jan to Dec 2021 were included. Results of investigations, clinical details on diagnosis and management were obtained from electronic records.
**Results:** Thirty-three children were referred; 72.7% were male. In 54% of males and 33% of females CAKUT was diagnosed antenatally; remainder presented in infancy. Main antenatal anomaly in males was PUVs (38.5%); other anomalies included UL HN or VUR, Pelvic Kidney, BL VUR and MCDK. Main antenatal anomaly in females was HN (66.6%) with rest having a duplex system.
Median age of post-natal presentation for males was 81 days: symptomatic E. coli urinary tract infection in 63.6%, E. faecalis/K. oxytoca infection in 9.1%. 9.1% were diagnosed incidentally; 9.1% had incomplete documentation. Median age of presentation for females was 90.5 days: E. coli infection in 50%, E. faecalis infection in 33%, 17% diagnosed when investigating auricular anomalies. PUVs (36.8%) was again the commonest anomaly in males; other anomalies being BL VUR, HN, UL VUR, horseshoe kidney, duplex kidney, renal agenesis. In females, equal numbers of BL VUR, UL VUR and HN were described."

**Discussion and Conclusions:** Males were more commonly diagnosed with CAKUT. Most diagnoses for males were made antenatally, with the opposite being true for females. The commonest antenatal finding in males was of PUVs versus significant dilatation or hydronephrosis in females; PUVs were also the commonest finding in males presenting with post-natal CAKUT. Current practice in infancy involves surveillance ultrasound performed on a 3 monthly basis if findings are stable; further investigations are performed depending on suspected diagnosis, for example: MAG-3, MCUG, DMSA scans. Approximately 10% of cases have an underlying genetic cause (Simone Sanna-Cherchi, 2007), (Weng, et al., 2009). There is no known treatment that may help prevent occurrence of CAKUT however screening and surveillance may help achieve earlier diagnoses, intervention and secondary prevention.

**Congenital anomalies as rare diseases: the importance of genomic linkage for congenital anomaly registries**

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Birth Defects Program on which the work is based: National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

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**Background and Objectives:** The National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) is a comprehensive registration service that collects and quality assures data on congenital anomalies and rare diseases in England. The Leeds neonatal service is one of the busiest in the U.K. and provides regional/supra-regional care. It has fetal medicine, surgical, cardiac, neurosurgical, renal and hepatic services and provides co-located care for infants requiring fetal medicine, specialist obstetric, paediatric surgical and cardiac input. As clinical lead for NCARDRS I provide a vital link between registration of congenital anomalies and the day to day clinical work caring for babies affected by such anomalies.

**Methods:** 3 challenging clinical cases are described. The 3 cases were all born at the neonatal service in Leeds within the last 2 years. All had antenatally diagnosed congenital anomalies and all had a genomic diagnosis made postnatally allowing clinical care to be directed appropriately.

**Results**: The exact genomic diagnosis has not been presented given the rarity of the conditions and therefore the potential for the cases to be identifiable.

- Case 1) Antenatally - fetal akinesia sequence with arthrogryposis. Postnatally findings confirmed. Died on Day 2. Genomic diagnosis consistent with an autosomal recessive arthrogryposis.
- Case 2) Antenatally – ventriculomegaly, MRI revealed lissencephaly. Postnatally also noted to have a ventricular septal defect. Progressing well at home with specialist care. Genomic diagnosis of lissencephaly syndrome.
- Case 3) Antenatally - short long bones. Postnatally also noted to be dysmorphic and have a protein losing enteropathy and hypoventilation. Died aged 1 month. Genomic diagnosis of a glycoprotein metabolism disorder.

**Discussion and Conclusions:** Cytogenetic data where available is routinely linked to congenital anomaly cases within NCARDRS. Increasingly genomic data is available and will, in the near future, be linked in the registry. In England there are two rapid pathways for genomic testing, 1 antenatally and 1 postnatally, offered alongside standard whole genome sequencing. The 3 cases presented highlight the importance of linkage to genomic data for congenital anomaly registries. Genomic diagnosis allowed for compassionate, patient and family focused care to be delivered in line with family wishes. Additionally, for ultra rare genomic diagnoses the importance of the collection of detailed accurate rich congenital anomaly registry data will allow for improved antenatal and postnatal counselling. Increasingly congenital anomalies will be identified as part of a rare disease with genomic diagnoses available, registries must evolve as NCARDRS is in order to move forward as genomic diagnoses rapidly advance and evolve.

# The unexplored effects of social and health inequality on adverse outcomes to children born with Spina Bifida: 2010-2020

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**Background and Objectives:** Spina Bifida is a congenital anomaly that arises from the abnormal development of the primitive spinal cord and brain within the first twelve weeks of pregnancy. A diagnosis of Spina Bifida often leads to profoundly complex, lifelong and life changing multisystem co-morbidities. The risk of severe adverse health outcomes for children born with Spina Bifida in the context of social and health inequality is under researched yet well described. The Leeds Neonatal Service is one of the busiest in the U.K. and provides regional/supra-regional care. It is the regional centre for the antenatal and neonatal care of babies born with Spina Bifida. Antenatal and postnatal data on pregnancies affected by Spina Bifida are collected by the National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) in England.

**Methods:** Retrospective cohort study was undertaken using routinely collected data. All children born with a diagnosis of Spina Bifida between 2010-2020 in the Yorkshire and Humber region were followed up for the first two years of life. Children were tracked to identify those admitted to a paediatric intensive care unit (PICU) or that did not otherwise survive.

**Results:** There were 91 cases of Spina Bifida identified. Overall 2-year mortality was 7.7% (n=7), with four (4.4%) children having been admitted to PICU due to complications of Spina Bifida. Of the four children admitted to PICU, two died on the unit. Those children admitted to PICU or who die within the first 2 years of life resided exclusively in the most deprived quintile within the UK. Over two-thirds of families with a child with Spina Bifida lived in areas allocated to the two most deprived quintiles of the UK as described by the Index of Multiple Deprivation (78.0%, n=71).

**Discussion and Conclusions:** In our work, we have explored the impact of socioeconomic background on children living with Spina Bifida, and their associated outcomes, in a regional population in Leeds. In order to influence national policy and care pathways this regional work will be scaled up to cover the whole of England using NCARDRS data. The data supplied will be linked to National Neonatal Research Database and the Paediatric Intensive Care Audit Network to produce a timeline from conception to birth and then define early life years progress of these children. The scaling up of this piece of regional research using nationally collected congenital anomaly registry data highlights the importance of congenital anomaly registries having effective clinical/research partnerships. Linkage of the NCARDRS data to other national data sources is key to providing meaningful long term data. European and International collaboration will allow such data to be validated further.

**Sibling Birth Defects Recurrence in Florida, 2000 to 2019**

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Birth defects program on which the work is based: Florida Birth Defects Registry

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**Background and Objectives:** Birth defects are the leading cause of infant death and can adversely affect the quality of a child's and family's life. With the average American family consisting of more than one child, it is important to quantify the sibling birth defect recurrence risk to create evidence for preventive care and health services for families. The purpose of this study is to investigate the recurrence risk of birth defects in siblings.

**Methods:** The Florida Birth Defects Registry was used to identify sibling pairs born between 2000-2019 with select birth defects, excluding chromosomal conditions. Using multivariable logistic regression models, recurrence odds ratios (ROR) were estimated to examine the risk of birth defects in younger siblings using the following three scenarios:
1) Risk of a birth defect in the younger siblings, comparing those whose older siblings did vs. did not have any birth defects
2) Risk of a concordant birth defect in a younger sibling, comparing those whose older siblings had the same body region birth defect to those whose older siblings had no birth defects
3) Risk of a body system birth defect in a younger sibling, comparing those whose older siblings had a concordant birth defect to those whose older siblings had a discordant birth defect.

**Results:** We observed an overall 210% (95% CI: 2.0-2.2) increased odds of birth defect recurrence. The highest odds of concordant recurrence were observed for orofacial defects (ROR: 18.7, 95% CI: 13.9-25.1 for scenario 2 and ROR:16.9, 95% CI: 11.0-25.7 for scenario 3) and central nervous system defects (ROR: 9.6, 95% CI: 4.3-21.5 for scenario 2 and ROR: 5.3, 95% CI: 2.2-12.5 for scenario 3).

**Discussion and Conclusions:** Infants whose older siblings have a birth defect are at increased likelihood of being born with a birth defect. Although the magnitude of this increased likelihood varied by the type of birth defect in the older sibling, our study findings support a direct association of birth defect recurrence.

**Prenatal detection of birth defects: pathway of care in obstetric ultrasound services in Bogotá, Colombia**

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Birth Defects Program on which the work is based: PREVERDEC Bogotá – Cali

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**Background and Objectives:** 85% of birth defects (BD) can be diagnosed prenatally by obstetric ultrasound (US-OB), prenatal diagnosis (PND) contributes to the optimization of perinatal management, favoring, among other aspects, specialized monitoring of fetal health, establishing the mode of pregnancy termination, referring patients to institutions with evaluation and treatment capacity, preparing the healthcare team and providing education for the family. In Colombia, prenatal screening for BD is mandatory by law, it is established the performance of US-OB for all pregnant women at weeks 11-14 and at weeks 18 to 24. However, PND is less than 34% in Bogotá. This study aims to describe the pathway of care in US-OB services in Bogotá to identify opportunities for improvement of PND.

**Methods:** Cross-sectional study developed in health institutions in Bogotá that perform US-OB during 2021 to 2022. For data collection, the instrument "Characterization of Structural and Operational Conditions in Healthcare Institutions Performing Obstetric Ultrasound" was designed using Microsoft Excel. The instrument was validated in a public and a private healthcare institution. Variables related to availability and characteristics of scanners, human talent, procedures, and parameters for performing US, monitoring of indicators and public health surveillance were analyzed using Microsoft Excel and SPSS (v.16).

**Results:** 81 institutions perform US-OB in Bogotá (83% being private and 17% public). 6.9% who perform US-OB are primary care physicians, 4.7% radiologists and 88% ob/gyn. Of the institutions 92.6% have a protocol for US-OB performance; 22% evaluated quality indicators like result coherence, prenatal notification, waiting times, and compliance with obstetric markers. 45.7% had induction and training processes, 67% applied checklists for reporting findings and 21% defined minimum percentages of US detection for BD. When a BD is suspected, 93.8% of the institutions reported that findings are explained to the patient and doubts are solved, 48.1% inform the Health Promotion Entity and 42% inform the healthcare provider who requested the US-OB. If a BD is detected, 80% of the institutions referred the case is redirected to the emergency department, of which 65% are rerouted to prenatal surgery services. However, 38% institutions do not report these cases to the public health surveillance system.

**Discussion and Conclusions:** In Latin America the number of prenatal US centers is increasing, however, in our study performance of US-OB does not adhere completely to the requirements by law and international guidelines. Regarding human talent, primary care physicians shouldn't be performing US-OB. Various factors can affect the quality of prenatal screening, such as the inconsistent exams, inadequate image capture, non-compliance with a checklist, low equipment resolution, lack of defined US-OB detection timelines, and weaknesses in training and personnel development. These factors can directly impede timely care and management of mothers and children with BD. PND and notification rates are lower than other reports, highlighting the need to prioritize the improvement of BD surveillance in our city. Enhancing the quality of OB-US and strengthening public health surveillance are essential for improving PND in prenatal care.

# Echocardiography Evaluation of Congenital Heart Disease with its Outcome in a Medical University Hospital of Dhaka, Bangladesh

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Birth Defects Program on which the work is based*:* NA

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**Background and Objectives:** Congenital heart disease is one of the most common types of birth defect affecting almost one in 100 babies which can contribute significantly in infant morbidity and mortality. The goal of this study was to identify the different patterns of congenital heart diseases by echocardiography evaluation with its outcome among admitted neonates in a tertiary care medical university hospital in Dhaka.

**Methods:** This prospective observational study was conducted over a period of 2 years from March 2020 to February 2022, among the neonates admitted to the Neonatal Intensive Care Unit of Bangabandhu Sheikh Mujib Medical University (BSMMU) a tertiary care teaching hospital in Dhaka. Neonates with structural congenital heart disease, diagnosed by routine echocardiography were included in this study. Pattern of the lesions was observed and analyzed. Patients were followed up to neonatal period to see the outcome.

**Results:** A total of 200 neonates were diagnosed with congenital heart disease during the study period and majority of them were acyanotic (98%) and combined lesions such as PDA with ASD (37.2%) followed by PDA only (36.2%). Males were predominant (60%). The majority of neonates were pre-term (79%) with low birth weight (68%). Consanguinity was present in 10% of cases. Resuscitation was required mostly among the combined type of CHD cases. Treatment was required in 67% of cases with a complete resolution of the defect in 89% of cases. Overall mortality was 14% mostly due to combined cardiac lesions.

**Discussion and Conclusions:** Among congenital heart diseases, acyanotic defect was more common than cyanotic with Patent Ductus Arteriosus alone or in combination with Atrial Septal Defect were the commonest lesion in this study.

**Prevention of neural tube defects in Chile: more than two decades of folic acid fortification**

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Birth defects program on which the work is based: NA

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**Background and Objectives:** Addressing micronutrient deficiencies has been a longstanding commitment in Chile for over 70 years. Strategies, such as the mandatory fortification of wheat flour with iron and B-complex vitamins since 1950 to prevent anemia, along with water fluoridation and iodine fortification of salt to prevent dental cavities and goiter, were implemented. In 2000, Chile took a significant step by including folic acid in the mandatory wheat flour fortification program to prevent neural tube defects (NTDs). Here, we present the strategies implemented in Chile to accomplish this objective.

**Methods:** The information was gathered from various sources, including peer-reviewed articles, official reports, websites, as well as the shared experiences of former and current stakeholders, along with the authors' expertise in the field.

**Results:** Following the implementation of this policy, a variety of strategies have been implemented to assess the impact of the folic acid fortification program. Initially, the prevalence rates of NTDs were monitored through a specially designed registry in the Metropolitan Region from 1999 until 2016. Subsequently, nationwide evaluation has been carried out by the National Registry of Congenital Anomalies of Chile (RENACH). Additionally, the Institute of Public Health has implemented appropriate methodologies (HPLC-DAD) for monitoring folic acid levels in flour, and microbiological assays for assessing folate levels in serum and red blood cells.

**Discussion and Conclusions:** All these combined efforts have resulted in a significant 48% reduction in the prevalence of NTDs. Ongoing evaluation and monitoring of this program remain crucial to ensure the continued success and effectiveness of this policy.

# WHO's Resolution calls for Micronutrient Fortification to Prevent Spina Bifida and other Neural Tube Defects

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**Background and Objectives:** Food fortification with folic acid (FFFA) is cost-effective and safe strategy to prevent spina bifida and anencephaly (SB-A). By 2019, only 58 countries have mandatory policy of FFFA, and this prevents 23% of all preventable SB-A in the world. In 2021, an article about the resolution titled ""Global Prevention of Folic Acid-Preventable SB-A through mandatory fortification of staple foods with folic acid by 2030", was conceived and published by a group of pediatric neurosurgeons who are members of the Global Alliance for Spina Bifida-F (GAPSBiF). Since only official UN Member States can submit resolutions for consideration by the other Member States in the WHA, Colombia agreed to sponsor the initiative. After evidence analysis, the scope of the resolution was expanded to include several micronutrients. The purpose of this report is to describe the multi-stakeholder advocacy process that preceded the adoption of the WHA76.19 resolution on food fortification in May 2023.

**Methods:** In May 2022, an urgent call to action was published by GAPSBiF, in collaboration with the ICBDSR and other stakeholders, to promote the WHA resolution empowering birth defects prevention advocates to reach policy makers in their countries and globally. In February 2023, the WHO Executive Board decided that a draft resolution would be included in the agenda for the 76th WHA. The resolution was sponsored by Colombia and co-sponsored by 37 other member states, including Australia, Brazil, Canada, Chile, Ecuador, the European Union, Israel, Malaysia, Paraguay, the United States of America, and Guatemala. GAPSBiF and a diverse group of stakeholders, participated in events to encourage member states to submit written statements of support to the WHA or deliver oral statements of support during the WHA sessions. In May 2023, Colombia, Malaysia, and Ecuador, together with the GAPSBiF, G4 Alliance, and others, co-sponsored a side event in Geneva for awareness building.

**Results:** The WHA resolution titled "Accelerating efforts for preventing micronutrient deficiencies and their consequences, including spina bifida and other neural tube defects, through safe and effective food fortification" was passed on May 29th, 2023 with unanimous support from the member nations. This resolution received statements of support from 15 countries.

**Discussion and Conclusions:** It has been thirty years since the first study provided unequivocal evidence on folic acid's preventive potential for neural tube defects, yet the pace of global prevention of these birth defects has been extremely slow, and laden with disparities. A WHA resolution on food fortification with folic acid brings the focus back to primary prevention of neural tube defects in over 100 countries that currently do not implement folic acid fortification of staple foods. By preventing the majority of neural tube defects through fortification, existing resources in low- and middle-income countries can be diverted to programs that aid surgical treatment, and rehabilitation of spina bifida cases that occur due to other causes. The ICBDSR members have a voice through their surveillance programs to influence policy makers using the WHA resolution, and enable effective implementation of food fortification in their respective countries contributing to improving birth defects prevention and care.

# Epidemiology and Risk Factors Concerning Transposition of the Great Vessels: A population-based case-control study in Bogotá and Cali, Colombia

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Birth defects program on which the work is based: PREVERDEC Bogotá – Cali

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**Background and Objectives:** Transposition of the great vessels (TGV) is a congenital malformation characterized by ventriculoarterial discordance, where the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle (1). This results in a cyanotic heart defect as oxygenated blood is redirected back to the lungs instead of reaching the systemic circulation. TGV is one of the most common forms of cyanotic heart disease, accounting for approximately 4% of all congenital heart diseases, with a prevalence of 1 in 3,500 live births (LB) (2). The objective of this study was to characterize the epidemiology and risk factors associated with TGV in the cities of Bogotá and Cali, Colombia, during the period of 2003-2019.

**Methods:** A retrospective case-control study design was employed, analyzing data from birth defect reports provided by the Program for the Prevention and Surveillance of Birth Defects and Rare Diseases (PREVERDEC) surveillance system. Cases included live births or stillbirths with TGV weighing more than 500g, while controls consisted of infants without congenital abnormalities, matched in terms of birth date and hospital. A case-to-control ratio of 1:4 was utilized. Prevalence was calculated as a rate per 10.000 LB, considering a 95% confidence interval using Poisson distribution, and risk factors were assessed through odds ratios obtained by a logistic regression model using IBM SPSS Statistics ©. The study received a waiver for ethical approval from the local Ethics Committee of Pontificia Universidad Javeriana, considering its retrospective nature and the fact that all procedures performed were part of routine care. The assigned approval code was FM-CIE-8324-14.

**Results:** With 552,841 births, a prevalence rate of 1.12 cases (95% CI 0.86-1.44) per 10.000 LB was estimated. Among the cases, 54.84% were male newborns. The mean birth weight was 2757.44 grams (SD 743.37). When categorized based on gestational age, 11.29% had low birth weight, 83.87% had an expected birth weight, and 4.84% had high birth weight. Regarding prenatal care, cases had a mean of 5.78 (SD 4.37) prenatal visits, with a mean of 3.29 (SD 2.76) obstetric ultrasounds (US). Among those who received an US, TGV was detected in 37.5% of cases (n=21). Regarding diagnosis and postnatal evaluation, clinical evidence of TGV was present at birth in 33.93% of the cases. Among all cases classified as TGV, initial evaluations using echocardiograms confirmed the presence of TGV in 39.29% of them. Odds ratios analysis demonstrated a statistically significant correlation between TGV and preterm birth (OR: 5.51, CI: 2.64-11.52) as well as birth weight below 2500 grams (OR: 7.37, CI: 3.29-16.48).

**Discussion and Conclusions:** The prevalence rate of TGV in this study was lower than that reported in global estimates (2.95 cases per 10,000 LB), but was superior to previous estimates from Bogotá (0.6 cases per 10,000 LB) and data reports by the Colombian National Institute of Health (0.8 cases per 10,000 LB). However, gaps in prenatal care and postnatal identification of TGV were identified. Risk factors such as preterm birth and low birth weight were also found to be associated with TGV, underscoring the importance of antenatal care and maternal health. Future studies should further aim to determine the influence of social characteristics on TGV. In conclusion, research on congenital heart disease is crucial for identifying preventable risk factors and sociodemographic characteristics that can inform public health interventions and antenatal care guidelines.

**Characterization of risk factors for Clubfoot in Bogotá and Cali, between 2002-2020**

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Birth defects program on which the work is based: PREVERDEC Bogotá – Cali

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**Background and Objectives:** Clubfoot (CF) is a congenital abnormality characterized by equinus positioning of the hindfoot, varus positioning of the calcaneus, a cavus arch, and metatarsus adductus. With a global prevalence of 5-20 cases per 10,000 live births (LB) in low to middle-income countries. Clubfoot presentation has been associated with several risk factors such as: maternal smoking during pregnancy, solvent exposure, early amniocentesis, male sex at birth, and a family history of CF. If left untreated, clubfoot causes severe consequences for the child; gait disturbances, reduced quality of life, and limited work opportunities. Our objective was to determine the prevalence of clubfoot and identify associated risk factors in Bogotá and Cali, Colombia, from 2002-2020.

**Methods:** A retrospective case-control study design was employed, analyzing data from birth defect reports provided by the Program for the Prevention and Surveillance of Birth Defects and Rare Diseases (PREVERDEC) surveillance system. Cases included live births or stillbirths with clubfoot weighing more than 500g, while controls consisted of infants without congenital abnormalities, matched in terms of birth date and hospital. Prevalence was calculated considering a 95% confidence interval using Poisson distribution, and risk factors were assessed through adjusted odds ratios obtained by logistic regression model. All statistical analyses were performed using SPSS Statistics from IBM.

**Results:** Of 558,255 births, 861 cases of clubfoot were identified, with a prevalence rate of 15.41 per 10,000 LB. In Bogota, the prevalence rate was 15.1 per 10,000 LB, whereas in Cali it was 17.29 per 10,000 LB. Family history of clubfoot within first-degree relatives was identified as a risk factor for clubfoot (aOR: 34.84; 95% CI 11.61-104.60).

**Discussion and Conclusions:** Prevalence rate obtained for CF was higher compared to those observed in the USA and Europe, with rates of 12.9 and 11.3 cases per 10,000 LB, respectively. However, compared to low-to-middle income (LMIC) countries like Colombia, prevalence rates have different behaviors. Turkey exhibited the highest prevalence rate of 20.3 cases per 10,000 LB, whilst the prevalence rate for the Americas (17.4 cases per 10,000 LB) was slightly higher than our overall prevalence but similar to Cali. Association between a family history of CF in first-degree relatives and the risk of CF occurrence in newborns was found, suggesting a potential hereditary mechanism. As a LMIC, ensuring accurate prevalence rates and investigating risk factors for clubfoot holds significant importance in terms of preventing and reducing morbidity within this population, addressing healthcare initiatives aimed at providing timely and effective treatment.

## Polydactyly risk factors in Bogotá and Cali, Colombia between 2002-2020: A case-control study

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Birth defects program on which the work is based: PREVERDEC Bogotá – Cali

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**Background and Objectives:** Polydactyly (PD) is a birth defect characterized by the presence of extra fingers on one or more extremities. With a prevalence of 6.03 per 10,000 live births (LB) in Colombia, polydactyly accounted for 17% of musculoskeletal congenital abnormalities in 2021. The aim of this study was to determine the prevalence of polydactyly and identify associated risk factors in Bogotá and Cali, Colombia, between 2002 and 2020.

**Methods:** Through a retrospective case-control study design, data analysis was conducted from birth defect reports provided by the Program for the Prevention and Surveillance of Birth Defects and Rare Diseases (PREVERDEC) surveillance system. The cases in this study included both live births and stillbirths with polydactyly, while the group control consisted of infants without congenital abnormalities, matched in terms of birth date and hospital. Prevalence of polydactyly was calculated and risk factors were evaluated through adjusted odds ratios obtained by logistic regression models, considering a 95% confidence interval. All statistical analyses were performed using SPSS Statistics (IBM).

**Results:** A total of 558,255 newborns were recorded, 848 had PD. Among these cases, 833 were live births, and 15 were stillbirths. Prevalence of PD was found to be 15.19 per 10,000 LB (95% CI 14.18–16.25) between 2002 and 2020. More specifically, a prevalence of 14.44 per 10,000 LB (95% CI 13.38–15.57) and a prevalence of 19.45 per 10,000 LB (95% CI 16.57–22.68) were calculated for Bogota and Cali, respectively. Risk factors for PD were found; low birth weight <2,500g (aOR: 1.76; 95% CI: 1.01–3.07), male newborn sex (aOR: 1.52; 95% CI: 1.08–2.14). The presence of a family history of PD in first-degree relatives of consanguinity was found to be strongly associated with the development of PD in the newborn (aOR: 655.99; 95% CI: 89.93–4,785.04). No difference between postaxial and preaxial configuration was found considering family history. Maternal pregestational diabetes was also found to be associated with the presentation of PD (aOR: 4.14; 95% CI: 1.39–12.39).

**Discussion and Conclusions:** Observed prevalence of PD was higher than that reported in European countries during the same period. This finding could be related to PD being an inherited condition and larger family sizes in regions like South America. Low birth weight was found to be associated with an increased risk of PD, although it is evident after birth it cannot be addressed as a direct risk factor. Male newborns were also found to have a higher risk of PD, particular factors behind this difference remain unknown. Family history of PD among first-degree relatives was identified as a significant risk factor, correlating the hereditary nature of PD. Pregestational diabetes increases risk of PD in newborns, which is likely due to the teratogenic effects of hyperglycemia. These results emphasize the significance of public health measures that target the identification of polydactyly and the adoption of notification strategies to enhance well-being of individuals living with PD.

**Severe congenital protein C deficiency: epidemiology, diagnosis and long-term management**

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Birth Defects Program on which the work is based*:* NA

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**Background and Objectives:** Severe congenital protein C deficiency (SCPCD) is a rare, autosomal recessive genetic disorder, caused by homozygous or compound heterozygous mutations in the protein C gene located on chromosome 2(q13-14). Information about the disease and management is scarce. This paper aims to provide an overview of the key characteristics, diagnosis and management of patients with SCPCD.

**Methods:** The scientific literature including case reports and conference proceedings related to SCPDC was reviewed and summarized.

**Results:** The estimated prevalence of SCPDC is 1 in 500,000 to 1 in 750,000 births. Most infants are born in consanguineous families. SCPCD is associated with severe antenatal and postnatal thrombotic or hemorrhagic complications, and may lead to long-term morbidities. The main clinical manifestation among neonates are purpura fulminans and severe disseminated intravascular coagulation, often with concomitant venous thromboembolism. Diagnosis of SCPCD includes laboratory tests and genetic analysis. Protein C levels measured are usually <0.01 IU/ml. If left untreated, SCPCD leads to early death. Acute treatment options include fresh-frozen plasma, vitamin K antagonists, heparin, and plasma-derived protein C concentrate (PCC). However, long-term prophylaxis and management of patients is critical to avoid complications. It includes individualized replacement therapy with PCC with intravenous or subcutaneous administration and vitamin K antagonists with regular monitoring of plasma protein C levels

**Discussion and Conclusions:** SCPCD is an ultrarare disorder. The true prevalence is likely to be higher due to under-diagnosis and under-reporting. The recently published guidelines by the International Society on Thrombosis and Haemostasis provide details of diagnosis and management of patients with SCPCD. Awareness and early diagnosis of SCPCD are critical for successful long-term management.

**Sex ratio and congenital anomalies in children born after assisted reproduction.**

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Birth defects program on which the work is based: National Registry of Congenital Anomalies of the Czech Republic

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**Background and Objectives:** Retrospective analysis of the frequency and sex ratio of children born with congenital anomalies in the Czech Republic, differentiated according to the method of conception: children born after methods of assisted reproduction and children born after spontaneous conception

**Methods:** In the work, we used data from the National Registry of Congenital Anomalies and the National Registry of Assisted Reproduction kept at the Institute of Health Information and Statistics of the Czech Republic (ÚZIS CR). The analyzed period covers the years 2013 to 2020.

**Results:** In our study we demonstrated statistically significantly more cases of children born with congenital defects in the group of children born after assisted reproduction compared to the group of children born after spontaneous conception. In the group of children born after AR, congenital defects of the central nervous system, congenital heart defects and congenital defects of the gastrointestinal tract were diagnosed more often. In some groups of congenital defects, a higher proportion of boys compared to girls and a higher representation of cases with a congenital defect in children born from multiple pregnancies were also found.

**Discussion and Conclusions:** In the group of children born after assisted reproduction, we found a higher proportion of cases of birth defects than in children born after spontaneous conception. This finding applies both to birth defects in general and to some groups of diagnoses. For some diagnoses, we found a higher representation of boys than girls compared to children born without assisted reproduction.

**Application of Photon counting CT in the diagnostics of Post mortem fetal malformations for the assessment of skeletal , external skin surface and vasculature anomalies.**

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**Background and Objectives:** Aim: To check the feasibility of the use of Photon Counting Computed Tomography (PCCT) in the post mortem assessment of fetal malformations. To try to assess skeletal and external skin surface and vasculature anomalies

**Methods:** Data collection and acquisition: Two cases of fetal malformations where selected in-order to prove the application and efficacy of photon counting CT in post mortem fetal anomalies. Studies where preformed during the month of November 2022. Analysis: Acquisition of PCCT series (both Native and contrast) for postmortem fetuses studies. Second stage of using the series in order to achieve 3D reconstruction of the fetuses. Acquisition and analysis where taken in the imaging center of Semmelweis University in Hungary . Instrument use: PCCT NAEOTOM Alpha with Quantum Technology. Contrast material: Ultravist 370.

**Results:** Two selected cases for PCCT imaging and 3D reconstructions where preformed. Surface imaging, skeletal imaging and angiography where Successfully preformed. Additional contrast material series where later acquired with insertion of contrast material through Umbilical vein of the umbilical cord in-order to demonstrate vasculature.

**Discussion and Conclusions:** In our study we succeeded to demonstrate that Photon counting CT may be a useful tool in the assessment of fetal anomalies in case of postmortem studies. The demonstration of skeletal malformations , external surface/skin and vascular anomalies has shown to be of superior diagnostic value. The advantage of the use of PCCT techniques is the ability to store 3 dimensional view reconstruction of the fetus.The imaging data may be useful in the future to assist with AI applications in combination with additional genetic information.

## Characterization of environmental exposures in the French ATENA registry

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Birth Defects Program on which the work is based*:* ATENA registry

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**Background and Objectives:** In more than half of congenital anomaly cases, no specific cause can be identified, and the etiology is thought to be multifactorial. In this context, interest in environmental risk factors is growing, and better characterization of environmental exposures is needed. Seventh registry in France, the ATENA registry has been set up in the South West region in 2022 to ensure epidemiological surveillance of congenital anomalies in the Nouvelle-Aquitaine population. In addition to the surveillance aspects, the registry aims to systematically assess environmental and drug exposure among parents of cases included in the registry.

**Methods:** The ATENA registry aim to collect all children and fetuses having a congenital or chromosomal abnormality diagnosed antenatally or postnatally up to one year of life. After validation of the congenital anomaly and inclusion of cases in the registry, a self-assessed questionnaire will be sent to parents to collect data on their environmental exposures over the three months before pregnancy for both parents and during pregnancy for the mother. The questionnaire will collect data on drug use and various domestic and occupational exposures, such as household characteristics, household chemical use or occupational chemical exposure. In addition to these self-reported data, publicly available geographical data will be used to better characterize the living environment, using the residential address history provided by the parents. Job history will also be collected to enable the use of job-exposure matrices to assess occupational exposures of all parents in a standardized way.

**Results:** The combination of several data sources will allow a comprehensive description of parental exposures during the relevant time window for congenital anomaly occurrence. For instance, pesticides exposure will be assessed at home and at work using (a) self-reported data (domestic and occupational pesticide use), (b) a job-exposure matrix and (c) geographical data (land use data and pesticides sales data).

**Discussion and Conclusions:** The systematic assessment of environmental exposures will contribute to the registry's surveillance goal and could help generating hypotheses for future etiological research.

**Multidisciplinary consultation in fetuses with malformations: prenatal exome experience in a tertiary public hospital.**

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Birth defects program on which the work is based: NA

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**Background and Objectives:** The detection of a fetus with malformations constitutes a challenge for diagnosis and management of decisions about the pregnancy. Indeed, parents and health care practitioners are facing a problematic situation that needs to be diagnosed and resolved in a short period of time. One of the challenges in the prenatal context is that the fetal phenotype is limited to the information obtained by ultrasound or fetal autopsy and, furthermore, the prenatal presentation of most of the postnatally recognizable genetic syndromes is unknown. Whole exome sequencing in the prenatal setting allows increasing the diagnostic rate in fetuses with malformations. This study describes the experience of a multidisciplinary approach to prenatal exome application in a tertiary public hospital.

**Methods:** Prospective and retrospective study of 150 fetuses with malformations, QF-PCR and normal arrayCGH and whole exome carried out during February 2018-Januray2023. The interpretation of the data as well as the reanalysis of inconclusive cases has been carried out by a multidisciplinary team (obstetricians, clinical geneticists, genetic counselors, laboratory geneticists, radiology and pathology experts, together with psychological support to the parents). Secondary findings disclosure was also offered to the parents.

**Results:** The overall diagnostic yield of the exome was 38.6% (58/150). The yield in fetuses with multisystem involvement has been 52% (19/37). The highest diagnostic yield was obtained in fetuses with involvement of the skeletal system (77%; 15/19) and in fetuses with increased NT or fetal hydrops (72%; 16/22). In this last group, the identified causes have been very heterogeneous, mainly RASopathies, congenital anemias and hereditary lymphedema, allowing specific management in each case. High speed resolution of some cases was achieved in a few weeks. The reanalysis of exome of the inconclusive cases in a mean period of 2- years made it possible to increase the diagnostic rate by 7%.

**Discussion and Conclusions:** In our experience, the multidisciplinary approach was essential to obtain a relevant diagnostic rate of the prenatal exome. This has been high, especially in fetuses with suspected skeletal dysplasia and persistent NT. Likewise, new phenotypes of genetic diseases of which very little is known about their prenatal presentation helps to expands and improve the delineation of known and new syndromes.

## Prevalence of Congenital Heart Defects Among Boys with Hypospadias in England

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Birth Defects Program on which the work is based*:* National Congenital Anomaly and Rare Disease Registration Service (NCARDRS)

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**Background and Objectives:** Hypospadias is a birth defect of the male urinary tract that may be isolated or co-occur with other structural malformations, including congenital heart disease (CHD). The risk for co-occurring CHDs among boys with hypospadias remains relatively unknown, which limits early identification strategies. Previous research in the US suggests boys with hypospadias have a higher risk of CHDs than boys without hypospadias. This study, a collaboration between the US authors and the English National Congenital Anomaly and Rare Disease Registration Service (NCARDRS), part of the National Disease Registration Service, aimed to explore the prevalence of hypospadias and the prevalence of co-occurring CHD for boys with hypospadias. We also assessed prevalence of CHD co-occurring with any other congenital anomaly, apart from hypospadias. In addition, we explored associations between hypospadias, ethnicity and deprivation to assess potential inequalities in these domains as identified by the US study.

**Methods:** NCARDRS data were used to identify children born from Jan 1 2018 and Dec 31 2020 with congenital anomalies, including hypospadias and CHD, tracked to age 2 for correction surgery. Anomalies were defined using relevant ICD-10 codes and BPA extensions. Deprivation was assigned according to maternal postcode of residence, based on the English Index of Multiple Deprivation (IMD), this multi-faceted measure of small areas includes education, health, employment, income, crime, barriers to housing and services and the living environment. IMD score was categorised into quintiles. Maternal ethnicity was reported by hospital as self-reported data and categorised into White, Black, Asian, Mixed, Other and Unknown. Prevalence was calculated as the number of babies with an anomaly born alive divided by the total number of live births. Prevalence of each anomaly type was calculated by recording total cases with at least one code for the anomaly.

**Results:** Between 2018-20 there were 935,082 live male births in England, of these 20,480 had a recorded congenital anomaly; 4,103 boys with hypospadias (43.9 / 10,000 live births) and 5,395 with cardiac anomalies (57.7 / 10,000 live births). There were 165 boys with hypospadias and co-occurring CHD. The prevalence of CHD amongst those with hypospadias was 4.0% (95% CI, 3.5%-4.7%). Of these 63 had a severe CHD diagnosis. There were 3938 boys with CHD co-occurring with any other congenital anomaly, except hypospadias. Maternal ethnicity was more often recorded for the co-occurring group than the all-anomalies group (75.8% versus 51.7%, respectively of cases had ethnicity recorded). Of those with co-occurring hypospadias and CHD with known ethnicity, 67.2% were White, 21.6% were Asian, 5.6% were Black, 3.2% Other and 2.4% Mixed. IMD scores were available for all boys with co-occurring hypospadias and CHD, 31.5% were from the most deprived quintile and 23.6% were from the second most deprived.

**Discussion and Conclusions:** Direct replication of the US study was not possible owing to no direct equivalent maternal education and low completeness of ethnicity variables in the full dataset. The prevalence of hypospadias and cardiac anomalies in England was lower than those in the original US study. The prevalence of hypospadias and co-occurring CHD of 4.0% in NCARS is also lower than the US study (5.5%–7.0%). There are several factors that may contribute to these differences including differences in coding, ascertainment methodology or population demographics. Differences between healthcare systems may also be a factor. Lower prevalence in our data may suggest that the benefit of additional CHD screening for boys with hypospadias may be more limited in England. Further analysis will use Poisson regression models to explore prevalence rates of CHD for boys with hypospadias and for boys without hypospadias with any other anomaly. The models will adjust for IMD and ethnicity to assess potential inequalities.

***Printed and supported by***

***Pontificia Universidad Javeriana***

***Human Genetics Institute of the Pontificia Universidad Javeriana***

***Secretary of Health of Bogotá***

***Program for the Prevention and Surveillance of Rare Diseases and Congenital Defects (PREVERDEC)***