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ConcePTION

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WP1 – Moving beyond pregnancy registries to enhance our understanding of disease-related pregnancy outcomes, medication use and safety of use during pregnancy

D1.2 Core evidence elements for generating medication safety evidence for pregnancy using population-based data

Core data elements, design and analytical foundations

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Abbreviations

ACOG	American College of Obstetricians and Gynaecologists
ADHR	Attention deficit hyperactivity disorder
ADR	Adverse drug reaction
AHRQ	Agency for Healthcare Research and Quality
ATC	anatomical therapeutic chemical
ART	assisted reproductive technologies
bDMARDs	biologic disease modifying anti-rheumatic drugs
BMI	Body mass index
CA	congenital anomalies
CDC	Centers for Disease Control and Prevention
CHD	congenital heart disease
CIOMS	Council for International Organizations of Medical Sciences
CPRD	Clinical Practice Research Datalink
csDMARDs	Conventional synthetic disease modifying anti-rheumatic drugs
CV	cardiovascular
DDD	defined daily dose
her	Electronic health record
EMA	European Medicines Agency
EncePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EP	ectopic pregnancy
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
FGR	fetal growth restriction
GA	gestational age
GAIA	Global Alignment of Immunization Safety Assessment in Pregnancy
GDM	gestational diabetes mellitus
GDP	gross domestic product
GPP	Guidelines for Good Pharmacoepidemiology Practices
ICD-8/9/10	International Classification of Diseases $8^{th}/9^{th}/10^{th}$ Revision
IEA	International Epidemiological Association

IMD	index of multiple deprivation
IQR	inter quartile range
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcome Research
IV	instrumental variable
LMP	last menstrual period
MoBA	Norwegian Mother, Father and Child cohort Study
MOOSE	meta-analysis of observational studies in epidemiology
MSMs	marginal structural models
NSAIDs	nonsteroidal anti-inflammatory drugs
OGTT	oral glucose tolerance test
OTC	over the counter
PASS	post-authorisation safety studies
PS	propensity score
SES	socio-economic status
SGA	small for gestational age
SMFM	Society for Maternal-Fetal Medicine
SmPC	summary of product characteristics
SPVS	Spanish Pharmacovigilance System
STROBE	Strengthening the reporting of observational studies in epidemiology
THIN	The Health Improvement Network
tsDMARDs	targeted synthetic disease modifying drugs
TOPFA	termination of pregnancy for fetal anomaly
VSD	ventricular septal defect
US	ultrasound scan
WHO	World Health Organization
WP	work package

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Abstract

Currently, the comparison of research results on medication use in pregnancy is complicated by heterogeneity in the identification and the definitions of the key pregnancy and maternal outcomes of interest, exposure to medications, risk factors, and confounders, as well as a large range of designs and statistical tools available. Therefore, the ConcePTION project, which aims to conduct high quality and clinical meaningful population-based pharmacoepidemiological studies among pregnant and lactating women, identified the need for a unifying document to clarify key concepts and research methods. This will help the public and industry researchers in conducting more standardized high quality and clinically meaningful pharmacoepidemiological population-based studies among pregnant women is needed.

Task 1.2 of WP1 aims to select, identify and define core evidence elements, design foundations and analytical considerations to allow assessment of medication utilisation and safety in pregnancy using population-based data to inform healthcare professionals and patients and to meet regulatory requirements and standards for potential inclusion in product labels.

This document presents:

1) core data elements:
    a. core outcome data elements (non-live and live birth, childhood and maternal outcomes);
    b. medication exposure and aetiological window;
2) design considerations;
3) analytical methods;
4) statistical power and sample size considerations and
5) limitations and quality.

Finally, the document describes the list of “default” core evidence elements that has been compiled based on published evidence and expert knowledge within the ConcePTION consortium.

In a second stage, the document was reviewed, discussed and validated in a multi-stakeholder and expert consultation meeting that took place in October 2020.

1. Introduction

The ConcePTION project mission is to build and to test a comprehensive and reliable panEuropean ecosystem for generating, monitoring, and providing robust and rapid real-world evidence on medication safety in pregnancy and breastfeeding in a collaborative and standardized manner to inform medication labels, women, families and healthcare professionals.

To achieve the goals of the ConcePTION project, eight work packages (WPs) were devised, with cross cutting themes to make the project coherent and geared towards a shared common goal. WP1-4 addresses generation of evidence from different underlying data sources. WP1 uses existing population health data, e.g. from healthcare databases and registries.

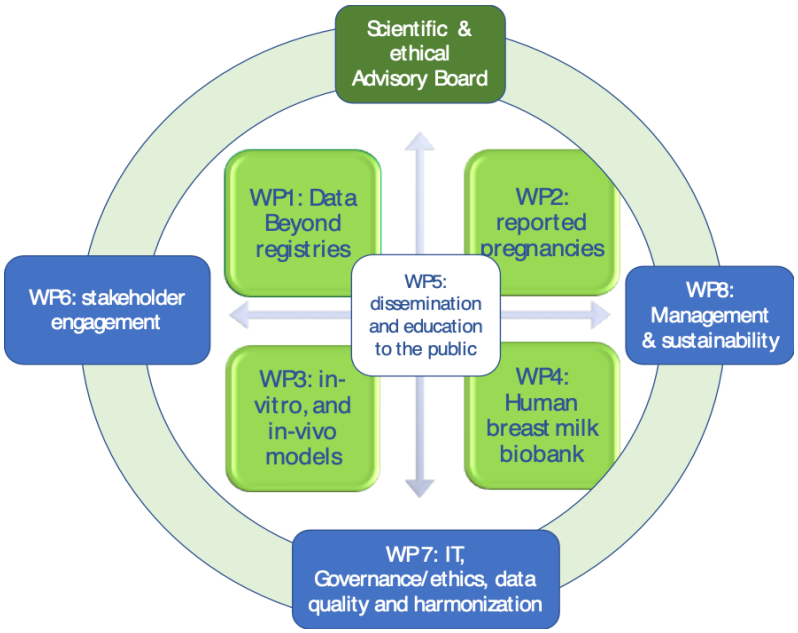

Figure 1. ConcePTION work packages

This report focuses on secondary use of population-based data. Thus, data collected for the primary or sole purpose of pharmacovigilance are out of its scope.

The overall objective of WP1 is to generate timely evidence about pregnancy outcomes, including perinatal and long-term effects in offspring following medication use during pregnancy, to allow healthcare professionals and patients to make informed benefit-risk decisions and thus providing benefit to women, their babies and their families. The aim is to move beyond medication specific pregnancy registries to enhance our understanding of disease-related pregnancy outcomes, medication use and safety of use during pregnancy. The WP1 work will test state of the art approaches in five complex demonstration projects, each dedicated to a disease/medication topic, which will form the starting point for identifying suitable data sources, validating data and definitions, conducting medication utilisation studies and conducting pregnancy outcome studies. For three demonstration projects (depression, multiple sclerosis /systemic lupus erythematosus and neuropathic pain), a

systematic search was conducted using metaPreg (metaPreg, 2020) and is included as a good example of well validated search strategies (Annex 1).

Currently, there is poor homogeneity in studies in the identification and the definitions of the key pregnancy and maternal outcomes of interest, exposure to medications, risk factors, and confounders, as well as a large range of study designs and analytical approaches available. Therefore, the need for a unifying document that will help the public and industry researchers in conducting high quality and clinically meaningful pharmacoepidemiological population-based studies among pregnant women has been identified.

Hence, task 1.2 of WP1 has been designed to select, identify and define core evidence elements, design foundations and analytical considerations to allow assessment of medication utilisation and safety in pregnancy using population-based data to inform healthcare professionals and patients and to meet regulatory requirements and standards for potential inclusion in product labels.

2. Purpose

The aim of the document is to provide foundations for conducting pharmacoepidemiological population-based studies among pregnant women. The document, which is complementary to reference guidelines such as GVP ((European Medicines Agency, 2020), describes the core elements a study must include to generate medication utilisation and safety evidence for pregnancy ("core evidence elements") to optimise benefit-risk decision-making for the patient and for healthcare professionals.

Core evidence elements are defined as elements needed in population-based data studies that investigate medication safety in pregnancy. These elements include core data elements such as outcomes of interest, medication exposure, relevant covariates and maternal conditions, and other core elements such as design and analytical considerations that could influence the interpretation of medication safety information. The core elements should be further defined by researchers in pharmacoepidemiology, together with prescribing clinicians and experts concerned by the disease or outcome or area of research as well as representatives of patients and end-users of the information. When designing a study that will be used for a regulatory purpose, regulators could also be consulted in order to support adoption of an adequate set of core elements relevant for medicines evaluation. Here, this document describes the core evidence elements that should be used to study medication safety in pregnancy, taking into consideration the medication of interest.

3. Methods

The basis for the definitions of core elements is mainly formed by the expert knowledge of the partners, including review of best practices for defining outcomes for research on maternal and pregnancy outcomes, within and outside the field of pharmacoepidemiology.

The core elements are compiled based on the results of dedicated reviews of the following publicly available resources including guidance documents and label information and expert knowledge within the ConcePTION consortium. The document was reviewed, discussed and validated in a multi-stakeholder and expert consultation meeting.

3.1. Publicly available reference and regulatory guidance documents

- Guideline on the exposure to medicinal products during pregnancy: Need for post-authorisation data (European Medicines Agency, 2005);
- Post-approval pregnancy safety studies draft guidance for industry (Food and Drug Administration, 2019a);
- Pregnancy, lactation, and reproductive potential: Labelling for human prescription drug and biological products – content and format draft guidance for industry (Food and Drug Administration, 2019b);
- Guideline on risk assessment of medicinal products on human reproduction and lactation: From data to labelling (European Medicines Agency, 2008);
- Systematic overview of data sources for drug safety in pregnancy research (European Medicines Agency, 2012);
- Draft Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations III: Pregnant and breastfeeding women (European Medicines Agency, 2020).

3.2. Additional searches

Three searches were conducted as a complement of the expert opinions.

3.2.1. General literature search

A general literature search for pharmacoepidemiology studies in the past 10 years that assess medication use in pregnancy has been performed. These studies underwent a detailed review to extract the following elements: database(s), exposure and etiological windows, maternal outcomes, perinatal outcomes, fetal outcomes, child outcomes (longer-term), validation, sample size, estimated effect size, comparators, statistical methods, covariates, duration of follow-up. This literature search is detailed in Annex 2.

3.2.2. Studies registered in the EU PAS Register

Pregnancy studies were identified using the applicable search tool in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register) register on 30-01-2019 by searching for "Pregnant women" in the "Other population" field. This search identified a total of 147 pregnancy studies which were manually reviewed to identify medication safety studies based on secondary data collection methodology. A total of 128 studies were deselected as they did not fulfil the criteria defined above. Main reasons for deselection were: Clinical trial, observational study with primary data collection, or drug utilization study. A total of 19 studies fulfilled the selection criteria (Annex 3).

3.2.3. Studies referred to in product labels of prescribed medications, currently approved by European Medicines Agency (EMA)

Between 24 November-23 December 2019, the most recent European public assessment reports - Product Information for all human medicines authorized in the EU (on November 24, 1123 medicines were authorized) were accessed at the EMA website (www.ema.europa.eu). For all those medicines, Section 4.6 (Fertility, pregnancy and lactation) was screened for information on observational studies in humans performed for the respective medicines or the medication class to which they belong. When data on human observational studies were available, the relevant study text was extracted and copied by a first reviewer to a spreadsheet. Subsequently, the same reviewer summarized available information in section 4.6 by medication class, medication name, indications, summary of product characteristics (SmPC) date, data source, pregnancy-related outcomes, additional information on birth defects, study sample size, study design features (i.e. comparators used and definition of exposure window) and outcome measures in the same spreadsheet. Quality control was performed by a second reviewer (Annex 4).

3.3. Redaction and review

The results of literature, guidance documents and label information together with the expertise in specific areas from partners were drafted by 19 authors, then reviewed and discussed by members in WP1. The first draft of the document was discussed during a consultation meeting with stakeholders with various expertise, the draft was enhanced accordingly.

Core elements have been defined not only as core data elements but also as relevant ways to use and interpret them (study design, analytical methods, limitations, validation of data quality, …). Furthermore, a minimal recommended list of core evidence data elements were compiled to serve as a "default" for studies (i.e. these should be used unless feasibility or specific aims require other choices…)

assessing the safety profile during pregnancy of a medication. The feasibility of applying and analysing the proposed core evidence elements will be tested in the WP1 demonstration projects.

4. Core evidence elements

Core evidence elements are considered key elements to conduct pregnancy safety studies. These elements include core data elements such as outcomes of interest, medication exposure, relevant covariates and maternal conditions, and other core elements such as design and statistical. The document describes:

- core data elements:
    a. core outcome data elements;
    b. medication exposure and aetiological window;
- design considerations;
- analytical methods;
- statistical power;
- sample size considerations and
- limitations and quality.

The adoption of a set of core elements across pregnancy studies does not exclude collection of additional data or adoption of additional methodology.

4.1. Core outcome data elements

The identification and selection of relevant outcomes for a pregnancy safety study should take into consideration the literature, guidance documents, mechanism of action of the medication of interest and the gestational timing of exposure for each of the outcomes. The review of the literature, the guidance documents and the EU PAS Register identified the following list of elements: major and minor congenital anomalies, specific anomalies such as cardiac anomalies, renal anomalies, intestinal anomalies, congenital hypothyroidism; live and non-live birth outcomes such as small for gestational age or intrauterine growth retardation, fetal hypoxia, preterm birth, premature rupture of membranes, fetal loss, neonatal death, infant mortality, neonatal complications and morbidities, low Apgar scores, treatment in neonatal care unit and need for resuscitation, drug withdrawal syndrome in neonate and serious infections of the infant, brain development; childhood outcomes such as developmental milestones, neurological abnormalities, immune system abnormalities, attention deficit hyperactivity disorder, and autism spectrum disorder.

The core outcome data elements considered in this document cover most of these including gestational age, pregnancy outcomes (live and non-live births), congenital anomalies (CA), long-term

neurodevelopmental outcomes, infant/childhood outcomes and maternal outcomes. The definition as well as the background rates of the selected core outcome data elements is presented below.

4.1.1. Gestational age

Gestational age (GA) is measured from the first day of the last menstrual period (LMP) and expressed in weeks and days (e.g. 40+5 = 40 weeks + 5 days), completed weeks (e.g. 40 weeks = all births 40+0 to 40+6), or in days (e.g. 280 days = 40+0 X 7). While gestational age has traditionally been calculated from the reported LMP (which depends on women to recall their LMP and assumes that women ovulate on average two week after LMP), estimates based on fetal biometric measures from ultrasound scans (USs) are increasingly used. Ultrasound dating can be used to confirm or adjust LMP (if there is a large enough discrepancy, GA is determined by the US estimate; otherwise the LMP is used) or the US estimate can be used without regard to LMP, i.e. the US results are used to predict delivery date. The tolerable discrepancy differs across studies, providers, time periods (+/- 2, 3, 7 or 14 days), and is partly related to how early in pregnancy the US is carried out. Current recommendations from the American College of Obstetricians and Gynaecologist (ACOG), the Society for Maternal-Fetal Medicine (SMFM), Euro-Peristat Network recommend the best obstetric estimate, which is the best estimate used by the obstetrical team or the birth attendant, rather than LMP alone. Hence, in Europe, Australia and USA, estimate of gestational age is based on ultrasound dating, rarely on LMP alone due to reporting errors.

Embryologists generally define the start of pregnancy as the time of conception as opposed to obstetricians who use the first day of the LMP to establish the length of gestation. In population-based data sources, the gestational age is often recorded in completed weeks or weeks and days for live births, stillbirths and terminations (elective or therapeutic), but it is rarely available for all ectopic pregnancies or miscarriages. In these cases, the gestational age might be estimated by algorithms using other data available in the data sources such as diagnostic and procedure codes (Muanda, 2017) or by setting a fixed gestational age of the event, for example 8 weeks of gestation for ectopic pregnancies and 10 weeks of gestation for spontaneous abortions (Matcho, 2018; Thai, 2020). It should always be made clear when an algorithm rather than reported gestational age has been used.

4.1.2. Pregnancy outcomes

4.1.2.1.Non-live birth outcomes

The outcomes below are those considered to be most relevant for this document.

- Fetal death that includes early (miscarriage) and late fetal death (stillbirth)
- Ectopic pregnancy
- Other termination of pregnancy

1) Fetal death

A fetal death is defined as a death prior to the complete expulsion or extraction from its mother of a fetus; the death may be diagnosed in utero or at the time of expulsion and is confirmed by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles (draft version of the ICD-11). Fetal deaths can be divided into early fetal death, known as miscarriage, occurring before a pre-defined gestational age threshold and late fetal death, known as stillbirth, occurring after a pre-defined gestational age threshold.

This gestational age threshold varies from definition to definition and may have changed over time due to advances in medical care and increased probability of survival around the threshold. Most European countries, the WHO and the EMA use a threshold of 22 completed weeks of gestation or a birth weight of 500 g to define stillbirths, with miscarriages defined as fetal deaths occurring before these thresholds (WHO, 2006; EMA, 2005). In the US, Canada and Australia, the threshold is at 20 completed weeks of gestation (Smith, 2020; Kowaleski, 1997), and some groups such as the ACOG (Committee on Practice Bulletins, 2015). The upcoming ICD-11 guidelines will likely define stillbirth from 22 weeks of gestation onwards with miscarriage referring to deaths before 22 completed weeks of gestation.

Whilst an agreement on a common cut-off to determine whether a fetal death should be considered a miscarriage or a stillbirth would be useful for research, this is difficult to reach because of the differences in regulations and practices by country. Hence, it is essential that studies assess which definitions make it possible to accurately ascertain stillbirths, given the country context, and that they report clearly how they defined early or late fetal deaths to facilitate international research and comparisons.

2) Late fetal death or stillbirth

Stillbirth is a fetal death at or after a pre-defined gestational age threshold. For comparative studies in high-income countries with good ascertainment, EURO-Peristat recommended using a threshold of 24 completed weeks of gestation or more or if gestational age is missing the inclusion criteria is a birthweight of 500 grams or more (Smith, 2018). This makes it possible to have a comprehensive measure of the potential burden of stillbirth while avoiding problems of comparability in the ascertainment of fetal deaths at less than 24 completed weeks of gestation. For studies in lower-resource countries or high-income countries where a higher threshold is used for stillbirth definitions or in comparisons over a longer time period, this threshold should be 28 completed weeks of gestation and over (or if gestational age is missing, a birthweight of 1000 grams). The threshold values relate to the gestational age at delivery, and not the gestational age at which the fetal death occurred. Recording the

gestational age at death has been proposed by some (Joseph, 2018), but is considered unfeasible by others since this information is not systematically known (Smith, 2017).

It is important to note that established thresholds, as noted above, will exclude a significant number of stillbirths (estimated at 15% at 22 to <24 weeks of gestation and 20% at 24 to <28 weeks of gestation). Furthermore, this creates discrepancies with the management of live births for which these thresholds are not applied (Smith, 2018).

Screening and termination policies and practices in individual countries determine whether terminations for fetal anomaly are carried out after the gestational age threshold for defining stillbirths. There are also differences in legislation about termination of pregnancy and the extent to which terminations are reported as stillbirths and can be distinguished from them. These differences can have a major influence on reported stillbirth rates at early gestations, particularly from 22 weeks of gestation to less than 24 weeks of gestation. Furthermore, the large variation in the timing of screening and regulations in Europe makes it necessary to exclude termination for congenital anomalies from stillbirth rates in cross-country comparison studies. However, it is recommended to include terminations for other reasons (maternal or fetal complications e.g. very early rupture of membranes, fetal growth restriction) because of differences in practices between countries (Monier, 2018). Information should be ascertained on how terminations are reported and recorded in all data sources (Blondel, 2018).

Further analyses of stillbirths may be important; these could be presented by GA sub-group, birthweight sub-groups and timing of stillbirth (antepartum/intrapartum). Analysis by cause of death may also be warranted in order to identify stillbirths associated with congenital anomalies, hypertensive disorders and growth restriction and/or infection. Several classifications of cause of death are proposed in the literature and most include GA sub-groups. However, in general, no cause can be attributed in between 20 and 30% of cases of stillbirths (Reinebrant, 2018). The availability of autopsies will affect the percentage of unknown causes.

Background rates in the general population

In Europe in 2015, of 33 countries providing data on stillbirth rates, these were: at ≥22 weeks of gestation, the median rate was 3.7 per 1000 births with a range from 2.4-7.3 and an inter quartile range (IQR) of 3.4-4.44; using a threshold of 24 weeks of gestation, the median rate was 3.4 per 1000 total births (range 1.8-6.9, IQR: 3.0-3.9) and, finally, with a threshold of 28 weeks of gestation the median rate was 2.7 per 1000 total births (range 1.4-5.7, IQR: 2.4-3.1) (Zeitlin, 2019).

3) Early fetal death or miscarriage

Miscarriages are fetal losses before the gestational age or birthweight threshold for defining stillbirth. As such, the definition of this indicator varies by country. Miscarriages which occur early in pregnancy are often not clinically recognized and not recorded in register-based data sources. Moreover, women

might not declare the occurrence of a miscarriage or it might be managed in emergency room or in primary healthcare which leads to underestimation of miscarriages in pregnancy studies using maternity data. However, some databases such as the Danish registries capture early miscarriages (from gestation weeks 7-10) that require any hospital contact including emergency room contacts.

Background rates in the general population

The proportion of miscarriage is estimated as high as 31%, though it decreases to approximately 10% when considering only miscarriages occurring in clinically recognized pregnancies (Magnus, 2019). The proportion of second-trimester miscarriages (up to 20 weeks of gestation) is less than 1% (Wyatt, 2005). It is important to be aware that the denominator to estimate the proportion of miscarriages should be, in theory, all detected pregnancies, however as very early miscarriages are difficult to identify this denominator is likely to be inexact. The definition of the denominator should be explicit in all studies.

4) Ectopic pregnancy

Ectopic pregnancy (EP) is a pregnancy in which the developing blastocyst becomes implanted at a site other than the endometrium of the uterine cavity. The most common extra uterine location is the fallopian tube, which accounts for 96% of all ectopic gestations (Bouyer, 2002). It is presented as an acute event that can be life threatening and it is an important cause of maternal morbidity and mortality. EP, infertility and assisted reproductive technologies (ART) are interlinked as EP increases the risk of infertility, which leads to the use of ART, which in turn increase the risk of EP. EP may be recorded in databases, but is often not done; especially when EP leads to a miscarriage, only the latter is recorded. Because of this, some studies report both outcomes combined.

Background rates in the general population

It is difficult to estimate the prevalence of EP. Early pregnancy failures that do not result in delivery or hospitalization are often not counted in the denominator of ectopic pregnancy. The proportion of EP has been reported using different denominators that are difficult to compare (1000 reported pregnancy, 1000 women of reproductive age, 1000 total births). Furthermore, miscarriage might lead to an underestimation of EP. The overall prevalence of EP is 1–2 % in the general population, and 2–5 % among patients who have utilized assisted ART (Barnhart, 2009; Marion, 2012).

5) Other termination of pregnancy

Other termination of pregnancy includes medical termination for maternal reason, and elective termination defined as an artificial interruption of pregnancy that can occur for non-medical or social reasons.

4.1.2.2. Live birth and infant outcomes

A live birth is defined as the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which, after such separation, breathes or shows any other evidence of life, such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached; each product of such a birth is considered live born.

The live birth and infant outcomes are those of most relevance for describing birth outcomes in research on maternal and child health (Annex 5). According to the scoping review (Annex 5), the most discordance on core outcomes was observed for recommendations concerning neonatal/infant morbidity. A proposed definition is given for all outcomes except neonatal morbidity for which there is no operational international definition.

1. Neonatal death / Infant death
2. Preterm birth (birth before term)
3. Sub-optimal fetal size and growth (small for gestational age, fetal growth restriction, large for gestational age)
4. Neonatal morbidity

1) Neonatal / Infant death

Definition

A neonatal death is a death on day 0 through day 27 after live birth (or before 28 completed days). Early neonatal deaths are those occurring from day 0 to day 6 and late neonatal deaths from day 7 to day 27. Infant death is defined as death occurring before one year of age after live birth. Although it extends beyond the perinatal period, infant death is included as a core outcome element because it reflects the longer-term consequences of perinatal morbidity. It is particularly relevant for very preterm or low birthweight babies or babies with congenital anomalies, as they remain at higher risk of death throughout their first year of life (MacDorman, 2014; Watkins, 2016)

Issues affecting comparability across geographic zones and time periods

There are no agreed guidelines for interpreting signs of life based on the above description and there is great variation in practice (Smith, 2017). Differences in interpretations of signs of life can have a substantial impact on neonatal mortality rates and international organizations have recommended using lower gestational age (or birthweight) cut-offs for reporting to ensure comparability (≥ 22 completed weeks of gestation, Euro Peristat, WHO, ≥ 28 completed weeks of gestation or ≥ 1500 g for international comparisons or in low-income countries).

Neonatal mortality can be reported as a cohort rate or an annual rate. For medication studies, neonatal mortality will be based on cohort rates (number of neonatal deaths for births in a given year,

expressed as a rate per 1000 live births in the same year). When cohort data is not available, annual data will be used (number of deaths occurring during the neonatal period occurring during the year, expressed as a rate per 1000 live births in the same year). It is recommended to present neonatal death subdivided by timing of death, gestational age, birthweight and by plurality (see Annex 5).

As described above in the section of stillbirth, a major concern in international classifications is misclassification of stillbirths as neonatal deaths and vice versa. One way of resolving this problem isto establish a cohort of pregnancies where the fetus is alive at onset of labour or arrival in hospital and report both intrapartum deaths and deaths immediately after birth (see additional age classifications, below) (Smith, 2017). However, this approach may not feasible for all population-based studies.

Data sources, linkage and ascertainment

Vital statistic certification and cause of death certificates are used to provide information on the neonatal mortality rate and on the causes of neonatal death. Some countries have specific neonatal cause of death certificates which include perinatal information (such as gestational age and birthweight). However, these certificates are not always linked with birth records and, in some data sources, neonatal deaths are ascertained using birth registers or hospital data. These sources may not have complete data on out-of-hospital deaths after discharge from the neonatal hospital. Information on whether death certificates are linked to birth records and the procedures for ascertainment of out of hospital deaths should be stated for all data sources. Information should also be provided on linkage of records for transfers between hospitals (whether this is done and the accuracy of linkage), which is needed to comprehensively report on outcomes of very preterm infants who are hospitalised for long periods, often with multiple inter-hospital transfers.

Background rates in general population

In Europe in 2015, of 33 countries providing data on neonatal mortality rates at ≥ 22 completed weeks of gestation, the median rate was 2.2 per 1000 live births (range:0.7-4.4; IQR:1.8-2.7). 26 countries could provide data on neonatal mortality rate with a cut-off at 24 completed weeks of gestation, likely to be more comparable over countries: the median was 1.7 per 1000 live births (range 0.5-4.3, IQR: 1.2-2.2) (Zeitlin, 2019).

2) Preterm birth

Preterm delivery is defined as delivery before 37 completed weeks of gestational age (or fewer than 259 days). This definition of preterm birth is recommended by the WHO (March of Dimes, 2012) and is used in the ICD-coding. In epidemiological studies, it is not recommended to use the diagnostic code for preterm birth, but instead use recorded gestational age. However, in case the gestational age is not available, the ICD codes might be used, preferably using the finest categorization available within the

ICD code (extremely preterm/ very preterm/ moderate to late preterm), so the extremely and very preterm that carry a higher risk of neonatal death can be identified.

Classification

Preterm birth is classified on the basis of GA by the extent of prematurity in the following subcategories: 22+0 to 27+6 weeks of gestation (extremely preterm), 28+0-31+6 weeks of gestation (very preterm) and 32+0-36+6 weeks of gestation (moderate to late preterm) (World Health Organization, 2018a). Some researchers use an additional group for babies born between 34 and 36 weeks of gestation, labelled "late preterm births" (Raju, 2017; Raju, 2006). To reflect the continuity of risk across the GA spectrum, the terminology "early term" is now used for births at 37 and 38 weeks of gestation.

Preterm births can be further classified by mode of onset: spontaneous onset and clinician-initiated deliveries. About two-thirds of preterm births occur following spontaneous preterm labour or preterm premature rupture of membranes, while others result from a decision of the provider because of fetal or maternal complication. Other classifications of preterm birth are based on the aetiology of the preterm delivery; these may be relevant when investigating specific exposures that may affect fetal growth which is a major indication for clinician initiated preterm birth, for instance.

Measuring gestational age

The definition of gestational age was provided above (section 1.1). The method for determining gestational age should be noted as this can influence the preterm birth rate. On average, compared to estimates based on reliable LMP, use of US dating leads to a higher preterm birth rate because the LMP estimates assume that all women have a 28-day cycle whereas average cycle length is actually slightly longer. However, errors are reduced when US is used and gestational age errors – which have more influence at the extremes of the distribution - increase the preterm birth rate. When there is high error in GA estimate, using US will reduce the preterm birth rate. The accuracy of measurement is improved when there is early US.

Issues affecting comparability across geographic zones and time periods

In addition to GA determination, other factors affect comparability of preterm birth rates. When defining and presenting preterm birth rates, it is important to specify whether rates include or exclude stillbirths. Most studies use rates computed on live births, as recommended in the WHO definition. Including stillbirths has a small impact on preterm birth estimates and country rankings except in low income countries with higher stillbirth rates and for very preterm birth rates. Another source of differences in rates is the inclusion or exclusion of multiple births. Most multiples are born before full-term, around 60% being born preterm. Multiples are about 3% of all births, but constitute about 30% of births before 34 weeks of gestation, 20% of late preterm births and 5% of early term births. Differences in the recording of births and deaths, known to strongly impact on perinatal mortality rates, are less

problematic for preterm birth rates (Delnord, 2017). Nonetheless, it is important to define a lower gestational age threshold for computing preterm birth rates when comparing across countries. The Euro-Peristat project uses the threshold of ≥22 weeks of gestation for all indicators based on stillbirth and live births.

Background rates in the general population

In Europe in 2015, of 33 countries providing data to Euro-Peristat on preterm birth rates at ≥ 22 completed weeks of gestation, the median rate was 6.5 per 100 total births (range: 4.2-10.6; IQR:5.1-7.7) (Zeitlin, 2019).

3) Small for gestational age and fetal growth restriction

Definition

Fetal growth restriction (FGR) refers to restricted growth with respect to each fetus' genetic potential, but this definition cannot be measured. Therefore, to capture sub-optimal growth during pregnancy, a proxy measure based on whether the fetus or newborn is small for its gestational age (SGA) is used, most often defined as an estimated fetal weight or birthweight less than the 10th percentile for gestational age based on an agreed upon growth chart. When fetal size is assessed during pregnancy, a measure of abdominal circumference under the 10th percentile may also be used instead of estimated fetal weight.. The 10th percentile is selected because this threshold is associated with higher mortality and morbidity in many studies. This definition is recommended for screening purposes during pregnancy (Committee on Practice Bulletin, 2015; McCowan, 2018) and used for epidemiological and clinical surveillance after birth. There is less consensus on the thresholds for defining severe SGA, but often <3rd percentile or <2 standard deviations is used. Sex-specific and geographic growth charts are used when SGA is based on birthweight for gestational age, but charts for estimated fetal weight are most often not sex-specific.

SGA can be determined from birthweight or estimated fetal weight. However, other terminology can be used; The ACOG uses the term SGA for birthweight <10th percentile and FGR to designate fetuses with an estimated fetal weight <10th percentile. Unlike ACOG, we use the term FGR to designate sub-optimal growth for pathological reasons.

Definitions of FGR usually require criteria in addition to having an estimated fetal weight <10th percentile, such as decelerating growth (also called poor interval growth velocity) after detection of SGA or other clinical signs including oligohydramnios, abnormal UA Doppler. Many definitions include severe SGA (<3rd or 5th percentile or ≤2 SD) as a criterion for FGR.

Issues affecting comparability across geographic zones and time periods

The main question for defining SGA and comparing SGA rates is the choice of growth chart. There are three main types of growth charts: intrauterine (refers to ultrasound biometric measurements and

estimated fetal weight computed from these measures), newborn (birthweight) and modelled (customised charts which use models based on intrauterine charts). References refer to growth charts that describe an unselected population (i.e. the aim is to be descriptive) while standards (or norms) are growth charts of a population with ideal growth, selected to be low risk (i.e. with a prescriptive aim) (Ananth, 2019). However, these terms are not used with consistency in the literature and there are no consensual criteria for defining ideal populations among researchers developing prescriptive growth charts (Ohuma, 2018). Therefore, while there is general agreement about using the 10th percentile to define SGA (and either the 5th or 3rd centile to define severe SGA), there is no agreement about which growth chart should be used. Given the absence of an international consensus, at this time, it is preferable to use charts in local or national use for defining SGA or, in international studies, to define an explicit protocol for the selection of charts which includes a validation component. The chart used in a study should always be explicit.

Background rates in the general population

The prevalence of SGA varies according to the growth references used. One of the difficulties in comparing rates of SGA across populations is that SGA is a distributional measure. When references are adapted to the local populations, the expectation is that 10% of births will be below the 10th percentile. Average country birthweight differs across countries. It is important to consider country when using SGA references or absolute measures like low birthweight <2500 g.

4) Neonatal morbidity

Definition

Guidance is lacking for defining neonatal morbidity (Lebreton, 2020). Mortality indicators focus on the most severe situations and a full measure of the health of newborns requires an assessment of morbidity. Furthermore, morbidity at birth is an important prognostic factor for future health and development. However, work is needed to assess which neonatal morbidity measures are relevant for pharmacoepidemiology research. The neonatal period is defined as the first 28 days of life (<28 completed days) and infancy covers the first year. However, some studies define neonatal morbidity to include events occurring in the first 28 days of life and also beyond if morbidity occurs during the neonatal hospitalisation. These broader definitions aim to include events associated with pregnancy and birth that lead to prolonged hospitalisation. This definition also has pragmatic underpinnings, as the timing of morbidity (unlike mortality) is not included in hospital discharge records;

Another key problem is the absence of a consensual definition for many of the morbidity indicators. There is likely wide variability in both the definitions and ascertainment of all these proposed morbidity indicators in routine data sources. One study by the Euro-Peristat project comparing the Apgar

score, for which there is a common definition, found marked differences in score distributions between European countries that were not correlated with health outcomes (Siddiqui, 2017).

One area where there is a good potential for development is morbidity indicators from hospital discharge data. In high-income countries, hospital discharge data are routinely collected and hospital activity is registered using similar nomenclatures. While there are many challenges with using hospital discharge data for epidemiological studies, principally because of the heterogeneity of coding practices, they are increasingly used in research (Lain, 2012; Knight, 2019). Indicators established from hospital data have been used in research, confirming the feasibility of this approach (Lebreton, 2020).

One indicator derived from hospital data to measure complications among low risk infants was recently endorsed in the United States by the National Quality Forum and adopted by the Joint Commission (California Maternal Quality Care Collaborative, 2020).

At this time, it is not possible to make evidence-based recommendations about neonatal morbidity indicators for international comparative research. EUROlinkCAT is evaluating length of stay in hospital, diagnoses and surgery/ procedures performed as indicators for morbidity (EUROlinkCAT, 2020a).

4.1.2.3. Congenital anomalies

Congenital anomalies (CA) include any structural or functional anomalies, chromosomal anomalies and genetic syndromes, diagnosed in the fetus, newborn or child. Collectively, CA are a major cause of perinatal mortality and childhood morbidity and disability. Minor anomalies are those that are considered to have less medical, functional or cosmetic consequences, and are often excluded from counts of CA because they are common and inconsistently diagnosed and recorded

The identification of CA in registers and data sources should be based on the use of validated algorithms using ICD or equivalent codes, as appropriate (EUROCAT, 2013) (annex 6). A congenital anomaly registry establishes the diagnosis through cross referencing multiple data sources or consulting medical records directly. If using healthcare databases rather than a registry, it may be necessary to establish and validate algorithms e.g. include a case only if there is a record of a surgical procedure, or only if there are at least two independently-coded records of the same diagnosis (Palmsten,2014).

In the definition of CA, the following elements need to be considered:

- The inclusion of all CA coded to Q chapter of ICD-10 (or equivalent ICD-9) but excluding a recognized list of minor anomalies e.g. EUROCAT list (Annex 6); data on minor anomalies may be collected and analysed separately where relevant, taking into account the potential for bias from diagnostic inconsistency and reporting differences between data sources.
- The inclusion of terminations of pregnancy for fetal anomaly (TOPFA) at any gestational age;

- The inclusion of diagnoses up to at least 1 year of age for non-externally visible anomalies such as Congenital Heart Disease (CHD);
- The inclusion of fetal deaths from 20 weeks of gestational age with congenital anomaly (EUROCAT, 2013).
- The exclusion of cases diagnosed with chromosomal anomalies and genetic syndromes (i.e. not potentially related to pregnancy medication exposure); data on chromosomal/genetic syndromes may be collected but should be analysed separately.
- The exclusion of cases with conditions associated with prematurity that are not true CA (e.g. among hydrocephalus and among CHD cases);
- Multiple pregnancies might be analysed separately, especially if the medication exposure is related to multiple birth, as the risk of CA in monozygous twin is higher. In addition, multiple pregnancies can be informative for concordance

Analysis should include all babies with CA (cases), as described above, as well as all cases per CA subgroup according to a pre-specified list of subgroups e.g. EUROCAT list of subgroups (Annex 6). A case should be counted once for each subgroup, but can be counted several times in different subgroups e.g. a baby with spina bifida and omphalocele is counted once in spina bifida, once in omphalocele, once in neural tube defects, once in abdominal wall defects, and once in total CA. A case with a ventricular septal defect (VSD) and pulmonary valve stenosis should be counted once in "all anomalies", once in "cardiac", once in "VSD", and once in "pulmonary valve stenosis"; a case with encephalocele and renal dysplasia should be counted once in "all anomalies", once in "central nervous system anomalies", once in "neural tube defects", once in "encephalocele", once in "urinary anomalies" and once in "renal dysplasia". It follows that the number of cases in different subgroups cannot be added together to find the total number of cases, as one case can be counted in more than one subgroup.

The purpose of a "classification" system is to group together anomalies which share etiological or clinical characteristics. There is a balance to be struck a) between "lumping" together heterogeneous sets of anomalies and "splitting" so finely that there are few cases in each group and b) between creating groups based on great precision and accuracy of diagnosis and coding and creating groups which take into account what can be realistically found in medical records and regional or national databases for most cases. EUROCAT Classification into subgroups is presented in Annex 6.

It is well established that teratogens tend to cause a risk of specific CA, rather than CA in general, and therefore that studying all CA combined may obscure the risks of specific CA (Mitchell, 2003). Besides studying CA as a single group, CA should be studied stratified by standard subgroups (Annex 6). If statistical power is insufficient to study specific subgroups, data (numbers of cases) should be presented by subgroup for future meta-analyses. Studies may also focus on specific CA subgroups

due to a prior hypothesis or signal. A case list showing each anomaly should be presented, to facilitate meta-analyses and to identify unusual anomaly patterns.

For denominators or non-malformed comparator population, all live births and stillbirths need to be counted. It is not necessary to include TOPFA in the denominator as they are a very small number compared to births. Terminations for any reason (including social) should not be included in the denominator as they are numerous in some countries and not examined for CA. The definition of standard prevalence rates (Total Prevalence, Birth Prevalence, Livebirth Prevalence) is given in Annex 6.

Background rates in the general population

According to EUROCAT (years 2011-2017), the prevalence of all CA (including genetic anomalies) per 10,000 births with 95% is 204.56 (confidence interval 203.31 - 205.82) in live births, 4.50 (4.32 - 4.69) in still births, 50.70 (50.08 - 51.33) in TOPFA, and 259.76 (258.36 - 261.18) in all combined (live births, still births, and TOFPA) (EUROCAT, 2020). Prevalence rates per subgroup are given in Annex 6. Public health indicators in Europe regarding perinatal mortality due to CA, prenatal diagnosis, TOPFA, and surgery, are given in EUROCAT (EUROCAT, 2014).

4.1.2.4.Long-term neurodevelopmental outcomes

Fetal brain development begins early in gestation and extends beyond the period of organogenesis. Alterations in the development of the brain can convey substantial and lifelong implications for the child. Often a secondary outcome, the impact on brain development from a prescribed medication exposure in the womb has been evidenced to have deleterious consequences and should have a more central focus in research and regulatory decision making. Long-term neurodevelopmental outcomes should be considered as a minimum in pregnancy safety studies of medications for which the mechanism of action might be related to a neurodevelopmental impact, for example a medication known to act upon the central nervous system and for, any medication that is associated with increased risk of major congenital anomalies (e.g., isotretinoin). Medications can be administered both as chronic treatments for which a woman might be exposed throughout pregnancy or as short treatments (e.g. acute diseases or episodes). This means that the developing brain may be exposed throughout gestation or for a single or multiple short period and that different patterns of exposure may convey a different pattern of impact on the brain and its later functioning (Adam, 2000).

Neurodevelopment is a wide-ranging term which covers a multitude of functional outcomes. It refers to early child development such as the attainment of milestones, through to the cognitive functions of adults and even older adults as the brain evolves throughout the lifespan. Such diversity means that

there are many outcomes which fall within the category of neurodevelopment and even more numerous ways to measure these outcomes. There are a number of neurodevelopmental outcomes which are diagnosed through health services and therefore have ICD-10 or ICD-9 codes in existing data sources or registers (Annex 7) and these include Autistic Spectrum Disorder and Attention deficit hyperactivity disorder (ADHD), which are frequently available in population datasets. However, there are other neurodevelopmental outcomes which may not routinely be reviewed or be reported within healthcare and therefore are less frequently recoded in population datasets (e.g. child IQ, memory or language development/functioning), and other methodologies such as prospectively ascertained observational cohorts are likely better placed for the investigation of these outcomes. Despite a degree of over lap between the different domains of neurodevelopment each should be viewed as a related but separate entities, which individually require investigation. For example, intellectual functioning in children and young people with autism varies greatly across individuals and therefore having an autism diagnosis cannot predict the level of intellectual functioning. Also, having intellectual difficulties may place the child at a higher risk of an additional diagnosis of autistic spectrum disorder but will occur in less than a quarter of those with learning or intellectual disability (Deb, 1994). The pattern of functional difficulties noted following an exposure in utero will depend on the pattern of impact the exposure has had on the brain during development. Whilst there can be overlap across different neurodevelopmental outcomes, the pattern of functional deficits and brain insult varies remarkably across different exposure types. Therefore, it is important that a number of different neurodevelopmental outcomes are investigated for a particular exposure; and this may require a collaboration across different methodological types for best results.

Most of these outcomes are diagnosed within the first five to ten years after birth, so a long follow-up in the data source/register will be required to sample these outcomes. The age of ADHD diagnosis is around 7 years in most countries (Kieling, 2010) and intellectual disabilities following start of primary school (6-7 years depending on the country); although severe diagnosis may occur at younger ages. As the brain develops during the post-natal years it is expected to undertake more and more complex skills and therefore children can display deficits in areas they previously were in line with their peers for. An example of this is expressive language development, which at the age of 1 year of age is not very well developed in any child however as the child develops rapid improvement in ability is expected and if this does not occur the child will begin to differentiate from their peers. Executive functioning is a critical set of skills which surround planning, impulse regulation, emotional control, motivated action as well as directing and integrating the outputs of other areas of cognitive functioning for specific tasks. These skills are susceptible to the impact of neurobehavioral teratogens and are not fully developed until early adulthood (Rasmussen, 2005). Behavioural outcomes are not often included in pregnancy drug safety studies since these are difficult to identify and measure through population-based databases.

Three neurodevelopmental outcomes were notable in their availability in the population datasets and are covered in more detail below. Their inclusion is more one of pragmatism rather than priority and they should not be considered more important than other neurodevelopmental types. Further, it should be considered that disruption of child brain development leads to a vast number of different patterns of outcome and therefore not every medication exposure, even if it did alter fetal brain development, would lead to an impaired pattern of behaviour which would meet the diagnostic threshold for either autism spectrum disorders, ADHD or intellectual disability. Therefore, more than for any other outcome, the contribution of population datasets must not be in isolation from data from other sources such as blinded IQ assessments in cohort studies or educational examination results which may be available through the linking of datasets where possible.

The most frequently reported long-term neurodevelopmental outcomes identified in population datasets were:

- Attention deficit hyperactivity disorder
- Autism spectrum disorder
- Intellectual disability or disorders of intellectual development

ADHD (Annex 8) is characterized by a persistent pattern (at least 6 months) of inattention and/or hyperactivity-impulsivity, with onset during the developmental period, typically early to mid-childhood (Faraone, 2015). The degree of inattention and hyperactivity-impulsivity is outside the limits of typical variation expected for age and level of intellectual functioning and significantly interferes with academic or social functioning. Inattention refers to significant difficulties in sustaining attention to tasks that do not provide a high level of stimulation or frequent rewards, distractibility and problems with organization. Hyperactivity refers to excessive motor activity and difficulties with remaining still, most evident in structured situations that require behavioural self-control. Impulsivity is a tendency to act in response to immediate stimuli, without deliberation or consideration of the risks and consequences. The relative balance and the specific manifestations of inattentive and hyperactive-impulsive characteristics varies across individuals, and may change over the course of development. To be diagnosed, the behaviour pattern must be clearly observable in more than two settings and impact on everyday functioning.

Autism spectrum disorder (Annex 9) is characterized by persistent deficits in the ability to initiate and to sustain reciprocal social interaction and social communication, and by a range of restricted, repetitive, and inflexible patterns of behaviour and interests (Masi, 2017; Ousley, 2014). The onset of the disorder occurs during the developmental period, typically in early childhood, but symptoms may not become fully manifest until later, when social demands exceed limited capacities. Deficits are

sufficiently severe to cause impairment in personal, family, social, educational, occupational or other important areas of functioning and are usually a pervasive feature of the individual's functioning observable in all settings, although they may vary according to social, educational, or other context. Individuals along the spectrum exhibit a full range of intellectual functioning and language abilities.

Intellectual disability or disorders of intellectual development (Annex 10) are a group of etiologically diverse conditions originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately two or more standard deviations below the mean (approximately less than the 2.3rd percentile), based on appropriately normed, individually administered standardized tests (Centers for Disease Control and Prevention, 2020). The term learning disability may also be used interchangeably with intellectual disability. Where appropriately normed and standardized tests are not available, diagnosis of disorders of intellectual development requires greater reliance on clinical judgment based on appropriate assessment of comparable behavioural indicators and will likely mean that only the most severe cases are identified (for example if the child is non-verbal). It should be considered that a reduction in IQ abilities, but not to the level required for a diagnosis of a formal intellectual disability, can still have a substantial impact on a child's educational attainment and future occupation and that such an impact is unlikely to be detected utilizing ICD codes as the routine clinical assessment of IQ does not occur.

The availability of other outcomes in population datasets

There are a number of databases which include infant developmental assessments, often in the form of clinician or parent completed checklists or questionnaires. Whilst these are not considered to be a core outcome element here, due to their limited availability across databases, researchers should consider them where possible. These measures are provided routinely to all families and therefore provide data on all who complete them; which is in contrast to diagnosis data where only those referred and who obtain a diagnosis are known about. Additionally, certain reviewed datasets have the capacity to link to educational outcome data or data on special educational needs. It is of note that, the EUROlinkCAT study looked at educational outcomes, including special educational needs for children with and without congenital anomalies (EUROlinkCAT, 2020b) and have found large differences in education data across countries, making it impossible to standardise this outcome across the European datasets. However, when working within one or more comparable datasets information regarding examination results could provide useful data for a multifacested approach for the detection of impaired child development following medication exposures in utero.

Background rates in the general population

There is large variation in the backgrounds rates of the three core neurodevelopmental outcomes across countries. In childhood, ADHD is among the most common psychiatric disorders with a prevalence rate of 2–7 % (Sayal, 2018), with an additional 5% of children falling just outside of the diagnostic criteria

but who experience symptoms (Sayal, 2018). The prevalence of ADHD declines with age and in adults across twenty countries was recently estimated at 2.8%, with a range between 1.4 - 3.6% (Fayyad, 2017). Regarding autism spectrum disorder, in Europe, the programme Autism Spectrum Disorders in the European Union (ASDEU), scrutinised 631,619 children, with an average estimated prevalence of 12.2 per 1000 (one in 89) children aged 7-9 years. Overall ASD prevalence estimates varied among European countries, from 4.4 - 19.7 (percentiles 10 and 90) per 1000 aged 7-9 years (Autism Spectrum Disorders in the European Union, 2018). Rates of intellectual disability vary from country to country but generally an estimate of 10/ 1000 is accepted (Maulik, 2011). Estimates are likely higher when formal IQ assessments have been utilized in the diagnostic process (Maulik, 2011).

4.1.2.5. Other infant/childhood outcomes

Medication exposure during pregnancy may be responsible for other long-term effects; they are generally not apparent at birth and diagnosed several months or years after birth. No risk period during pregnancy has clearly been identified for the infant and childhood outcomes, so these risks may concern all periods of exposure during pregnancy. The infant/childhood outcomes after prenatal medication exposure depend on the pharmacological action of the medication and should be considered as part of the risks associated with in utero exposure. Such outcomes can sometimes be predicted thanks to the pharmacological properties of the medication, preclinical and clinical data, and predictors from juvenile toxicity studies.

The document describes some examples of infant/childhood outcomes, but the list is not exhaustive. These outcomes can be identified in existing data sources and registers through codes in ICD-9, ICD-10 or others, as appropriate.

The first example of “other childhood outcome” is the occurrence of **infant/childhood infections** (Annex 11). In particular, the occurrence of recurrent or persistent infections, severe infections requiring hospitalization or unusual infections that do not usually cause problems in most people at the patients ‘age. Prenatal exposure to immunosuppressive medications can impair or delay the maturation of the immune system resulting in an increased susceptibility to infections in the offspring (Palosse-Cantaloube, 2016). Immunosuppressive medications include glucocorticoids, cytostatics, tsDMARDs (targeted synthetic disease modifying drugs), bDMARDs (biologic disease modifying drugs), csDMARDs (conventional synthetic disease modifying drugs), and drugs acting on the immunophilins. The duration of the effect depends on the elimination half-life of the medication. For example, some antibodies require long times to be eliminated, which extends the infant/child immunosuppressive period (Djokanovic, 2011).

The second example is **childhood long term digestive effects** (Annex 12). These effects have been identified after prenatal exposure to anticholinergic medications (Benevent, 2019). The cholinergic system plays an important role in gastrointestinal function. The activation of the digestive acetylcholine

muscarinic receptor leads to smooth contractions of the muscle and to exocrine secretions. Many medications, from various pharmacological classes, are competitive antagonists of cholinergic muscarinic receptors. This antagonist effect is called atropinic property. It is mostly a side property that can cause digestive adverse effects through a decrease in both peristalsis and secretions, leading to constipations, abdominal pains or even intestinal atonies and bowel obstructions. Digestive disorders in fetuses and newborns have already been widely described in both animals and humans. Moreover, the blockage of the muscarinic receptors during the implementation of the fetal cholinergic system might increase the number and/or the sensitivity of the cholinergic receptors, leading to long-term digestive effects (Benevent, 2019).

The third example is **hearing loss**, also known as hearing impairment, that is a partial or total inability to hear (Annex 13). Hearing loss may be caused by a number of factors, including: genetics, ageing, exposure to noise, some infections, birth complications, trauma to the ear, and certain medications or toxins. The ear development extends from the 4th to the 30th week of pregnancy; after this, the fetus can react to external auditory stimuli. Therefore, in utero exposure to ototoxic medications could lead to hearing impairment. Certain infections during pregnancy, such as cytomegalovirus, syphilis and rubella, may also cause hearing loss in the child (Golderis, 2014; Cohen, 2014; Kenna, 2015). Hearing loss in infants, even mild, negatively impacts language and speech development, and delays social-emotional development. Evidence tends to indicate that the earlier an intervention is performed (before 3 or 6 months-old), the more the language skills improve.

Lastly, cancers, hormonal disorders and impairment of fertility can be considered. Prenatal exposure to medications assimilated to endocrine disrupting can cause serious long term and transgenerational effects. These effects are mediated by the endocrine system. Diethylstilbestrol (DES), a non-steroidal oestrogen, which is considered as a model of endocrine disrupting, induces clear cell carcinoma among young women, genital anomalies, infertility, etc (Tournaire, 2014). Long term adverse effects could affect at least two generations. Specifically, long term endocrine effect should be considered when the medication is a hormone (Goodman, 2011).

4.1.3. Maternal outcomes

Maternal outcomes are health outcomes that occur during pregnancy. These include maternal death and problems that could arise during pregnancy and pre-existing problems that could lead to complications during pregnancy.

Maternal death is defined as the death of a woman while pregnant or within 42 days of the termination of pregnancy, irrespective of the duration and site of the pregnancy, for any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes (WHO,1992). Moreover, late maternal death has more recently been defined by the WHO to characterize maternal death occurring between 42 days and one year after the termination of pregnancy (WHO,

2012). Briefly, in France the maternal mortality ratio before 42 days of termination of pregnancy was estimated to be 8.1 (95% CI: 7.9-10.4) per 100,000 live births between 2013 and 2015. (INSERM, 2021). Maternal illnesses and complications include gestational diabetes, pre-eclampsia; mode of delivery (induction of delivery, caesarean delivery), maternal hypoglycaemia, infections during pregnancy, severe peripartum infections, postpartum haemorrhage/bleeding and pregnancy-associated complications. In this report, only two conditions related to severe maternal morbidity in Europe are presented: gestational diabetes and pre-eclampsia. These maternal conditions could also be investigated as confounders of the association between a medication exposure and a pregnancy outcome (see section 4.3.5).

4.1.3.1. Gestational diabetes

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance with onset or first recognition in pregnancy (Alberti, 1998). The most important difference with regards to the definition relates to the oral glucose tolerance test (OGTT) testing used (75 vs 100 mg glucose) and the Fasting plasma glucose cut(s) used to define GDM (Annex 14). Efforts have been made to harmonize these clinical definitions, for instance by the Brighton Collaboration Gestational Diabetes Working Group (Kachikis, 2017). These case definitions use the Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) definitions for gestational diabetes are outlined in the Annex 15 (Kachikis, 2017).

GDM is a clinical syndrome characterized by the absence of a pre-gestational diabetes diagnosis AND the identification of sustained hyperglycaemia during pregnancy not due to other known causes (i.e. corticosteroids, beta-mimetic, etc.). Pre-gestational diagnosis is defined by

i) a previous diagnosis of diabetes while not pregnant, or

ii) a first trimester hemoglobin A1c level of ⩾ 6.5% (47.5 mmol/mol), or

iii) a first trimester fasting blood glucose 126 mg/dL/⩾7 mmol/L

The major criteria used to identify GDM is via the administration of the OGTT. The test consists of a blood test two hours after an administration of a liquid containing typically 75 g glucose (or 100 g, depending on the guideline) (Kachikis, 2017). However, the diagnostic criteria for GDM based on cut-offs for fasting plasma glucose levels and plasma glucose levels after OGTT vary across country guidelines (Kachikis, 2017).

The most suitable data sources to evaluate GDM are provided in Annex 14.

Background rates in the general population

Around 5% of pregnant women in Europe are affected by GDM (Eades, 2017). Across continents, the prevalence of GDM varies more markedly (from 1% to <30%), owing to lack of consensus on diagnostic criteria, differing antenatal screening practices, genetic variation, as well as to differences in maternal characteristics such as ethnicity and life-style (McIntyre, 2019).

4.1.3.2. Preeclampsia

Hypertensive disorders of pregnancy are a leading cause of maternal and infant morbidity and mortality. However, the aetiology of these disorders, in particular of preeclampsia, remains not fully understood. Hypertensive disorders include pre-existing and gestational hypertension, preeclampsia, and eclampsia.

Braunthal and Brateanu have recently shown that differences in case definition of hypertensive disorders of pregnancy exist across guidelines (Braunthal, 2019). However, efforts have been made to harmonise these clinical definitions, for instance by the GAIA (Alberti, 1998). The most important difference in several definitions is whether or not "Proteinuria" is part of the definition. "Proteinuria" is not part of the International Society for the Study of Hypertension in Pregnancy definition, used by most countries in Europe (Brown, 2018). The GAIA case definitions are outlined in Annex 15 (Alberti, 1998). Briefly, preeclampsia is defined as development of new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND new onset proteinuria after 20 weeks of gestation. Codes to identify preeclampsia in the data sources are presented in Annex 15.

Background rates in the general population

The prevalence of preeclampsia in Europe ranges from 2.8% to 5.2% base on two Nordic studies (Umesawa, 2017).

4.2. Ascertainment of medication exposure and aetiological window

In this section, we present how medication exposure can be ascertained and measured using population data sources and how exposure can vary according to medication pharmacokinetic characteristics. Then, the different relevant aetiological windows, as well as important considerations to the time of window of medication exposure will be described.

4.2.1. Medication exposure

Medication exposure can be defined as the time period when a medication and its metabolites (sometimes, its effects on endogenous systems) are present in the pregnant woman body and could potentially affect the development of the baby. Thus, medication exposure concerns not only the period when the woman receives treatment with the medication but also the time necessary to eliminate the medicine from the body, which depends on its pharmacokinetic characteristics.

In this sub-section, we will describe how data sources provide proxies to women's access to medications, how it can be measured and the need to consider pharmacokinetic characteristics of the

medication of interest.

4.2.1.1.Medication exposure measurement

What is often called “exposure to medication” is in fact the period during which a possible consumption by the pregnant woman can be identified. This possible consumption can be ascertained by prescription (e.g. CPRD primary care), reimbursement (data on payment for medication, namely claims data), or dispensing records (e.g. PHARMO outpatients pharmacy dataset), or self-reported intake in case of primary data collection (e.g. surveys). These are proxies to assess medication use and thereby exposure. The population included in data sources follows a process of attrition: medicines that are prescribed are not necessarily dispensed, and medications that are dispensed are not necessarily taken. Thus, a dispensation is probably closer to exposure than a prescription. However, neither dispensation or prescription of a medications means that is used as intended.

The “medication exposure” can be measured as a dichotomous variable (exposed or not exposed) or a continuous variable considering the frequency, amount and duration of exposure (representing the cumulative exposure). However, this choice is limited by the availability and the format of the exposure data.

For example, the cumulative exposure can be quantified using the dosage and the amount of prescribed (or dispensed) medications, as recommended by the WHO using The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) (World Health Organization, 2019). The DDD is a measure of drug consumption that assume average maintenance dose per day used for its main indication in adults as reflected by the ATC code. The ATC/DDD system, widely used to quantify medicines intake for drug utilization monitoring and research, covers most medications available on the market and only one DDD is assigned per ATC code and route of administration. The medications delivered (in number of units) can be translated into DDD to quantify the intensity of treatment exposure. For example, the total medications exposure can subsequently be transformed into number of DDD per month of pregnancy (or per trimester of pregnancy). However, this measure will not necessarily reflect the actual use for the individual woman. The Prescribed Daily Dose is on the other hand based on individual characteristics (e.g. age, type and severity of disease) and therefore likely to differ from the DDD. The PDD is defined as the average dose prescribed according to a representative sample of prescriptions, and it is important to relate the PDD to the diagnosis on which the medication is used. The PDD will give the average daily amount of a medication that is actually prescribed. Hence, the actual exposure to medications will be better reflected by the PDD. Other methods to estimate the exposure to the medications as precisely as possible has been developed (Tanskanen, 2017).

4.2.1.2.Pharmacokinetic characteristics of the medication

The dynamic physiological changes that occur in the maternal-placental-fetal unit during pregnancy

influence the pharmacokinetic processes of drug absorption, distribution and elimination, sometimes leading to the need of treatment adjustments (Loebstein, 1997).

Concerning the safety, two main pharmacokinetic characteristics are of interest: the medication ability to cross the placenta and the elimination half-life. Usually, a medicine is potentially harmful if it is present in the mother's body and it crosses the placenta. Therefore, medication exposure during pregnancy may lead to various risks according to the pharmacokinetics properties of the medicine. Low molecular weight (less than 500 Da), un-ionized and lipophilic molecules can easily cross the placenta. In addition, some molecules can cross the placenta through an active transport: for example, the transplacental transfer of monoclonal antibodies that mimics the immunoglobulin but occurs mainly during the second part of pregnancy. However, it can also be noted that some medications could potentially be harmful to the fetus via its effect on the mother (increase in blood pressure, direct effect on the placenta itself, hypoxia, alteration of the immune system -- all of which could potentially affect embryonic or fetal structure, growth or survival). Finally, it could be relevant to consider that some medication-induced-effects remain even after the medication and its metabolites have disappeared from blood. For example, aspirin anti-platelet action (blocking Thromboxan A2 production by irreversible cyclooxygenase inhibition) lasts for the lifetime of the platelets (7-10 days) when aspirin (and metabolites) half-life is about 3-4 hours. The second factor to consider is the elimination half-life of the medication from which the exact duration of the medication exposure can be estimated (usually it corresponds to the period of the medication intake + the 7 elimination half-lives that are necessary to eliminate 99% of the dose) (Dasgupta, 2020). For medication with long half-life, the use prior to pregnancy should be captured with the time frame that is relevant for the particular medication of interest. For example, several disease modifying medications for multiple sclerosis and some dermatological medications against acne or psoriasis have a long elimination half-life and thereby a long duration of exposure even after treatments have stopped as reflected in their SmPCs. Moreover, potential metabolites along with their half-lives or potential "long lasting effects" (such as those of irreversible inhibitors) have also to be considered.

4.2.2. Aetiological window

The aetiological relevant exposure period or "critical time window" is the period during which an exposure to a causal factor (such as a medication) is relevant to causation of a disease (adverse effect on the embryo or the fetus) (Porta, 2014).

The exposure to medications during pregnancy can lead to various issues according to the gestational timing of the medication exposure. The exposure periods of relevance can be divided into 5 periods (Moore, 2019) since the nature of the risk is different according to them (the start of pregnancy refers below to the day of conception):

- **Prior to conception**: the potential adverse effect of a medication could affect the gametes leading to fertility issues or early spontaneous abortions.
- **From conception to day 12 of pregnancy** (i.e. 3rd and 4th week post-LMP), an exposure to a teratogenic agent may lead to the death or to a damaged pre-embryo, or to a normal pre-embryo according to the "all or nothing rule" (established for ionizing radiations and then extrapolated to medications) because the zygotes contain omnipotent stem cells without any differentiation. Pre-embryos that are seriously damaged will not survive, and less seriously damaged ones will survive with complete regeneration.
- **From day 13 after conception to day 56** (i.e. 4th to 10th week post-LMP) constitutes the organs formation period of the embryo (called organogenesis). During this period, exposure to a teratogenic agent may induce CA, or miscarriage. No known teratogen increases the risk of all major CA. A specific defect or pattern of defects is associated with a specific teratogenic exposure during a critical period. Indeed, as organs formation follows a precise timetable, a congenital anomaly only occurs when exposure to the teratogenic agent happens during the specific formation period of the target organ. For example, the heart is sensitive to teratogenic agent between day 20 and day 40 of pregnancy, and limbs are sensitive between day 24 and day 36. The diagnosis of major CA is generally done during the second or third trimesters (if provided) ultrasound scan even if the CA occurred before this, although false positive cases exist.
- **From day 57 after conception to the end of pregnancy** (i.e. from the 11th week post-LMP) is the period of organs maturation. During this stage, medication exposure may lead to foetotoxic effects as fetal growth restriction, organ maturation anomalies including brain maturation and functional disorders. These foetotoxic effects could be evaluated by assessing small for gestational age, intrauterine growth restriction, preterm birth, low birth weight, stillbirth and neonatal death. For example, exposure to Nonsteroidal anti-inflammatory medications (NSAIDs) from month 6 of pregnancy (from 24 gestational week) can cause premature ductal closure that can lead to fetal death. Another example, angiotensin converting enzyme inhibitors should not be used after 12 weeks of gestation because they can cause fetal renal failure. The foetotoxic effects depend on the pharmacological action of the medications.
- **During the period right before delivery**: a prenatal exposure to a chronic medication that is potentially addictive (e.g. methadone, morphine, opioids) may lead to medication withdrawal (withdrawal syndrome or neonatal abstinence syndrome). Prenatal exposure of medications that are present at the end of the pregnancy and that cross the placenta may lead to perinatal effects related to the medicine itself (newborn impregnation syndrome).

A pregnancy usually lasts about 40 complete weeks measured from the last menstrual period to delivery. Various cut-offs for the trimesters of pregnancy exist. For example, the American College of Obstetricians and Gynaecologists used the following definition: the first trimester covers the period from LMP to 13 weeks +6 days of gestation the second trimester from 14 weeks +0 day of gestation to 27 weeks +6 days of gestation, and the third trimester from 28 weeks +0 day of gestation onwards (Committee on Obstetric Practice, 2017). The UK National Health Service (NHS) defines the first trimester from LMP to 12 weeks +6 days of gestation, the second trimester from 13 weeks +0 day of gestation to 27 weeks +6 days of gestation, and the third trimester from 28 weeks +0 day of gestation onwards. Hence, it is very important that studies define clearly what they meant by "first, second or trimesters" when this terminology is being used.

4.2.3. Exposure time window

The "exposure time window" should reflect, when possible, the period during which the exposure to medications is having its effects relevant to the outcome of interest. This will then be different from study to study depending on the medications, outcomes and limitations of the data sources. The document recommends that a fine categorization of the exposure time window should be used, preferably as finer as possible (e.g in days or weeks, or at the minimum in trimesters).

To summarize, the exposure time window should correspond to the period during which the exposure to the studied medication is hypothesized to have its effects, relevant to the outcome of interest. The time necessary for the medication (or its metabolites) to eliminate has to be taken into account. For example, for CA, the organogenesis period is the most relevant window, but if a specific anomaly is investigated the most relevant window is the specific period of the organ development. Hence, international consensus is needed on the precise aetiological windows for different congenital anomalies, and a study will be more sensitive to find teratogenic effects if it specifies the right window for each specific type of anomaly (Czeizel, 2008). The foetotoxic effects of the medications are evaluated during the second and third trimester of pregnancy. In relation to studies assessing the risk of long-term effects on the newborn, exposure window at risk is not well established.

Moreover, exposure to medication during late pregnancy can adversely affect other pregnancy outcomes or maternal outcomes. For instance, several studies have reported an increased risk for preeclampsia among women exposed to antidepressants after the first trimester (Palmsten, 2013; Toh, 2009).

4.3.Design considerations

The objective, the design of the study, and the available population data will define the suitable comparison group, the correct duration of follow up and the potential covariates (confounders,

mediators, moderators). This section reviews the types of population data sources available in Europe, and according to study objective, gives information on main study designs and elements that must be considered.

4.3.1. Population data sources in Europe

The data sources to conduct pharmacoepidemiological studies investigating pregnancy outcomes following medication exposure are multiple and diverse in design and content. The ConcePTION project produced a catalogue of population-based data sources. The advantages and the disadvantages of the main data sources are presented in Annex 16.

"Population data" as used here is an inclusive term for data which concern individuals in a geographical population entering the data regardless of medication exposure (ConcePTION WP2 concerns recruitment of cohorts of women exposed to specific medications). Strictu sensu, "population-based data" refer to all eligible residents of a defined geographical area, but the term is sometimes used more loosely in the literature. A population-based congenital anomaly registry is a registry that covers births from all women resident in a defined area. This can be contrasted to a hospital-based registry which is not strictu sensu population-based, and covers all women giving birth in one or more specified hospitals, regardless of residence. Hospital-based populations, particularly those covering only one or a few hospitals, can be subject to considerable selection bias, due to referral between hospitals of women with high risk pregnancies (e.g. a maternal disease or an abnormal result on prenatal screening suggesting fetal anomaly).

EUROCAT defines three categories of population-based data (EUROCAT, 2013):

- Population based I – All mothers resident in defined geographic area.
- Population based II – All mothers delivering within defined geographic area, irrespective of place of residence.
- Population based III – All mothers delivering in defined geographic area excluding non-residents of that area –
- Hospital based – All mothers delivering in selected hospitals.

Population-based I data is ideal but may not be practically feasible. The degree of bias in other categories depends on patterns of referral across population boundaries and between healthcare institutions.

"Registries" or "registers" are also terms that are used in different ways in the literature. Population-based disease registries record data on all cases of a specific disease within the population, validating these data usually for research and surveillance purposes. Disease registries may also be based on ad hoc reporting from clinicians, without reference to a specific population, as is commonly the case for

rare disease registries. In Nordic countries, "registries" refer to systematic health records for members of the population e.g. medical birth registries, prescription registries etc.

Population data sources include three main types:

- Healthcare and administrative databases, containing data for a population derived from delivering healthcare or other services (e.g. education, civil registration) to a defined population. These are created for operational rather than research purposes, but research is a secondary use. Examples are primary care databases, maternity databases, Nordic medical birth registries, hospital admissions/discharge/episode databases, prescription databases. In some instances, these data have been made "research ready" e.g. the UK primary care databases: Clinical Practice Research Datalink (CPRD) and The Health Improvement Network (THIN).
- Population-based and other research databases which are long term and updated on a yearly or more frequent basis, where the research objectives can be wider than medication safety. These include disease registries for both child (e.g. population-based congenital anomaly registries and cerebral palsy registries) and mother (e.g. multiple sclerosis registries); birth cohorts where pregnant women are recruited (regardless of exposure) and followed up until their child reaches a specified age (e.g. the Norwegian Mother and Child Cohort Study; cohorts of pregnant women with specific diseases (HIV or epilepsy); or cohorts of pregnant women linked with pregnancy outcomes and child health data (EFEMERIS and POMME in France).
- Where data linkage is possible (e.g. between different types of healthcare database, or between healthcare databases and disease registries), a very rich dataset can result which allows medication safety studies in pregnancy, and which combines the data quality advantages of different datasets (e.g. diagnostic quality of congenital anomaly registry data with high exposure ascertainment of prescription databases). "Hybrid" approaches are also possible, where population databases are linked to primary data collection, the primary data collection allowing more detailed or rigorous data collection on certain aspects of the exposure or outcome.

Record linkage also increases the information available about each mother-baby pair and can enhance the quality of pregnancy safety data by bringing together the information needed from different data sources (particularly linking mother to child), by harmonizing data systems, and ensuring completeness of outcomes (Delnord, 2016). A unique identifier number can be used to link existing databases, for instance in the Nordic countries a universal identification number is available in all their administrative and health databases. A universal identifier ensures a complete follow-up of the population in all the

data sources. Other countries such as the UK have unique health service numbers for each individual, but these do not apply to non-health data. In the absence of a unique identifier, the linkage can be performed using deterministic (using matching variables) or probabilistic methods. Whenever data linkage is used, it is important to report how the data linkage has been done, and its quality and potential for bias (e.g. % of unlinked cases and reasons for non-linkage)

4.3.2. Study objectives

Selecting a specific question that the study is aiming to answer is often known as the primary objective. Studies will often have secondary objectives but the study sample size calculations should be calculated with the aim to answer the primary objective.

When selecting a primary objective, it needs to be decided if quantification of an association between the medication and pregnancy outcome is of interest or if it is necessary to fully investigate the causal association between the medication and pregnancy outcome. When deciding which of these objectives is suitable, the issue of data availability must be considered, which plays a vital role in the feasibility of conducting a causal analysis. Accurate and complete information on potential confounders is required. Detailed knowledge about the underlying causal structure of the model needs to be understood in order to deal with confounders and mediators appropriately. If not dealt with appropriately the causal association is likely to be biased.

The issue of lack of data, particularly on potential confounders, and its poor quality is often encountered when conducting retrospective studies on population databases, and limits the use of causal models, Therefore, the quality of the data available should be reviewed before setting these objectives. Later in the section, a range of methods are described which will help identify causal and non-causal associations.

4.3.3. Main study designs suitable to population data

Most of the population-based study designs have in common the use of an internal comparator (i.e. non-exposed or non-case) that comes from the same study population as the exposed (or cases) population.

There are two main study designs: a cohort study and a case-control study, depending on data sources, outcome, and exposure.

A cohort study compares the incidence (or prevalence) of the outcomes in a cohort of women exposed to the medication of interest in pregnancy with those in a non-exposed cohort of women (or in a cohort of women exposed to an alternative medicine). A cohort study involves follow up of individuals from recruitment to the study population prior to or during pregnancy to outcome of the pregnancy or health of the child at a specified age. A case-control study compares the medication exposure history between cases with the outcome and controls free from the outcome of interest. A cohort study allows

the investigation of several outcomes whereas a case-control study allows the evaluation of several exposures.

The following study populations are in use in cohort studies in the literature, and are all able to generate reliable evidence:

I. An entire population cohort: all pregnancies or births, as applicable, in the population (of a nation, region or multiple nations/regions) in a defined time period are included in the study population, such as the medical birth registries in Nordic countries. The study base can then be linked to administrative or health registers or to healthcare databases (Jordan, 2016; Garne, 2016).

II. A recruited sample population cohort: all or nearly all pregnancies in the population (of a nation or region) are eligible for recruitment, but only a sample are recruited for primary data collection e.g. Norwegian and Danish birth cohorts (sample birth cohort). The women are followed up from the time of recruitment during pregnancy to the child outcomes at a specified age. While recruitment has some bias towards higher socioeconomic status (SES) and related person characteristics, the relationship between exposure and outcome should be unbiased. Information on the exposure is usually prospectively collected (i.e. before the outcome is known), but there may be a retrospective element (i.e. exposure ascertained after the outcome is known) if the recruitment occurs at birth. The sample cohort may be linked to routine healthcare databases (Frank, 2019; Lupattelli, 2017).

III. A sample population cohort: a sample of the pregnancies in the population are present in the data source but there is no recruitment of individuals for primary data collection. For example, in the CPRD and THIN General Practice (Primary Care) databases in the UK, only a small proportion of general practices choose to be included in the data collection system. Primary care databases such as the CPRD are only suitable in countries like UK where patients are registered with a single general practice, and that general practice is the centre for referral to all secondary and tertiary care, and issue most prescriptions (Ban, 2014). US cohorts based on specific insurance schemes are also an example of this design (Camelo Castillo, 2015).

IV. Disease cohorts: In this design, all those who meet a disease criterion in the population (e.g. HIV, multiple sclerosis, epilepsy) are included in the cohort, irrespective of treatment. We exclude here disease cohorts that are collected specifically for medication safety purposes e.g. EURAP (these are being covered in WP2 of ConcePTION). There are many different types. The cohort may be retrospectively established from prevalent cases or prospectively established (i.e. incident diagnoses followed up). Information on the disease and treatment may come from medical records, or from primary data collection. The cohort may include all those with the disease, women only, or pregnant

women only (Rough, 2018; Floridia, 2013; Wang, 2018). The disease cohort may be linked to other registers of pregnancy outcome (Wang, 2018).

Traditionally, case-control studies have been chosen for rare outcomes, in order to increase the study statistical power where primary data collection involves a substantial cost per study subject. With the advent of population database studies, this rationale is not so strong, and cohort studies can be done for rare outcomes if high quality data for very large populations are available. Specific outcomes, especially those difficult to measure such as congenital anomalies or neurodevelopmental outcomes, may need to be established by special data collection e.g. a population-based registry, and this registry can be linked to the cohort. However, linkage of registries to large cohorts is not always possible. Case-control studies are often criticised for being "retrospective" in design, but it is important to distinguish whether the source of data on medication exposure was prospectively collected before outcome was known (e.g. maternity records used by disease registries as a source of exposure data, or prospective data collection in nested case-control studies) or truly retrospective and therefore subject to recall bias (e.g. by maternal interview after birth). In EUROmediCAT congenital anomaly registries, for example, most exposure information is prospectively collected in maternity records (Bergman, 2018) and moreover linkage to (prospective) prescription records is possible for many (de Jonge, 2015).

Registries typically have well validated diagnostic information on pregnancy outcomes such as CA (EUROCAT/EUROmediCAT network) and cerebral palsy (SCPE network). Some registries choose one or two controls per case from the same birth population e.g. National Birth Defects Prevention Study (Interrante, 2017). An alternative is to use the case-malformed control design, where the congenital anomaly of interest (e.g. corresponding to a previous signal or pre-specified hypothesis) is compared to other CA (Given, 2017; Given 2018; Bergman, 2018). This is most suitable for use when there is a strong prior reason to be able to differentiate between anomalies which may be caused by the teratogenic exposure and other anomalies. When there is no prior hypothesis, the disproportionality analysis in signal detection can be used (Given, 2017).

4.3.4. Choice of comparison groups

As in any observational study, choice of comparison groups directly affects the validity of study results, clinical interpretations, and implications. In a cohort study, the ideal comparison group is a group that differs with respect to the exposure of interest but is similar in all other aspects that can influence the outcomes. In a case-control study, the ideal control group is a group that does not have the outcome of interest but is similar in all other aspects.

Often the ideal comparison group is absent, thus, the validity of the results will be enhanced by using multiple types of comparators aiming at limiting confounding (e.g. due to the indication) in the analysis. Example of comparison groups that can be used are::

- women not exposed to the medication of interest,
- women exposed to a different medication (with the same disease),
- women who do not receive the medication of interest (with the same disease),
- women exposed prior to but not during pregnancy (with the same disease),
- women exposed during the second and third trimester, but not during the first (with the same disease),
- negative and positive control groups (see below).

Negative and positive control groups are increasingly being used in epidemiology to strengthen inference regarding an exposure-outcome association when unobserved confounding is thought to be present (Dusetzina, 2015). A negative control is a control group exposed to a medication that is not expected to have causal effect on the outcome (Lipsitch, 2010). For example, paracetamol has been considered to be safe according to teratogenicity with respect to CA and represents the reference to treat pain. Consequently, this medication may define a potential negative control group in studies aiming to evaluate side effects of medications with pain indication. Another example in studying CA is a negative control group composed of women non-exposed during the first trimester of pregnancy but exposed during the rest of the pregnancy. Moreover, pre-pregnancy exposure can also be used as a negative control for comparison, bearing in mind the time needed to eliminate the medication. By contrast, a positive control is a control group exposed to a medicine known to cause the effects of interest. For example, valproate, used for various conditions such as epilepsy, is known to be associated with CA and adverse neurodevelopment outcomes after an exposure during pregnancy. Consequently, this medicine may represent a potential positive control in studies aiming to evaluate adverse effects of medications with epilepsy indication. Hence, positive controls are used as quality checkers. A study that is not able to detect the known effects of the positive control might suggest that the study will not be able to detect any true effect of similar magnitude (Bromley, 2016).

Hence, negative and positive controls show that the data correctly detect existing associations or correctly demonstrate lack of association when none is expected.

4.3.5. Covariates: confounders, mediators, moderators

4.3.5.1. Definitions

A covariate is a possible predictive or explanatory variable of the outcome of interest (Salkind, 2010).

The definition of **confounder** most widely adopted, and deployed here, is “a factor associated with both the exposure and the outcome, and not part of the causal pathway from exposure to outcome” (Figure 2) (Kahlert, 2017; Kestenbaum, 2019; Wolfgang, 2014). One way to ensure a variable is not on

the causal pathway is to establish occurrence prior to exposure (Rothman, 1998), and some authors stipulate precedence (VanderWeele, 2013). However, precedence is not always verifiable in datasets.

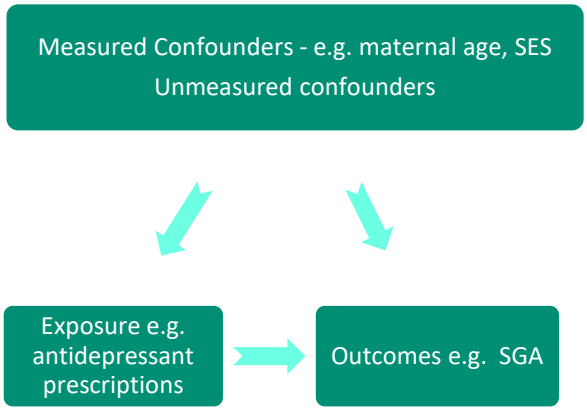

Figure 2. Illustration of a confounder

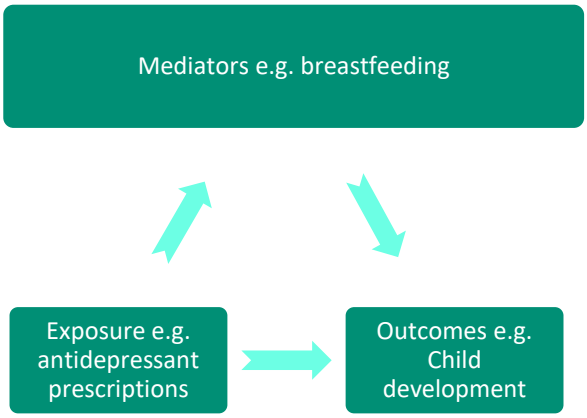

Figure 3. Illustration of a mediator

Mediators, in contrast, lie on the causal pathway between exposure and outcome (Figure 3). The distinction between confounders and mediators is not always apparent in any one situation.

Moderators (also called effect modifiers) affect the strength or direction of the relation between exposure and outcome (Baron, 1986). They are sometimes used to identify subgroups e.g. age groups, where the exposure may be more closely linked with the outcome (MacKinnon, 2011).

The covariates in pregnancy medication studies can be grouped in the following categories:

- maternal (or paternal) factors such as age, obstetrical and medical history (such as preeclampsia, gestational diabetes, and pre-existing conditions), lifestyle (such as tobacco and alcohol use, illegal drug use, nutrition, physical activity), BMI, SES, genetic risk factors, family history, paternal characteristics, breastfeeding. Where relevant, the timing of these factors in relation to pregnancy should be clearly specified.
- concomitant medication use, such as folic acid and vitamin use, and exposure to known teratogens, or to any other medications. Here, the concomitant medication, not the index drug, might be responsible for the observed effects.
- environmental factors, from pollution to access to care and rurality.

In multicentre studies, it can also be important to control for the data's provenance (geographical area or recording mechanism) as a covariate, or adopt meta-analytic or multi-level models.

Covariates should be selected *a priori* based on the existing literature, expert opinion, and knowledge of the population and related data sources. Studies should include as many covariates as possible that have potential to influence the association between exposure to medication and a selected outcome. However, it is likely that not all the potential covariates will be available in any one database, and certainly not in all data sources in multi-site studies. Hence, sensitivity analyses may usefully investigate the impact of "missingness" of some covariates on associations identified.

There are many potential risk factors for adverse pregnancy outcomes. However, space precludes detailed consideration in this document. Therefore, we have selected one important confounder and one mediator to illustrate the methodological challenges in the analyses of population data: socioeconomic status and breastfeeding.

4.3.5.2. Socioeconomic status as a confounder

Socioeconomic status (SES) is a combination of economic and social factors indicating a group's or individual's effective social situation, relative to the population. Social class, social stratification, social position and SES, are often used interchangeably. SES refers to the social and economic factors (income, education, housing tenure, occupation) that influence the positions individuals or groups hold within the structure of a society (Krieger, 1997), and encompasses concepts with different theoretical, historical and disciplinary origins (Galobardes, 2006). SES is a relative, not absolute, measure. The most disadvantaged of some countries may be better situated than the most advantaged of other countries.

Most epidemiological studies include a measure of SES including: income, time in education, occupation and address, which is used to calculate a deprivation score or rank based on census or other area-based information. The earlier indices of multiple deprivation (IMD) such as the Townsend index were based on census data (Townsend, 1988). Some later IMDs include health (e.g. percentage of low birthweight births) and education status. While these are essential for planning and policy purposes, their use as confounders for investigation of health and education outcomes introduces tautology.

SES is reportedly linked to: health e.g., SGA (Ruiz, 2015), asthma (Lewis, 2017), or depression (Hein, 2014), developmental and educational outcomes, and morbidity. It is associated with known risk factor for adverse outcomes, such as smoking, substance misuse and with exposures of interest, such as antidepressant and anti-asthma prescriptions (Jordan, 2015). When predictor variables are correlated, odds ratios are less vulnerable to bias, but entering correlated SES measures into a regression model increases the risk of co-linearity (Fewell, 2007).

The SES of any individual may change over time. This may be difficult to capture in databases: investigators should pre-specify whether SES at start of pregnancy or at birth is taken or whether it will be modified as mothers move house or parental income changes.

Databases can only offer proxies for context. Lifestyle factors, such as exercise, sleep, moderate alcohol use, recreational drug use, environmental pollution are not always recorded consistently. The use of SES as a proxy for these considerations warrants investigation for each database.

4.3.5.3. Breastfeeding as a mediator

Infants may be exposed to medicines via breastmilk. For most medicines, the quantity transferred is usually too small to be of clinical importance (Lawrence, 2015): however, the vulnerability of premature infants is relatively unexplored. More information is needed before full assurances can be given for

some medicines, particularly regarding long-term outcomes, and some case reports indicate risks for a few medicines (lithium, clozapine, radio-iodine).

Furthermore, exposure to some prescribed medicine in pregnancy and *intra-partum* may reduce breastfeeding initiation or continuation (Jordan, 2005; Jordan, 2009; Jordan, 2019). Therefore, breastfeeding is an important consideration in the analysis of late outcomes (e.g. neurodevelopmental outcomes, cognitive performance), since it may be a mediator for the effect of medication on outcome (Veilby, 2013).

Women using prescription medicines are less likely to breastfeed, particularly if there is little information about the transfer of the medicine to breastfed infants (Saha, 2015). Therefore, it is important to separate the effect of the medicines from the effect of 'not breastfeeding'. In Wales, antidepressant prescriptions in late pregnancy are associated with reduced breastfeeding prevalence at 6-8 weeks (Jordan, 2019).

The breastfeeding literature offers little consistency regarding the timing of data collection. Consequently, to compare data sets, commonalities will need to be determined. The definitions of exclusive, full and partial breastfeeding will need to be considered. It is recognized that the WHO categories of breastfeeding do not allow finer distinctions; for example, the mother giving an occasional formula feed, and therefore almost fully breastfeeding, and the mother giving an occasional breastfeed, and therefore almost exclusively formula feeding would both be classified as 'complementary feeders'. In addition, the WHO definition of complementary feeding does not allow distinguishing between feeding with and without the use of formula (e.g. breastfeeds plus solids). Monitoring systems, or more often operational research, may add categories to the WHO definitions in future (European Commission, 2004). Currently, some databases and databanks ask those entering data to estimate the proportion of nutrients derived from breastmilk e.g. National Health Service Wales 2017.

The categories of interest considered critical for decision-making (World Health Organization, 2018b) include:

- early initiation of breastfeeding within one hour after birth
- any breastfeeding at 4–6 weeks
- exclusive breastfeeding at 4–6 weeks
- any breastfeeding at 6 months
- exclusive breastfeeding at 6 months
- giving any additional foods or fluids in the first 2 days after birth
- use of artificial teats and bottles in the first 6 months.

Since many databases do not capture breastfeeding data at the same time point, some assumptions may need to be made e.g. an infant breastfed at 6 months is likely to have been breastfed at earlier ages. Initiation of breastfeeding is usually regarded as indicating intention, rather than successful breastfeeding (McAndrew, 2012).

4.3.6. Controlling for confounding by indication and/or severity

In observational studies, when an exposure appears to be associated with an outcome, the outcome may, in fact, be caused by the underlying disease for which the medication was used: confounding by indication. Moreover, not only the indication but also the disease severity and its course can act as a potential confounder when comparing two treatments (e.g. the more intensive treatment regime may appear to result in poorer outcomes). Confounding by indication and/or disease severity is very common in observational studies. It can occur in relation to both beneficial and harmful outcomes and can result in either an increase or a reduction in the apparent risk of the outcome. Studies with such potential confounding need appropriate designs and analyses. For example, outcomes for a woman receiving the medication of interest with a specific disease can be compared with outcomes in unmedicated women or with outcomes for a different medication. It is also possible to compare outcomes for those discontinuing medicines before pregnancy (Jordan, 2016) or after the first trimester (Jordan, 2019). To control for confounding by disease severity, patients with similar disease severity should be compared.

Protopathic bias

A protopathic bias exists in studies when the initiation of a drug (exposure) occurs in response to an early manifestation of the outcome of interest that is not diagnosed yet. Consequently, a causal relationship may incorrectly be reported between the drug and the outcome. For example, the association between NSAID use and spontaneous abortions may be biased by the fact that NSAIDs could be taken to relieve the pain due to early symptoms of the spontaneous abortion itself (Daniel, 2015). This bias can be controlled by including a lag time into the exposure period, i.e. by excluding a time period before the occurrence of the outcome.

4.4. Analytical methods

4.4.1. Exploratory analyses

Before testing any hypothesis, the data which any hypotheses are to be tested on must be reviewed. Some examples of exploratory analyses that should be assessed are:

- Prevalence of binary and categorical outcomes, overall and by covariate factors (e.g. maternal age)
- Distributions of continuous and ordered outcomes, overall and by covariate factors (e.g. maternal age)
- Treatment prevalence, overall and by covariate factors
- Covariate distributions, overall and by treatment and outcome (continuous or ordered categorical covariates)

- Outcome trends over time (where appropriate)
- Treatment trends over time (where appropriate)
- Covariate trends over time (where appropriate)

These simplistic reviews are critical when deciding the appropriate method to adjust for confounding factors or effect modifiers.

4.4.2. Choice of the statistical model

When selecting the appropriate analytical method for testing a hypothesis, the structure and background of the available data needs to be reviewed using the methods outlined in section 4.4.1.

As detailed in section 3, several study designs can be employed as well as a vast range of statistical methods. The statistical methods try to remove the remaining bias that the study design process cannot address. The selection of the methods should account for the individual hypothesis to be tested, the expected sample size and also the various biases that could occur within each specific data set, disease state or related to the exposure or outcome.

In this section, we have identified some of the key questions that one should ask before selecting which analysis is most appropriate to use:

- What is the hypothesis to be tested?
- How will the outcome be classified? (binary, continuous, categorical, …)
- What is the prevalence of the outcome among patients who were not exposed?
- How will the exposure be classified? (binary, continuous, categorical, time varying, …)
- Or what is the prevalence of the exposure among the control population?
- What is the data quality like, including accuracy of linkage if relevant?
- What biases are expected to be present within the data? (e.g. detection/ascertainment bias, self-referral bias, loss to follow-up, survival bias, ...)
- What confounders should be considered?

The table 1 presented in Annex 17 highlights a range of methods found in the literature to analyse observational data and explains which outcome and exposure forms they can support. The most common methods are logistic or multinomial logistic regression, Poisson regression and Cox proportional hazards regression. Additional notes on the advantages and disadvantages of each method are also provided.

4.4.3. Competing risk

It is important to note that adverse pregnancy outcomes are 'competing outcomes' and when analysing individual adverse pregnancy outcomes all other outcomes must be considered. For example, if a medication causes pregnancy loss, elective termination or miscarriage, misclassification errors might result from an incomplete identification of other outcomes such as CA.

For instance, when analysing the occurrence of a congenital anomaly, the occurrence of a spontaneous abortion or stillbirth may preclude the reporting of the congenital anomaly. In addition, fetuses with specific anomalies may be more likely to be spontaneously aborted. It is therefore important to consider each adverse pregnancy outcomes when analysing the data. However, sometimes the use of a composite "adverse outcome" could be the only alternative possible. Two hazard functions can be modelled: the cause-specific hazard function (from a Cox proportional hazard model) is the instantaneous rate of occurrence of the specific event in subjects who are currently event free (of all types of event) and the subdistribution hazard function (from a Fine-Gray model) which is the instantaneous rate of occurrence of the specific event in subjects who have not had the specific event. Survival analyses are not used for analysis of congenital anomaly because the onset of the anomaly is unknown, so time is usually not considered. However, for studying preterm birth survival analyses should be preferred.

4.4.4. Controlling for measured confounders

When conducting a hypothesis test in a population-based observational study, the influence from confounding factors cannot be avoid in the same way as in a RCT. Therefore, confounding factors and effect modifiers must be adjusted for within the analysis.

4.4.4.1. Common multivariable statistical methods

Multivariable linear regression, logistic regression, and Cox proportional hazards regression (survival analysis) adjust for measured confounders by including the confounders as covariates in the models. The number of subjects or the number of events limits the number of confounders that can be included in the model; a ratio of 10–15 subjects or events per independent variable is often specified (Austin, 2017). A disadvantage of these models is the danger of extrapolations when the overlap on covariates between exposure groups is too limited. Moreover, when exposure groups have different covariate distributions the results are heavily dependent on the chosen relationship (e.g. linearity).

4.4.4.2. Confounder summary scores

Confounder summary scores, such as a propensity score (PS), disease risk score (preferred in the case of rare exposures) or polygenic risk score (useful for cases when genetic confounding) have also been used to control for confounding (Jackson, 2017). These summary scores reduce a large amount of information about an individual into a single summary score. The distribution of measured baseline covariates will be similar between the exposed and control subjects; hence any differences in outcome will likely be attributable to the exposure to the medication of interest. It should be noted that two individuals can have the same summary score but different confounder values but the distribution of confounders will be equivalent. Once a score has been computed, this score can be used in three different ways to adjust for the uncontrolled assignment of exposures: (i) as a matching variable, (ii) as a stratification variable, and (iii) as a continuous variable in a regression model (covariance adjustment). The aim is not to stratify the analysis looking at any differential effect among the combination of covariates but to remove as much measured confounding as possible to estimate the effect of the medication on the outcomes. Unmeasured confounding, if not proxy to these measured confounding factors, will remain as a concern of the study.

These scores require several assumptions, including exchangeability (no unmeasured confounding) and positivity (nonzero probability of treatment). However, the first assumption is difficult to assess and it is a limitation like in a standard multivariable regression analysis. Nonetheless, high-dimensional PSs, which include thousands of variables can be useful for adjusting for as much as possible measured confounders.

4.4.4.3. Marginal structural models

Marginal structural models (MSMs) address time-varying exposure (e.g. acute medication) and confounding (e.g. breastfeeding) where factors that are confounders in one part of the causal structure are mediators in another part (Cole, 2008). At each measurement time t, the investigator uses logistic regression to construct the numerator (probability of exposure) and denominator (probability of exposure, given baseline predictors and history of exposure at time $t-1$). The total weight is the product of the weights at each time point, and analyses are conducted in the weighted population, or pseudo-population, in which individuals who are likely to be exposed are down weighted, while those who are unlikely to be exposed are upweighted, producing balance of measured confounders within strata of exposure.

MSMs allow consideration of time-varying exposure and confounding - important due to changes in fetal vulnerability through pregnancy and the tendency of women to change their medication use during pregnancy. They also require positivity, exchangeability, and consistency for unbiased effect estimates. When the treatment-covariate association is very strong very wide confidence intervals may be produced, which fail to include the true effect

4.4.5. Statistical power and sample size considerations

The number of patients needed to provide sufficient precision according to the expected effect size (the sample size) will be determined by the study design used, the prevalence of exposure and how the outcome is measured. In this section, we focus on the sample size requirements for the simplest techniques, which are cohort and case-control studies (Annex 18). As the core outcome elements list include mainly binary outcomes (Yes/No), the following section focuses on these types of outcomes. It should be noted that in case of multinomial outcomes, more advanced techniques should be used (Jiang, 2011). We provide in table 10 Annex 18 the sample size requirements for continuous outcomes.

4.4.5.1. Cohort study sample sizes

To calculate the sample size of a cohort study certain information is required:

- The power of the study (i.e. the degree of certainty that the effect identified will be true);
- The acceptable level of statistical significance (i.e. the probability of identifying an effect when no effect exists);
- The treatment prevalence in the population;
- The expected outcome incidence or prevalence in the unexposed;
- The expected risk ratio.

Within the tables (Table 1-5) presented in Annex 18, the study power was set at 80% and the level of statistical significance was set at 5%. Both of these levels are commonly used. However, if a stricter degree of effect certainty is required, then an increase of power to 90% can be used to generate similar tables in which the sample size requirements would be larger. We would not recommend a study power under 80%, or a statistical significance cut off greater than 5% total.

Tables 1-5 presented in Annex 18 offer an idea of the size of cohort required, as well as the number of patients required to be exposed to the medication of interest within the cohort for varying levels of exposure prevalence within the population. Within each table, the columns express different levels of outcome prevalence within the unexposed group and the rows express different risk ratios that may be expected. The table then generates the sample size required to identify the corresponding risk ratio or a risk ratio of greater magnitude when the outcome prevalence is at that level.

These tables offer loose guidelines as to the size of the cohort that will be required under varying treatment and outcome circumstances. The initial tables expressing low treatment prevalence's within the population are most relevant if the study population is the general population. However, if the study population is patients with a certain disease then the tables reviewing the patients with a higher

proportion on treatment within the population may be more useful, as specific medications may be common amongst this cohort.

4.4.5.2. Case-control sample sizes

When considering the sample size requirements for case-control studies, the following information are required:

- The power of the study (i.e. the degree of certainty that the effect identified will be true);
- The acceptable level of statistical significance (i.e. the probability of identifying an effect when no effect exists);
- The ratio of cases to controls;
- The treatment prevalence in the controls;
- The expected odds ratio.

Similarly to the cohort calculations, the study power was set at 80% and the level of statistical significance was set at 5%. Matching ratios of cases to controls from 1:1 up to 1:9 are reported, with three tables produced for each ratio; the number of cases required, the total number of patients required, and the number of patients required to be on treatment (Tables 6-9 in Annex 18). The columns in each table express a range of treatment exposures within the controls and the rows express a range of expected odds ratios. These tables highlight that as the ratio of cases to controls grows, both the number of cases needed and the number of cases exposed needed will reduce. Not all case-control studies are matched case-control studies. Sometimes all the available controls are selected to avoid any selection bias in the controls. In this case, the sample size calculation will be a similar process as for a cohort study. And as above, we would not recommend a study power under 80%, or a statistical significance cut off greater than 5% total.

4.4.5.3. Common adjustments

When making sample size calculations, it is wise to adjust the calculation appropriately to account for the presence of missing values within the data. Missing information is common when dealing with population databases. Data may not have been ever recorded or may have been lost during the database linkage process. To account for loss of data within the sample size calculations, the predicted sample size needs to be multiplied by a scaling factor. For example, if 10% of cases are lost during database linkage, the required sample size will be 1.1 times the unadjusted sample size estimate.

5. Default list of core evidence elements

In the previous sections, foundations were presented for conducting pharmacoepidemiological population-based studies among pregnant women. In this document, which is complementary to reference guidelines such as the Guideline on Good Pharmacovigilance Practices (GVP), core elements needed in population-based data studies investigating medication safety in pregnancy were first described. Core data elements such as outcomes of interest, medication exposures, relevant covariates including maternal conditions, and other core elements such as design and statistical considerations could influence the interpretation of medication safety information.

In this section, a minimal set of core evidence data elements is presented as "default". To determine the safety profile of a medication during pregnancy all these items should be explored. Such a default list can help to standardize pregnancy and lactation labelling language across prescribed products to enable clinical decision making. The list of "default" core evidence data elements was compiled following literature review, review of pregnancy studies in the EU-PAS, review of SmPCs and was based on expert knowledge within the ConcePTION consortium. The proposed list was subsequently reviewed, discussed and validated through external multi-stakeholder and expert consultation. These core evidence data elements are those considered essential for all medicines and on which greater amounts of resources should be allocated to ensure data quality. Other evidence data elements will be variable according to factors such as the studied medication, prior evidence from non-clinical studies and the aim of the study. In practice, deviation from the default list would require justification, for example studying a medication only prescribed in the third trimester may allow for removal of congenital anomalies occurring after a first trimester exposure. The list of default elements also makes it easier to identify which elements of evidence are missing when safety evidence is evaluated for potential inclusion in product labels. In practice, this list will make it easier to set standards with regards to the quality of the data and the suitability of data sets used. Note that some data sets might not necessarily include all of these default core evidence data elements but can still be valuable to address specific risks related to specific drug exposure during pregnancy. The list can be tailored when specific research questions or individual outcomes need to be addressed. For example, according to the studied medication, other core evidence data elements crucial for certain medications (such as long-term neurodevelopmental outcomes for medications that cross the brain-blood barrier) could be considered of interest and useful for some stakeholders. Based on biological plausibility, mode of action of medication and/or pre-existing data, it can be decided if studies into childhood are needed.

Table 1: Default minimal set of core evidence data elements pregnancy safety studies

Default core evidence data element category	Specific default elements
Gestational age (p. 17)	• use best obstetric estimate; use first day of LMP when ultra-sound dating is not available • expressed in weeks and days
Non-live birth outcomes (p. 17-21)	• termination of pregnancy • miscarriage • stillbirth
Live birth outcomes (p. 21-26)	• small for gestational age (SGA) • preterm birth • neonatal death
Major congenital anomalies (p. 26-28)	• overall congenital anomalies (CA) • specific major anomalies • including termination of pregnancy due to fetal anomaly
Maternal outcomes (p. 33-35)	• maternal death
Medication exposure time window (p.35-39)	• exposure should be minimally available per trimester of pregnancy, but preferentially by pregnancy week • the exposure periods of relevance are divided as described
Dose/duration of medication (p. 36)	• date of dispensing, name, ATC code, galenic form, quantity of drug dispensed, number of units
Confounders (p. 45-49)	• relevant confounders such as those described p. 45-49

6. Quality

6.1. Research quality criteria checklists

The most commonly used published checklists that aim to identify and convey research standards to researchers and readers are listed below. Table 1 summarizes available guidance that can be used for pregnancy safety studies.

- The Bradford-Hill criteria (Bradford-Hill, 1965) – seminal work
- Sackett (1979) (seminal work) catalogues 35 biases to be checked around: literature reading and reporting, sample selection, execution and measurement of exposure and outcomes, analysis and interpretation.
- The GRADE criteria and quality of evidence for bodies of evidence and individual studies (Schünemann, 2013).
- Cochrane handbook, chapters for non-randomised studies (Reeves, 2019), adverse effects (Peryer, 2019).
- ROBINS-1 Risk of bias in non-randomised studies (Sterne, 2016)
- Population vs. case-control studies (Thygesen, 2014)
- EQUATOR network and reporting guidelines: https://www.equator-network.org/. The 419 guidelines include: STROBE (observational studies) (von Elm, 2007), PRISMA (systematic reviews) (Moher, 2009) & SPIRIT (protocols). Many disease areas have their own unique guidelines. For example, there are 12 guidelines for studies in obstetrics, and 17 for 'pharmaceutical medicine', including RECORD-PE for pharmacoepidemiology using routine healthcare databases (Langan, 2018). 4 guidelines include 'pregnancy', but none of these relate to observational studies or medicines. 2 relate to nomenclature of CA. The validation of each major component of the EQUATOR suite is described (Arundel, 2019), and their impact has been commented (Johansen, 2016).
- The US National Library of Medicine has compiled a summary list of checklists (https://www.nlm.nih.gov/services/research_report_guide.html)
- ENCePP 2010/2018 Guide on Methodological Standards in Pharmacoepidemiology
- EMA /ENCePP 2018 ENCePP Checklist for Study Protocols
- Newcastle-Ottawa for study review
- Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) for observational studies (von Elm, 2007)
- Regulatory grade RWE (Cave, 2019; Miksad, 2018)

None of the established research standard checklists above specifically mention pregnancy. To address this hiatus, the EMA (2020) has guidelines for consultation (European Medicines Agency, 2020). This builds on earlier European guidelines for:

- Description of assessing the risk of an adverse reproductive/developmental effect in humans using reproductive toxicity studies in animals plus human clinical data. It addresses information to be included in the summary of product characteristics on how to use the medicinal product taking into account the nature of the risk (EMA, 2008).
- Providing criteria to select medicinal products for which active surveillance for collecting post-authorisation data in pregnancy is necessary (EMA, 2005).
- Key considerations for developing a testing strategy to identify hazard and characterize reproductive risk for human pharmaceuticals. The guidance informs on the use of existing data (including animal data) and identifies potential study designs to supplement available data to identify, assess, and convey risk. General concepts and recommendations are provided that should be considered when interpreting study data and assessing reproductive risk in support of clinical development and marketing approval (European Medicines Agency, 2020).

Table 2. Available guidance that can be used for pregnancy safety studies.

Guidance	**Organization**	**Document link/reference**	**Comments**
Guidelines for Good Pharmacoepidemiology Practices (GPP)	ISPE	International Society for Pharmacoepidemiology, 2015 https://www.pharmacoepi.org/resources/policies/guidelines-08027/	Referenced in PV and RM guidances: ICHE2E, FDA and EMEA guidances
Epidemiology	IEA		
International Ethical Guidelines for Epidemiological Studies	CIOMS	Council for International Organizations of Medical Sciences, 2009	About to supersede 1991 version
Reporting observation studies	STROBE	von Elm, 2007	
Registries for Patient Outcomes	AHRQ		Revision started
Database research	ISPOR		Final recommendations not available yet
Database analysis	German Society for Epidemiology	Hoffmann, 2019	

Adverse Event Reported for Publication		Kelly, 2007	
Pharmaco-vigilance	SPVS	SPVS´s Good Pharmacovigilance Practices	Electronic Document not available yet No English version available.
Drug Utilization. Recommendations of an European Expert Meeting on indicators of prescribing quality in drug utilization research	euroDRUG	Hoven, 2005	
Meta-analysis of observational studies	MOOSE	Stroup, 2000	
Volume 9A of the Rules Governing Medicinal Products in the EU – Guideline on Pharmacovigilance for Medicinal Products for Human Use		https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-9/pdf/vol9a_09-2008_en.pdf	Update ongoing. Public comments through January 2020. Will be replaced by EMA, 2020
Guidance documents from EMA and FDA on topics like: pregnancy registries, risk management, etc			

AHRQ: Agency for Healthcare Research and Quality; CIOMS: Council for International Organizations of Medical Sciences; EU: European Union; IEA: International Epidemiological Association; ISPE: International Society for Pharmacoepidemiology; ISPOR: International Society for Pharmacoeconomics and Outcome Research; MOOSE: Meta-analysis of observational studies in epidemiology; SPVS: Spanish Pharmacovigilance System; STROBE: Strengthening the reporting of observational studies in epidemiology

6.2. Limitations in pregnancy safety studies

This section addresses some of the main limitations of pharmaco-epidemiological safety studies in pregnancy that may threaten their validity. This includes both limitations related to the data sources, pharmacoepidemiologic studies in general and the specific constrains inherited in pregnancy safety studies.

6.2.1. Study size

In the investigation of uncommon exposures and/or rare outcomes, inadequate sample size can result in low precision of the effect estimate (wide confidence intervals), limiting the inferences that can be drawn. In most European populations, both the prevalence of many adverse pregnancy outcomes (e.g. specific congenital anomalies), and the prevalence of exposure to newly marketed medicines or medicines restricted to rare conditions among pregnant women, are low. The simplest way to increase precision of the effect estimate (and reduce random error and confidence intervals) is to enlarge the study size (Rothman, 1998). Hence, collaborative studies that combine data from multiple sources in several countries (e.g. ConcePTION) is an attractive approach to increase sample size in pregnancy safety studies.

However, in very large studies some clinically meaningless associations with small absolute risk differences may sometimes be statistically significant biasing interpretation. Accordingly, some journals stipulate inclusion of absolute risk differences and numbers needed to harm along with relative risk differences.

6.2.2. Missing data

Missing data can occur in any variables: exposure, outcomes and covariates. Missing data can be of 3 types:

- missing completely at random (MCAR): the reason for missingness is completely random, meaning that the probability that an observation is missing is not related to any observed or unobserved patient characteristics;
- missing at random (MAR): the reason for missingness is related to observed patient characteristics that are available at the time of analysis;
- missing not at random (MNAR): the reason for missingness is related to unobserved patient characteristics (e.g. the value of the observation itself).

Different approaches have been used to address missing data (Sterne, 2009). One method is to include only complete cases in the analysis (i.e. individuals with missing values in any variable are excluded

from the analysis). Only with MCAR data does this method not lead to biased estimates. However, for all missingness reason, this method may exclude a substantial proportion of the population, reducing precision and power. Other techniques include replacing missing values with values imputed from the observed data (for example, the mean of the observed values or the last measured value carried forward) or using a missing category indicator. However, these techniques are not statistically optimal and will lead to biased estimates for all type of reason for missingness. In case of MCAR or MAR data, an alternative method is the multiple imputation technique that will give unbiased estimates. It replaces each missing value with a set of plausible values that represent the uncertainty about the right value to impute. These multiple imputed data sets are then analyzed by using standard procedures for complete data and combining the results from these analyses (Rubin, 1987). However, in case of MNAR data, valuable information that cannot be predicted from the others characteristic of the patient are missing in the data; hence, there is no optimal method to handle such type of missingness.

Inadequate follow up of the entire cohort may fail to uncover longer-term outcomes. For example, some congenital anomalies may go undiagnosed for years, and discontinuing follow up at birth underestimates their prevalence.

6.2.3. Information bias

Information biases are systematic errors in the measurements of exposures, outcomes, or covariates. Measurement errors in discrete variables are referred to as misclassification and if the errors depend on the values of other variables it is referred to as differential misclassification. Misclassification that does not depend on the values of other variables is referred to as non-differential misclassification. (Rothman, 1998)

6.2.3.1. Exposure misclassification

An accurate exposure assessment is a pre-requisite for an efficient study design. Pharmaco-epidemiological studies based on data from primary care, outpatient pharmacies, or insurance claims use prescription, dispensing or reimbursement records as a measure of exposure. The records often include information on the specific type of medication, dose and duration, but medication initiation and adherence to prescribed regimens cannot be ascertained from data. Medications that are prescribed are not necessarily dispensed at pharmacies (primary non-adherence) or the dates may not align. Primary non-adherence is not uncommon, it is estimated that approximately 10% all prescriptions are not redeemed at the pharmacy, but this depends on several factors (Pottegård, 2014). Furthermore, medicines that are dispensed are not necessarily taken (secondary non-adherence). Likewise, the date of dispensing may not be the date of ingestion.

Non-exposed misclassified as exposed

The issue of non-adherence is further complicated by women deliberately discontinuing their medicine in anticipation or upon discovery of pregnancy or refusing medicines they need, due to (often misplaced) fears of harm to the fetus (Huybrechts, 2019). These issues potentially lead to exposure misclassification where truly unexposed pregnant women are classified as exposed affecting the specificity of the exposure measurement.

In pregnancy safety studies of intermittent medication use, misclassification of the timing of exposure is a problem that also need to be addressed. Furthermore, measurement errors in gestational age and the date of LMP may also lead to misclassification of the timing of the exposure during pregnancy. Early pregnancy losses, where gestational age is more uncertain, are particularly subject to this bias.

Exposed misclassified as non-exposed

The use of old prescriptions during pregnancy, use of someone else medication, use of medication purchased on the internet or over-the-counter (which varies from country to country) may lead to exposure misclassification. In these scenarios, truly exposed pregnant women are classified as unexposed, affecting the sensitivity of the exposure measurement.

Different approaches can be used to examine exposure misclassification, from sensitivity analyses examining different exposure assumptions to more advanced bias analyses. The latter quantify the impact of exposure misclassification on the effect estimate, using thechniques such as probabilistic bias analysis.

6.2.3.2. Outcome misclassification

The potential for outcome misclassification varies between data sources. One major concern is the validity of the diagnostic codes contained in the database. In administrative health database, diseases are primarily coded for billing and not for research. However, certain outcomes may be under-reported, e.g. some neurodevelopmental outcomes will be unrecognized when restricting to the ICD9-10 coding. Pregnant women exposed to certain medicines may be more carefully checked for some pregnancy outcomes, including both maternal disease and perinatal outcomes such as neuro-behavioural problems that might otherwise go unreported. This may bias effect estimates.

6.2.3.3. Covariate misclassification and co-morbidities

There may be no consistency in the collection of covariates within and between data sources (e.g for maternal tobacco or alcohol use), and it is important to be aware of the reporting accuracy of the covariates in each data sources. Information on covariates related to medical history may be inaccurate or incomplete in healthcare databases. Therefore, it may be necessary to infer diagnosis and severity

from prescriptions (particularly those with a single indication) i.e. prescriptions serve as proxies for co-morbidities. However, many medicines have several indications, which could lead to misclassification of co-morbidity. For example, pregabalin is indicated for neuropathic pain, general anxiety disorder and as an adjunct for focal seizures. Thus, the medical condition may only be ascertained by reviewing the full prescription record and if there are no other antiepileptics, the prescription of pregabalin is probably to treat neuropathic pain or anxiety.

6.2.4. Selection bias

Selection bias is the introduction of error due to systematic differences in characteristics between those selected and those not selected for a given study. It renders the selected study sample unrepresentative of the target population to which the findings will be extrapolated.

Bias from conditioning on fetal survival/live-birth

In pregnancy safety studies, a form of selection bias (sometimes referred to as live-birth bias) may arise from conditioning on fetal survival in the selection of the study population when examining prenatal exposures. It occurs when non-live birth outcomes are not (or not well) captured in the data source (e.g. early spontaneous or elective abortions) and the study is limited to live birth or certain non-live birth outcomes (e.g. stillbirths) (Huybrechts, 2019). Outcomes that are ascertained at a specified gestational age will be missing for those who do not survive until that time point, e.g. a spontaneous abortion before a congenital anomaly can be detected by ultrasound or at birth. Therefore, studies investigating major congenital anomalies may lead to biased results if only live births are considered. Ideally, studies should include terminations of pregnancy for fetal anomaly, stillbirths and miscarriages. Survival bias should not be confused with competing risk. In the presence of a competing risk, having one outcome precludes another outcome later in pregnancy. In the case of selection bias, the outcome had occurred but was not observed. When we have competing risks, the second outcome will not occur; leading to a real reduction of the risk for one outcome mediated through having another outcome.

Adjusting for common causes of the outcome under investigation and fetal loss can reduce selection bias, and risk factors for pregnancy loss should be identified and included in the analysis, where possible. Moreover, the Heckman model, developed in econometrics, can reduce or eliminate the bias due to selection in the estimates of regression models (Annex 19). It is especially useful in cases where the mechanism of selection or the factors related to the presence or absence of subjects in the study population are known.

6.3.Methods for validating data quality

The main attributes related to data quality include completeness, accuracy, comparability and timeliness. Completeness refers to the degree to which the data source includes the outcomes of interest. Accuracy refers to the extent to which data are exact, correct and valid. Comparability includes the representativeness and generalizability of a given data source or selected population. Timeliness refers to whether results can be obtained in a reasonable time period to inform patients and health care providers. These attributes can affect two aspects of data quality; quality of a data source and quality of the methods utilized and thus the evidence generated.

6.3.1. Quality of a data source

Routinely collected healthcare data, including administrative databases and registries, are excellent sources of pregnancy information, however the quality of the data can affect the results observed. There are factors related to a data source itself that can affect the quality of an observational study of medication safety in pregnancy.

The data source needs to include:

1) information to identify pregnancy, including live birth and non-live birth outcomes;

2) information that allows mother-infant linkage;

3) information on medication exposure, including time of initiation and cessation of treatment;

4) information on gestational age, including start and end of pregnancy, to determine timing of exposure relative to gestational age;

5) information on maternal and birth outcomes, including CA;

6) information on potential confounding factors, including indication for use, co-medication, lifestyle, and reproductive factors;

7) information on long-term follow-up of infants or mothers, if long-term effect of prenatal exposure is of interest (Andrade, 2017).

The validity of a study relies heavily on the data source's ability to provide accurate and complete information on these data components (Andrade, 2017). Examples of aspects that could affect these factors and hence the data quality include missing values; duplicate entry of cases; errors in the diagnosis codes, description or coding of CA and biases related to lack or excess of representation. Information on certain potential confounding variables of interest is also variable across healthcare databases. Certain maternal characteristics including reproductive history, maternal level of education, race/ethnicity, tobacco, alcohol, obesity, life-style factors and OTC medication and vitamin/supplement information can be variable across data sources and if relevant to the research question should also be validated.

An estimate of the degree of completeness can be obtained by comparing the data source with one or more independent reference sources, in which the whole (total) or part (partial) of the target

population is registered. Usually no reference standard for the evaluation of secondary data sources exists; thus, the degree of completeness will often be given as the degree of agreement with one or more reference data sources (Sorenson, 1996). The total number of cases or rates in the data source is compared with the total number or rates in other sources, or the expected number of cases is calculated by applying epidemiological rates from demographically similar populations (Sorenson, 1996). The external validity of estimates of pregnancy outcomes such as live birth, miscarriage, termination, and prematurity rates can be assessed by comparing with national vital statistics and published estimates. This can ensure that there is complete recording of a pregnancy outcome but it also ensures comparability regarding age, geographic region, time and other relevant confounding factors. It is important for CA to take into account any diagnostic and timing differences that could occur between data sources that are to be compared.

It is also important to compare the population that is selected from a given data source to that of the overall pregnant population within the data source, either exposed or diseased depending on the question. This will help determine the representativeness of the sample and thus the generalizability to other populations.

6.3.2. Quality of methods and evidence

There is not a quantitative definition of data quality for pregnancy studies; most researchers define data quality in the context of how the data will be used. Ideally, a validation study will use a gold standard as a measure to guide the accuracy and reliability of the pregnancy variables. The methods applied in a given study can also influence the quality. Similar factors to those listed above related to data source can also be applied to determine the quality of the methods utilized in observational studies of medication safety.

Validated high-performing algorithms, reviews of medical charts and medical diagnoses from hospitals, reviews by clinical experts and/or linkage to birth defect registries and/or birth certificate data can be used to validate exposure and outcomes.

Algorithms to identify pregnancy, pregnancy outcomes including live birth and non-live birth outcomes and mother-infant linkage need to be validated against a gold standard depending on the data source. Ascertainment of pregnancies, their timing, pregnancy outcomes and medication exposure are most often the concepts that need to be validated for a robust study. A woman's gestational length can be misclassified which could result in exposure misclassification. Validation of gestational age has been accomplished by several methods; using gestational age obtained from ultrasound data or the infant birth certificate are examples. Methods based on live born deliveries may result in trimester-specific misclassification.

The validity of algorithms for some CA requires confirmation through medical record review. Birth certificate data can be useful to accurately identify select infant outcomes, maternal diagnoses and

newborn, maternal, and paternal characteristics (Andrade, 2013). However, there are some outcomes where medical record performs better. ICD-9, ICD-10 codes and other coding systems depend on the healthcare system they are utilized in and validations might not be extrapolated to other cohorts.

Each method of data collection on medication exposure needs to be validated depending on how the data is collected. Electronic pharmacy files can demonstrate that a medication was dispensed, but information on whether the medication was actually taken is not available from those sources. While some studies have shown that prescription fillings are valid estimates for actual medication use (Van Gelder 2018), others have reported that noncompliance for some medications may be common among pregnant women, especially in the first trimester (Andrade, 2017).

Many studies use self-reported questionnaires or maternal interviews to assess medication use during pregnancy. Although both prescription and OTC medication use may be assessed, validation studies have shown that medication use, particularly medication for short-term use, can be underreported using these methods of data collection (Van Gelder, 2018).

Biological monitoring or screening on medication may overcome the potential for exposure misclassification associated with using self-reported information or routinely collected data (Arbuckle, 2010). This analytical method might not be sufficiently sensitive to detect medications with low serum concentrations, including inhalation medication and dermatological preparations.

As a gold standard for assessing medication use in epidemiologic studies is unavailable, medication use has been validated through examination of medical records, patient questionnaires, pharmacy records, and screening of serum samples. Novel methods of data collection, such as mobile applications to daily record medication intake, may improve ways to validate exposure assessment of medication use during pregnancy (Van Gelder, 2019).

Completeness and accuracy of pregnancy ascertainment, pregnancy timing, pregnancy outcomes and medication exposure need to be measured dependent upon the data source selected and the research question.

7. Conclusion

The aim of this document is to provide foundations for conducting pharmacoepidemiological studies among pregnant women by means of secondary use of large population-based data. The document aims to describe the main core evidence elements to consider when generating medication safety evidence for pregnancy to optimise benefit-harm decision-making for patients and healthcare professionals. It also provides a list of "default" core evidence elements to be used consistently when assessing safety of medication use during pregnancy.

Finally, in 2024, this document will be revised, in the light of experience from Demonstration Projects and further literature, as part of Task 1.6 regarding Recommendations and Guidelines from ConcePTION WP1 and submitted for Qualification advice.

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9. Annexes

Annexe 1. Literature search strategies for the systematic review of some therapeutic areas covered by the Demonstration Projects.

A systematic review focusing on the therapeutic areas of three Demonstration Projects (task 1.5) concerning depression, multiple sclerosis /systemic lupus erythematosus and neuropathic pain (DP1.1, DP1.2, DP1.3) has been conducted. The search has been conducted using Metapreg. It is a project supported by Agence Nationale de Sécurité du Médicament (ANSM), Hospices Civils de Lyon and University Lyon-1 – Laboratoire de Biométrie et Biologie Évolutive (LBBE) and managed at Pharmacology and Toxicology department of Lyon's university and teaching hospital (metaPreg, 2020), accessible at: metaPreg.org. Pubmed, Scopus and Web of Science were searched from databases inception to February 28, 2020. The results from the electronic search are accessible online; These lists need to be analysed by each DP partners to evaluate the relevance of the individual studies found by the systematic research. The research strategies can be found below.

DP 1.3 Multiple sclerosis

Results of the search: http://metapreg.org/admin/outsourcing.aspx?exposition=292

(Rituximab OR ofatumumab OR mitoxantrone OR glatiramer OR natalizumab OR fingolimod OR teriflunomide OR alemtuzumab OR ocrelizumab OR dimethyl fumarate OR Siponimod) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR "prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage " OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "registry" OR "birth register" OR "observational study" OR "population-based health datasets" OR "population health data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal

Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "compared with controls" OR "case-control" OR "healthy controls" OR disproportionality OR "proportional reporting ratio") AND (humans[Mesh])

DP 1.3 Lupus

Results of the search: http://metapreg.org/admin/outsourcing.aspx?exposition=320

(heparin OR azathioprine OR methotrexate OR mycophenolic acid OR belimumab OR hydroxychloroquine) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR "prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage " OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "birth register" OR "observational study" OR "population-based health datasets" OR "population health data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "case-control" OR disproportionality OR "proportional reporting ratio") AND (humans[Mesh])

DP 1.2 selective serotonin reuptake inhibitors

Results of the search: http://metapreg.org/admin/outsourcing.aspx?exposition=149

(“Serotonin Uptake Inhibitors” OR “5-Hydroxytryptamine Uptake Inhibitors” OR “5 Hydroxytryptamine Uptake Inhibitors” OR “Serotonin Reuptake Inhibitors” OR “5-HT Uptake Inhibitors” OR “5 HT Uptake Inhibitors” OR “Selective Serotonin Reuptake Inhibitors” OR alaproclate OR Amoxapine OR Citalopram OR Clomipramine OR femoxetine OR Fenfluramine OR Fluoxetine OR Fluvoxamine OR indalpine OR Norfenfluramine OR Olanzapine OR Paroxetine OR Sertraline OR

Trazodone OR Vilazodone Hydrochloride OR Vortioxetine OR Zimeldine OR) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR "prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage " OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "birth register" OR "observational study" OR "population-based health datasets" OR "population health data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "case-control" OR disproportionality OR "proportional reporting ratio") AND (humans[Mesh])

DP 1.1 analgesics

Results of the search: http://metapreg.org/admin/outsourcing.aspx?exposition=321

(Morphine OR Oxycodone OR Codeine OR Tramadol OR Tapentadol OR Ziconotide) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR "prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage " OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "birth register" OR "observational study" OR "population-based health datasets" OR "population health

data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "case-control" OR disproportionality OR "proportional reporting ratio") AND (humans[Mesh])

DP 1.1 Antiepileptics (gabapentin, pregabalin, lacosamide, carbamazepine)

Results of the search: http://metapreg.org/admin/outsourcing.aspx?exposition=322

(gabapentin OR Pregabalin OR lacosamide OR carbamazepine) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR "prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage " OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "birth register" OR "observational study" OR "population-based health datasets" OR "population health data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "case-control" OR disproportionality OR "proportional reporting ratio") AND (humans[Mesh])

DP 1.1 miscellaneous

Ropinirole, Amitriptyline, Clomipramine, Imipramine, Duloxetine, Lidocaine, Capsaicine, Botulinum toxin, Cannabis sativa extract, Levorphanol

Results of the search: http://metapreg.org/admin/outsourcing.aspx?exposition=131

(Ropinirole OR Amitriptyline OR Clomipramine OR Imipramine OR Duloxetine OR Lidocaine OR Capsaicine OR Botulinum toxin OR Cannabis sativa extract OR Levorphanol) AND ("birth defects" OR "birth defects-drug exposure" OR "teratogenic risk" OR "teratogenicity" OR "prenatal exposure" OR

"prenatally exposed" OR "fetal exposure" OR "congenital anomaly" OR "fetal anomalies" OR "congenital anomalies" OR "congenital malformation" OR "congenital malformations" OR "congenital major malformations" OR "congenital disorders" OR "cardiovascular defects" OR "preterm birth" OR "stillbirth" OR "miscarriage " OR "spontaneous abortion" OR "use during pregnancy" OR "exposure in pregnancy" OR "exposure during pregnancy" OR "exposed in utero" OR "first-trimester exposure" OR Teratogens OR "Birth defect"[Mesh] OR "Congenital Abnormalities"[Mesh] OR "Fetal Death/chemically induced"[Mesh] OR "Fetal Development/drug effects"[Mesh] OR "Fetal Diseases/chemically induced"[Mesh] OR "Fetus/drug effects"[Mesh] OR "Stillbirth"[Mesh] OR "Teratogens"[Mesh] OR "Abortion, Spontaneous"[MESH]) AND ("cohort study" OR "prospective study" OR "prospective observational study" OR "case-control study" OR "prospective follow-up study" OR "prospective follow-up" OR "meta-analysis" OR "systematic review" OR "retrospective study" OR "birth register" OR "observational study" OR "population-based health datasets" OR "population health data" OR "Cohort Studies"[MESH] OR "Prospective Studies"[Mesh] OR "Case-Control Studies"[Mesh] OR "Observational Study"[ptyp] OR "Meta-Analysis"[ptyp] OR "Longitudinal Studies"[MESH] OR "Registries"[MESH] OR "Retrospective Studies"[MESH] OR "Randomized Controlled Trial"[ptyp] OR "matched controls" OR "matched control" OR "case and control" OR "case-control" OR disproportionality OR "proportional reporting ratio") AND (humans[Mesh])

Annex 2. A general literature search for pharmacoepidemiology studies in the past 10 years

Linguamatics IE2 tool was used to search for research papers on Medline (PubMed). Keywords, MESH terms and and their expanded synonyms from ontologies were used. MeSH and NCI Thesaurus were used to search for indications/diseases, NCI Thesaurus to search for drugs, and Entrez and GO for genes. The keywords and MESH considered were related to "epidemiology or pharmacoepidemiology" and pregnancy outcomes: "Ectopic pregnancy, Spontaneous abortion, miscarriage, Elective termination, Still birth, fetal death, Preterm live birth, premature birth, Neonatal death, Congenital malformation, congenital anomaly, Major congenital malformation, major congenital anomaly, fetal anomaly, birth defect, congenital abnormalities, postpartum hemorrhage, preeclampsia, Congenital heart defect, Congenital heart disease, Heart Defects, cardiac defects, Neonatal Intensive Care Unit, Infant Small for Gestational Age, Low Birth Weight, Small for Gestational Age, Very Low Birth Weight, Extremely Low Birth Weight, Long term development outcome, attention deficit, autism spectrum, and developmental delay". The search was limited to observational or comparative studies that were published within 2009-2019.

The literature search returned 440 papers which were manually reviewed. Studies were excluded if the paper did not pertain to maternal and child associations or medication in pregnancy. Outcome only studies, studies of impact of disease alone, maternal mortality only, studies that assessed associations with non-drugs (e.g. levels of hormones, tobacco exposure), randomised controlled trials, prevention of disease during pregnancy, characterization of diseases in pregnancy and non-human studies were also excluded. After these exclusions were applied, 68 studies were retained.

The literature review was conducted to collect study information for 68 studies. Forty-five of the 68 studies had information that fulfilled the criteria for evaluation: secondary data collection and mother and infant exposure. The summaries below are only for the 45 studies that fulfilled the criteria.

Databases

Relevant information on the databases was provided in 45 studies.

- US claims/EHRD: 12
- CPRD: 4
- European healthcare databases: 21
- Canadian healthcare databases: 2
- Australian healthcare databases: 1
- Multiple databases: 5

Disease areas covered

Hypertension, gestational diabetes, multiple sclerosis, HIV, bipolar disorder, rheumatic disease, depression, fibromyalgia, asthma, H1N1 and seasonal influenza, HPV, epilepsy

Etiological window

Relevant information was provided in all studies. Some studies had multiple etiological windows prior to pregnancy and during pregnancy.

- Prior to pregnancy:
    - One year/anytime prior: 8
    - Three months prior: 2
    - Four weeks prior: 5
    - Two weeks prior: 2
- During pregnancy:
    - Whole pregnancy period or not specified: 11
    - First trimester and second/third trimester: 25
    - Early/late exposure: 1

In majority of studies etiological window was dependent on study outcome, for example spontaneous abortion.

Maternal outcomes

29 studies included maternal outcomes as endpoints.

- The main endpoints recorded were:
    - Spontaneous abortion, elective termination, stillbirth, postpartum hemorrhage/bleeding, preeclampsia, mode of delivery, gestational diabetes, pregnancy-associated complications
- Definitions of spontaneous abortions and still births differed between studies (ex. 20 weeks, 22 weeks, 23 weeks, 24, weeks)

Perinatal outcomes

38 studies had perinatal outcomes as endpoints. Endpoints frequently recorded are listed below.

- Most common outcomes were:
    - Major or minor congenital anomalies and malformations, preterm birth, small for gestational age
- Less common outcomes were:
    - Perinatal mortality (first 4-12 weeks of life), APGAR score, treatment in neonatal care unit, IUGR

Fetal outcomes

7 studies had fetal outcomes as endpoints. Endpoints frequently recorded are listed below.

- Brain development, ADHD, cardiac-related outcomes, non-specific abnormalities

Validation

Relevant information was provided in 30 studies.

- Medical chart reviews and medical diagnoses from hospitals were most commonly done for study validation
- A few studies used algorithms that were validated on medical chart reviews as a validation tool
- 1 study validated using physician or patient referral and another using an independent classification committee

Sample size calculation

Sample size was specified in 30 studies. In the majority of studies, sample size was calculated based on the primary endpoint for the sample size needed overall and stratified by exposure status.

- For those exposed to the drug of interest, sample size ranged from 124 to 19,513
- For those unexposed to the drug of interest, sample size ranged from to 124 to 499,729
- Overall sample size ranged from 89 to 949,504

Estimated effect size

The estimated effect size was specified in 17 studies:

- Most estimating an odds ratio of 2.0 to 3.0
- Range of typical odds ratios was 1.15 to 3.5

Drug utilization information

35 studies had relevant information for drug utilization information.

- 9 of these studies had a drug utilization conducted
- 26 of these studies did not have a drug utilization conducted

Study design

Relevant information on study design was reported in 45 studies. Prospective cohorts were the most commonly done study design. Retrospective cohorts were the second-most commonly done.

- Case-control: 1
- Prospective cohort: 26
- Retrospective cohort: 13

- Nested cohort: 1
- Matched prospective cohort: 2
- Meta-analysis: 1
- Design unspecified: 1

Comparators

Relevant information on comparators was provided in 45 studies. Some studies had multiple types of comparators.

- Specific or nonspecific active comparator: 19
- Unexposed control group: 22
- Unexposed diseased (levels of disease severity): 6
- Multiple comparators/unspecified: 7

Statistical methods

Relevant information was provided in 43 studies. Some studies used multiple statistical methods.

- Regression model (Linear, Log-binomial, Logistic): 22
- Cox proportional hazards model: 12
- Regression model with propensity scores (Matched analysis): 13
- Subgroup analysis: 5
- Sensitivity analysis: 5
- Univariate analysis: 4

Covariates

Relevant information about covariates was provided in 41 studies. Covariates frequently recorded are listed below.

- Age, obstetrical history, smoking/alcohol/illicit drug use, infections during pregnancy, depression and anxiety, demographic characteristics, medical history, medical comorbidities like diabetes and asthma, psoriasis and arthritis, influenza vaccination status, chronic disease score, congenital anomalies, social economic status, health care utilization, folic acid intake, BMI

Duration of infant follow-up

Relevant information was provided in 22 studies, duration dependent on specific outcome as follows:

- Major congenital malformations and anomalies: 3-12 months typically with one study reporting 2 years and two studies 5+ years

- Neurodevelopmental outcomes: 1 year and 5+ year follow up frequently recorded

Annex 3. Methodological review of population-based studies in the EU PAS Register

Relevant information for individual studies covered the following areas:

- Sponsor
- Completion (Y/N)
- Database(s)
- Therapeutic area
- Etiological window
- Maternal outcomes
- Perinatal outcomes
- Fetal outcomes
- Child outcomes (longer-term)
- Validation
- Sample size
- Estimated effect size
- Drug utilization information
- Study design
- Comparators
- Statistical methods
- Covariates
- Duration of infant follow-up
- Study findings
- Regulatory commitment (Y/N)
- Label update

Table 1. List of the 19 pregnancy studies with secondary data collection filed in EU PASS register.

Name of study	Sponsor	completion (yes/no); if yes, provide a date	Database(s)
Observational study to assess maternal and foetal outcomes following exposure to albiglutide during pregnancy	GSK	Yes - 2019	Truven Health MarketScan
Pregnancy outcomes in Multiple Sclerosis populations exposed and unexposed to interferon β - a register-based study in the Nordic countries	Biogen, Bayer, Novartis, Merck Serono	Yes - 2018	Multiple Databases in Sweden, Norway and Finland including Prescription -, Medical birth -, Hospital - and Multiple Sclerosis registries
Observational study to assess maternal and fetal outcomes following exposure to Ixekizumab	Lilly	No	HealthCore Integrated Research database
Assessing the safety of oseltamivir exposure in pregnant women	**Roche**	Yes - 2017	Prescription, Medical birth and hospital databases in Denmark
Asthma treatment in pregnancy and the frequency of adverse pregnancy outcomes (WEUSRTP4850)	**GlaxoSmithKline**	**Yes: 2013**	United Kingdom's General Practice Research Database (CPRD)
Isotretinoin and the effectiveness of the pregnancy prevention programmes in Europe	**EMA**	**Yes: 2013**	Population-based healthcare DB from UK (CPRD; SAIL), Italy (Region Emilia-Romagna; Tuscany) and Norway (Norwegian MBR and prescription database)
Safety of the second generation antipsychotics during pregnancy	**Finnish Medicines Agency**	**No**	Finnish national health registers: National Birth Register, the Register of Congenital Malformations, and the Drug Prescription Register
Infant and childhood neurodevelopmental	**NIMH**	**unknown, Planned**	Finland national registers: Medical Birth Register,

outcomes following prenatal exposure to selective serotonin reuptake inhibitors: overview and design of a Finnish Register-Based Study (FinESSI)		**completion date 31/12/2015**	Hospital Discharge Register, Drug Reimbursement Register, and Population Register
Consequences for life of children with in utero exposure to metformin in Finland – a register-based cohort study	**Merck KGaA**	**No, planned final study report 30/08/2019**	Finland national registers: Prescription register, Medical Birth Register, Register of Congenital Malformations, Care Register for Health Care, Register of Primary Health Care Visits, Population Register Centre, Statistics Finland, and Regional laboratory databases
Pregnancy and birth outcome assessment in a population-based cohort after exposure to Trumenba	**Pfizer**	**No**	This study will engage several large national and regional healthcare systems that have established electronic administrative claims databases and are current participants of the Sentinel System. Possible participants include Meyers Primary Care Institute, Group Health Research Institute, Harvard Pilgrim Health Care, Aetna, HealthCore, Inc., Blue Cross Blue Shield of Massachusetts, Optum Epidemiology, and Vanderbilt University Medical Center.
Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine (F1J-MC-B059)	**Lilly**	**No**	Danish and Swedish national birth register
Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine (F1J-	**Lilly**	**Yes: 2018**	National Pregnancy Registry

MC-B057)			
Pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study	**Merck**	**No**	Automated healthcare databases in 7 European countries: Denmark, Finland, France (OFSEP data source), Germany (German MS pregnancy registry), Norway (Nordic Health Registers), Sweden, and Scotland (MEMO database)
Asthma medication during pregnancy : a cohort study in EFEMERIS	**ANSM, CNAMTS, PHRC**	**Yes; Dec 2012 (information on infant outcomes from poster presentation)**	EFEMERIS database
Pregnancy outcome in women exposed to dopamine agonists during pregnancy: a study in EFEMERIS database	**ANSM, CNAMTS, PHRC**	**Yes; Dec 31 2010**	EFEMERIS database
Safety of influenza AH1N1 pandemic vaccination during pregnancy: a comparative study using the EFEMERIS database	**ANSM, CNAMTS, PHRC**	**Yes; Nov 30, 2010**	EFEMERIS database
114101 - Post-marketing safety study to assess the risk of spontaneous abortions in women exposed to Cervarix in the United Kingdom	**GlaxoSmithKline**	**Yes: 2012**	Clinical Practice Research Datalink General Practicioner OnLine Database (CPRD Gold)
Observational study to assess maternal asthma during pregnancy and its association with fetal outcomes	**GlaxoSmithKline**	**Yes: 2018**	Medicaid Analytic eXtract (MAX) and Truven Health MarketScan databases

Exposure to REMICADE® (Infliximab) during Pregnancy in Patients with Inflammatory Bowel Disease, Rheumatoid Arthritis, Psoriatic Arthritis, Ankylosing Spondylitis and Psoriasis: a Review and Analysis of Birth Outcomes from the Swedish, Danish, and Finnish Medical Birth Registers	**Janssen**	**Yes, 2016**	Swedish, Danish and Finnish MBRs, Patient Registers and Prescribed drug registers

Summary of 19 pregnancy studies with secondary data collection filed in EU PASS register

Sponsor

Relevant information provided in all studies:

- Health Authorities: 6 studies (EMA, Finnish Medicines Agency, French Medicines Agency)
- Pharmaceutical Companies: 13 studies

Completion

Relevant information provided in all studies:

- Yes: 13 studies
- No: 6 studies

Database(s):

Relevant information was provided in all studies:

- US claims/EHR databases: 5 studies
- CPRD: 2 studies
- Data Registries in Nordic countries: 7 studies
- French healthcare database: 3 studies
- Multiple databases: 2 studies

Therapeutic area

Type 2 Diabetes Mellitus (T2DM), Gestational DM, Multiple Sclerosis, Psoriasis, Influenza, Asthma, Acne vulgaris, Depression, Psychosis, Vaccines, Parkinson.

Etiological window

Relevant information was provided in 18 studies:

- Prior to pregnancy:
    - One year prior: 2 studies
    - Three months prior: 4 studies
    - Four weeks prior: 3 studies
    - Two weeks prior: 2 studies
- During pregnancy:
    - Whole pregnancy period or not specified: 12 studies
    - First trimester and second/third trimester: 6 studies
    - Early/late exposure: 3 studies

In majority of studies etiological window was dependent on study outcome, for example MCA: first

trimester. SGA/pre-term delivery: early exposure. Spontaneous abortions/stillbirth 90 days before diagnosis.

Maternal outcomes

13 studies included maternal outcomes as outcomes:

- Most of these 13 studies included spontaneous abortions, stillbirths, elective terminations as maternal outcomes. Of note definitions of spontaneous abortions and stillbirths differed between studies (20 weeks, 22 weeks, 23 weeks, 24 weeks). In addition:
    - 2 studies had pre-eclampsia as an outcome
    - Mode of delivery (induction of delivery, cesarean delivery) outcome in 3 studies
    - Two studies had product specific maternal outcomes like maternal hypoglycaemia (T2DM), infections during pregnancy, serious peri-partum infections (monoclonal antibody)

Perinatal outcomes

11 studies had perinatal outcomes as outcomes:

- Most of these 11 studies had Preterm birth, SGA as perinatal endpoints
- 5 studies had perinatal death as endpoint (definition differed between studies, first 4-12 weeks of life)
- Apgar score endpoint in 5 studies
- 3 studies had product specific perinatal outcome: macrosomia, hypoglycaemia congenital hypothyroidism (T2DM)
- 2 studies had fetal hypoxia, treatment in neonatal care unit, need for resuscitation

Fetal outcomes

12 studies had fetal outcomes as outcomes

- Most of these 12 studies had major and minor malformations as outcomes (2 studies specifically mentioned TOPFA, one study mentioned specific malformations)
- 2 studies had product specific outcomes: Serious infections of infant, antibiotics prescribed, neutropenia

Child outcomes (long-term)

3 studies had childhood/long-term outcomes

- These included (dependent on disease area/product type): Diabetes mellitus, PCOS, hypoglycemia, psychiatric or neurodevelopmental outcomes (including depression, anxiety, autism spectrum disorders, ADHD)

Validation

Relevant information was provided in 13 studies

- Studies conducted in US claims/EHR databases: In all studies outcomes were either directly validated through medical chart reviews or based on algorithms already validated against chart reviews
- Studies conducted in CPRD/French database (EFEMERIS): All studies included validation/review of outcomes
- Studies conducted in Nordic countries: No validation was conducted, diagnoses were considered already validated (medical diagnoses from hospitals)

Sample size

Specified in 17 studies. In majority of studies sample size was calculated based on primary outcome.

- in 9 studies primary outcome was MCA (in 2 of these additional outcomes were included in sample size calculation as well: serious infections and spontaneous abortions)
- in one study primary outcome was spontaneous abortions
- in one study primary outcome was a composite endpoint including TOPFA, MCA and stillbirth.

NB – follow-up required in 6 studies.

Estimated effect size

Specified in 10 studies:

- Most of these studies indicated that they would be able to detect increases in MCA between 50%-300%
- One study able to detect a 77% increase in composite outcome (see above)
- One study able to detect a 70% increase in serious infections of the infant and a 90% increase in serious infections of mother
- One study able to detect a 60% increase in rate of spontaneous abortions

Drug utilization information

15 studies had relevant information:

- In 10 studies the answer was “Drug utilization data not available/assessable before conduct of safety study” – several of these answered “not necessary, due to mature product” or similar.
- In 5 studies the answer was “Yes”, in one case it was specified as a separate drug utilization study.

Study design

Relevant information in 18 studies

- All these were conducted as retrospective cohort studies

Comparators

Relevant information in 17 studies:

- Specific active comparator: 5 studies
- Non-specific active comparator (for example drug class or similar): 4 studies
- Unexposed control group: 8 studies

Statistical methods

Relevant information was provided in all 19 studies:

- Majority used logistic regression with control for relevant confounders.
- A few studies used regression analysis using propensity score matching.

Covariates

Relevant information in 18 studies:

- Most studies collected information about the following covariates: Age, mother demographic characteristics, mother medical history, mother obstetric history, mother lifestyle habits (smoking, alcohol)

Duration of infant follow-up

Relevant information in 15 studies, duration dependent of specific outcome as follows:

- MCA: Majority of studies had between 3-12 months of follow-up, one study 2 years, one study 5 years
- Neurodevelopmental outcomes: 2 studies with this endpoint, one had follow-up till 14 years, one till 20 years of age

Study findings

Reported in 6 studies

Regulatory commitment

Relevant information was reported in 15 studies:

- 5 studies were conducted as regulatory commitments

Label update

In two studies specific wording was included in product SmPC

Annex 4. Studies referred to in product labels

Methodology

Search strategy

Between 24 November-23 December 2019, the most recent EPAR - Product Information for all human medicines authorized in the EU (on November 24, 1123 medicines were authorized) were accessed at the EMA website (https://www.ema.europa.eu/en/medicines/field_ema_web_categories%253Aname_field/Human/ema_group_types/ema_medicine/field_ema_med_status/authorised-36?sort=search_api_aggregation_ema_medicine_title&order=asc). For all those medicines, Section 4.6 (Fertility, pregnancy and lactation) was screened for information on observational studies in humans performed for the respective medicines or the drug class to which they belong. When data on human observational studies were available, the relevant study text was extracted and copied by reviewer 1 to a spreadsheet. Subsequently, reviewer 1 summarized available information in section 4.6 by drug class, drug name, indications, SmPC date, data source, pregnancy-related outcomes, additional information on birth defects, study sample size, study design features (ie. comparators used and definition of exposure window) and outcome measures in the same spreadsheet (Appendix x). Quality control was performed by another reviewer.

Results

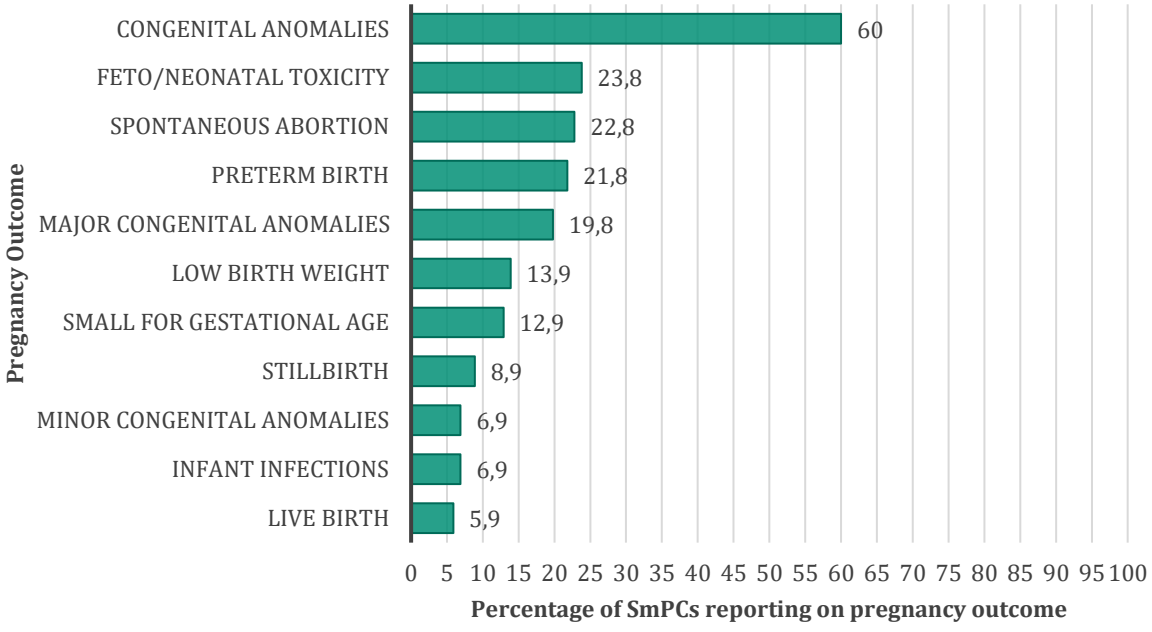
Out of 1123 screened authorized medicines' product information, 101 contained information/data on pregnancy related outcomes possibly derived from observational studies. For many of those the origin of the data was not mentioned, thus it was not always possible to determine the exact data source (literature-derived; routine pharmacovigilance collected by the MAH, registry results, population-based study results, clinical trial results…).

For those medicines with information on human data in section 4.6, the content (structure) was not consistent across SmPCs. Some include an overall summary of all information on the medicine available to the MAH (eg. derived from a totality of all postmarketing cases in company safety database or based on literature review), sometimes followed by results of medicine-specific pregnancy studies. In other product labels, only pregnancy information for the class is included, while for others no information on the class is provided. In addition, definitions and classifications used for outcomes such as malformations and for effect estimates such as risk are not provided.

The aim of this review was to summarize pregnancy study design features and outcome information that qualified to be cited in the authorized product labels, aiming at presenting the current benchmark for the presentation/description of pregnancy risk information in the SmPC. All SmPCs that cited information possibly derived from observational studies were included in this analysis.

The most frequently reported pregnancy outcome in the EU SmPCs for authorized human medicines were “congenital anomalies” (also referred to as birth defects, malformative effects, teratogenicity or malformative toxicity) in 61/101 (60.0%) of SmPCs in scope of the review. Other frequently reported outcomes were “neonatal toxicity” (also referred to as fetotoxicity) in 24/101 (23.8%), “spontaneous abortions” in 23/101 (22.8%), “preterm births” (PTB) in 22/101 (21.8%), “major congenital anomalies” (MCA; major structural defects, major congenital malformations) in 20/101 (19.8%), “low birth weight” in 14/101 (13.9%), “small for gestational age/intrauterine growth restriction” in 13/101 (12.9%), “stillbirths” in 9/101 (8.9%), “minor birth defects” and “infant infections” in 7/101 (6.9%) and “live births” in 6/101 (5.9%) of all SmPCs under review. Outcomes that were reported in less than 5% of those SmPCs include elective abortion, gestational diabetes, preeclampsia, premature rupture of membrane, postpartum hemorrhage, c-sections, infant death, infant malignancies, infant symptoms of beta-blockade, persistent pulmonary hypertension of the newborn (PPHN), hyperkalemia, neonatal adrenal insufficiency, hyperbilirubinemia, thrombocytopenia/anemia and neurodevelopmental disorders/delays.

Figure 1: Frequency (%) of selected pregnancy outcomes for which results are included in EU SmPCs



Note that 11/101 (10.9%) of those SmPCs were for anti-TNFs to treat autoimmune diseases (includes biosimilars). The risks evaluated in observational studies and reported for those biologics are similar for all but one and include at least MCA and PTB.

Very few pregnancy sections provided details on specific CA or (EUROCAT) subgroups of MCAs that were observed, except for the antivirals, cancer treatments, graft rejection treatments and for methotrexate.

For most pregnancy sections, it was not clear what the study sample size was and for the few that did mention the study size, it ranged between 22 to 10.000 exposed. Information on study design features such as the comparators used to assess risk was also very limited and not consistent across medicines (untreated disease controls, disease control treated with other medication, unvaccinated controls, general population, disease matched or population-based estimates). Finally, there was also no consistency in the description of the extend of the observed pregnancy risk. Effect estimates for prevalence rates and relative risks (OR) were reported for some, but for many the vague terms “no risk” or “increased risk” were used to describe the exposed pregnancy risk.

Annex 5. Scoping review for core definitions of outcomes: Non-live birth, live birth and infant outcomes

Selection of non-live birth, live birth and infant outcomes

Scoping review

There have been numerous initiatives over the recent years to establish common core outcomes to improve the quality of research and reporting on health and care during pregnancy and at birth (Dildy, 2017). A review of these main initiatives was undertaken in order to identify the working set of relevant outcomes for this task.

For this document, we included recommendations from: Euro-Peristat (Zeitlin, 2003), Gaia (Bonhoeffer, 2016), ICHOM (Nijagal, 2018), MoniTor (Moller, 2018) and reviews from initiatives to produce core outcome sets (COS) which are registered with COMET (one on preterm birth and one on growth restriction): COS_GONet (van 't Hooft, 2016), COSGROVE (Healy, 2019). We also included a Delphi about what variables should be systematically included for studies of growth restriction (Khalil, 2019). Table 1 provides a brief description of these initiatives.

As shown in this table many of these outcomes cover a broader range of indicators than those relative to non-live birth and live birth/infant outcomes, in particular, longer term neurodevelopment, maternal health and health care. Many are intended for use in prospective studies and do not provide detailed definitions. Finally, some are developed for use in a global as opposed to a high-resource context. The context for the application of the recommendations – in particular when applications use routine data – is important to consider because many outcome measures depend on investigations during pregnancy that may not be systematically available in low-resources settings.

This initial list derived from these recommendations will be checked against other outcome sets. There are currently over 30 core outcomes series either completed or ongoing related to maternal and child health listed on the Comet initiative website; (to see list of initiatives on the Comet website: http://www.comet-initiative.org/studies/searchresults?guid=ff69d75e-3544-44d1-aad2-7764aec4be9c). Several other completed or on-going initiatives are particularly relevant: miscarriage (Smith, 2017), diabetes (Nielsen, 2018), obesity in pregnancy (Dadouch, 2018), hyperemesis gravidarium (Koot, 2018). Furthermore, reviews that could be useful for the validation of the list of outcomes and their definitions were identified. For instance, there are recent consensus statements on maternity quality of care indicators, including a Delphi on consensus indicators to support maternity service quality improvement (Bunch, 2018) and indicators of quality for intrapartum care (Sibanda, 2013). We also note two detailed reviews of existing recommended indicators: one as part of work to specify indicators for maternity care in a circumpolar context (Rich, 2016) and another more general review of indicators for monitoring

maternal and neonatal quality care (Saturno-Hernandez , 2019). The reviews focusing on indicators generated from routine sources will be of particular interest.

Table 2 provides an overview of the outcomes proposed by these initiatives. It is divided into outcomes related to: non-live birth, death following live birth, gestational age, birthweight, infant morbidity, pregnancy complications, mode of delivery, maternal death and maternal morbidity. Although the first five categories only relate directly to the topic considered here, pregnancy complications and mode of delivery could have relevance for defining infant outcomes. Maternal outcomes were included to look at consistency across the recommendations.

This table shows high thematic concordance related to the overall categories of outcome, but more diversity in approaches to how the outcomes are labelled and defined. This can be seen in relation to outcomes linked to gestational age and birthweight. For instance, some refer to gestational age, without providing cut-offs or classify by mode of onset (spontaneous/indicated).

The most discordance is observed for the recommendations concerning neonatal/infant morbidity. The following morbidity outcomes were recommended, with minimal overlap: Respiratory distress/respiratory morbidity/oxygen dependency/use of MV/bronchopulmonary dysplasia/chronic lung disease (4 out of 7), neonatal encephalopathy/hypoxic ischemic encephalopathy (3/7), neonatal Infection (2/7), APGAR score at 5 minutes (2/7), neonatal morbidity composite, but undefined (2/7), fetal distress/hypoxia/umbilical artery pH (2/7) and only one time: neonatal length of stay, neonatal seizures, birth injury, gastrointestinal morbidity, necrotizing enterocolitis. Many of the morbidity indicators were not defined. It is likely that continued review of existing consensus/recommendations on outcomes would expand this list further.

While mode of delivery is a pregnancy intervention, the need for an emergency CS is included as an outcome for studies of fetal growth restriction.

Working list of outcomes

Based on the review above, the following working list of outcomes is proposed

Non-live birth:

1. Stillbirth
2. Spontaneous abortion or miscarriage
3. Ectopic pregnancy

Live birth and infant:

1. Neonatal death
2. Infant death
3. Preterm birth (birth before term)

4. Sub-optimal fetal size and growth (Small for gestational age, fetal growth restriction, large for gestational age, macrosomia)
5. Neonatal morbidity (APGAR, length of stay/transfer for higher level care, respiratory morbidity, morbidity composite).

Table 1. Sources for review of non-live birth and live birth outcome

Name of source	Purpose	Definitions	Number of indications	Application
Euro-Peristat (www.europeristat.com)	Indicators for reporting using routine data sources	Yes	11 outcomes/ 30 core and recommended + 5 future	Retrospective, using already collected data
Gaia	Definition of outcome for monitoring of vaccines	Yes	19 out of 21 (see Annex below)	Prospective
ICHOM (International Consortium for Health Outcomes Measurement, www.ichom.org)	To define a minimum, internationally appropriate set of outcome measures for evaluating and improving perinatal care with a focus on outcomes that matter to women and their families.	Yes		Not specified
GONet_core outcome set for prevention of preterm birth	To develop a consensus on a set of key clinical outcomes for the evaluation of preventive interventions for preterm birth in asymptomatic pregnant women.	No		Prospective
COSGROVE; A Core Outcome Set for the prevention and treatment of fetal growth restriction	To develop consensus among international stakeholders o na set of core outcomes that should be used in trials that evaluate (1) preventative or (2) therapeutic interventions for FGR.	No	22 outcomes - fetal, neonatal, maternal and childhood. 5 childhood indicators not included	Mainly for clinical trials, but they are also suitable for cohort studies, clinical audits, and other research methods
Mother and Newborn Information for Tracking Outcomes and Results (MoNITOR) Technical Advisory Group www.who.int/ maternal_child_adolescent/ epidemiology/monitor/en/)	To compile existing maternal and newborn indicators proposed by or in use by different agencies, academic, and professional groups, including key metadata such as indicator definition, numerator and denominator, and data source. This scoping review was designed to address the research question: What is the range of indicators currently in use or recommended for global, national and subnational monitoring of maternal and newborn health?	Yes	15 impact indicators/140 in scoping review	Studies to monitor and to evaluate maternal and child health, application is global
Delphi on variables in studies of fetal growth restriction (FGR)	To reach consensus on a list of clinical variables that should be considered essential to report in any study on FGR	No	16 essential (of which 6 outcomes) and 30 recommended (of which 5 outcomes)	Prospective clinical research study

Table 2. Non-live birth, live birth, pregnancy and maternal outcomes

Indicators	Euro-Peristat	Gaia	ICHOM	CoNet	Monitor	COSGROVE	Delphi on data in studies of FGR
Non-live birth outcomes	Fetal mortality rate by terminations of pregnancy, gestational age, birth weight, plurality Fetal deaths due to congenital anomalies Other causes of death (Future)	Abortion Stillbirth	Stillbirth	Offspring mortality	Stillbirth	Stillbirth	Stilllbirth intrapartum death
Live birth outcomes - mortality	Neonatal mortality rate by gestational age, birth weight, plurality Infant mortality rate by gestational age, birth weight, plurality Neonatal deaths due to congenital anomalies Other causes of death (Future)	Neonatal Death	Neonatal death	Offspring mortality	Neonatal mortality rate Neonatal mortality as % deaths <5	Neonatal death	Neonatal death
live birth outcomes - birthweight	Birth weight distribution by vital status, gestational age, plurality	Fetal Growth Restriction Low birthweight Small for gestational age		Birth weight	Low birthweight Small for gestational age	Birthweight Birthweight <10th percentile Birthweight <3rd percentile	Birthweight Birthweight centile
Live birth outcomes gestational length	Distribution of gestational age by vital status, plurality	Preterm birth (including Gestational Age Assessment Algorithm)	Spontaneous preterm birth iatrogenic preterm birth	Gestational age at birth	Preterm birth rate	Gestational age at birth Extremely preterm birth (delivery at <28 weeks Preterm birth (delivery <37 weeks gestation)	gestational age at delivery

Indicators	Euro-Peristat	Gaia	ICHOM	CoNet	Monitor	COSGROVE	Delphi on data in studies of FGR
Live birth outcomes morbidity	Distribution of APGAR score at 5 minutes neonatal morbidity (Future) Prevalence of neonatal encephalopathy (Future)	Neonatal Infection Respiratory distress Neonatal Encephaolopathy	Neonatal length of stay Oxygen dependence Birth injury	Offspring infection Gastrointestinal morbidity Respiratory morbidity	Neonatal morbidity rates	Need for mechanical ventilation Bronchopulmonary dysplasia/chronic lung disease Necrotizing enterocolitis Neonatal seizures Hypoxic ischemic encephalopathy	Five-minute Apgar score Umbilical artery pH Signs of fetal distress/hypoxia on FHR monitoring
Fetal status		Reassuring Fetal Status					
Preganancy complications (both live and non-live birth)		Hypertensive disorders of pregnancy/ Pre-Eclampsia/ Eclampsia Pre-mature Labour Antenatal Bleeding Gestational Diabetes Dysfunctional Labor		Preterm rupture of membranes		Maternal Preeclampsia Eclampsia	
Mode of delivery	Mode of delivery by parity, plurality, presentation (of fetus), previous caesarean section, Robson classification				(Caesarean section rate, included in "outcomes" services provided)	Mode of delivery	Mode of delivery Need for emergency caesarean section Onset of labour

Indicators	Euro-Peristat	Gaia	ICHOM	CoNet	Monitor	COSGROVE	Delphi on data in studies of FGR
Maternal death	Maternal mortality ratio by maternal age Maternal mortality by cause	Maternal death	Maternal death	Maternal mortality	Maternal mortality ratio, Total maternal deaths Lifetime risk of maternal deaths Maternal cause of death Maternal near miss ratio Percentage of maternal deaths among adolescents	Maternal death	
Maternal morbidity	Prevalence of severe maternal morbidity Prevalence of tears to the perineum	Postpartum Haemorrhage		Maternal infection or infammation	Maternal morbidity rates		

Stillbirth by timing and gestational age sub-group

Relevant gestational age and birthweight classifications for stillbirth

Birth weight groups are defined by weight intervals of <500 grams, from 500 grams i.e. 500 – 999 grams, 1000-1499 grams, to ≥5000 grams.

Gestational age groups can be divided as follows

<20 weeks (under 140 days) **

20-21 weeks (under 154 days), **

22-23 weeks (154-167 days) **

24-27 weeks (167-195 days) **

28-31 weeks (196-223 days)

32-36 weeks (224-258 days)

37-41 weeks (259-293 days)

42+ weeks (294 days)

** < 20 weeks: considered to be spontaneous abortionsmiscarriage in most countries

** 20-21 weeks: recorded as stillbirths in some countries

** 22-23 weeks: recorded as stillbirths in most countries, but removed from analyses to ensure complete ascertainment and comparability

** 24-27, recorded as stillbirths in most countries, but removed from analyses to ensure complete ascertainment and comparability in contexts with weaker reporting.

Neonatal death

Relevant analytic classifications

Suggested groupings for analysis by timing of death, are as follows:

By single days for the first week of life (< 24 hours (day 0), 1, 2, 3, 4, 5, 6 days), 7-13 days, 14-20 days, 21-27 days

Or

< 24 hours, 1-6 days, 7-27 days,

Or

< 7 days (0-6 days) (early), 7-27 days (late) (minimum classification)

Additional age classification for day 0 neonatal deaths:

< 1 hour, 1–11 hours, 12–23 hours

Note that many administrative databases measure calendar days, which does not make it possible to obtain information on hour of death.

Birth weight groups for neonatal mortality statistics are defined by weight intervals of <500 grams, from 500 grams i.e. 500 – 999 grams, 1000-1499 grams, …to ≥5000 grams.

Gestational age groups neonatal mortality statistics are divided as follows:

<22 weeks (under 154 days),

22-23 weeks (154-167 days)

24-27 weeks (167-195 days)

28-31 weeks (196-223 days)

32-36 weeks (224-258 days)

37-41 weeks (259-293 days)

42+ weeks (294 days)

Groupings for plurality are as Singletons and Multiples

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Annex 6. Congenital anomalies

Existing guidelines from EUROCAT.

All the following information can be found on the EUROCAT website, www.eurocat-network.eu, specifically in EUROCAT Guide 1.4 (https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/Full_Guide_1_4_version_28_DEC2018.pdf)

EUROCAT uses the World Health Organisation (WHO) International Classification of Diseases (ICD) version 10 for coding CA, with the British Paediatric Association one-digit extension for more specificity (ICD9 was used pre-2005).

CA subgroups, as defined by their ICD9 and ICD10 codes, are subgroups for which prevalence information is routinely produced and have been defined according to one or more of the following criteria:

- larger heterogeneous subgroups which show the relative health burden of anomalies in different organ systems
- subgroups which balance aetiologic homogeneity with the level of diagnostic specificity which can reasonably be expected by European registers
- subgroups which are relevant to health service provision, including prenatal diagnosis
- subgroups which are well defined and clinically diagnosed with a good level of consistency across Europe, and where specific codes are available
- subgroups that are consistent with the hierarchical classification of ICD10
- subgroups of reasonable frequency such that a yearly European prevalence can be meaningful.

Only major anomalies (i.e. not on the list of minor anomalies for exclusion) are allocated to subgroups. Where appropriate for aetiologic analyses, cases with chromosomal anomalies, skeletal dysplasia cases, genetic syndromes and microdeletions will be excluded from the analysis (e.g. a case of Trisomy 18 with spina bifida will be allocated to the Trisomy 18 subgroup but not to the spina bifida subgroup). All prevalence rates and counts for subgroups are based on cases, not malformations. Thus, a case with a VSD and pulmonary valve stenosis will be counted ONCE in “all anomalies”, ONCE in “cardiac”, ONCE in “VSD”, and ONCE in “pulmonary valve stenosis”. A case with encephalocele and renal dysplasia will be counted once in the count of “all anomalies”, once in “central nervous system anomalies”, once in “neural tube defects”, once in “encephalocele”, once in “urinary anomalies” and

once in "renal dysplasia". It follows that the number of cases in different subgroups CANNOT be added together to find the total number of cases, as one case can be counted in more than one subgroup.

EUROCAT list of Minor Anomalies for Exclusion

Cases with only minor anomalies and unspecified anomalies for exclusion should not be transmitted to EUROCAT. Minor anomalies should be described in text, coded and transmitted to EUROCAT when they are in association with major anomalies. If a case with one or more minor anomalies only is transmitted to EUROCAT, it will be excluded by computer if the minor anomalies have specific codes which allow recognition. Some minor anomalies do not have specific codes and cases with such isolated anomalies must always be recognised and excluded at local level on the basis of the text description.

"Minor" anomalies are excluded, when isolated, because they have lesser medical, functional or cosmetic consequences (although they may be indicators of other problems) and experience shows that their definition and diagnosis and reporting vary considerably. At the present time, it is not useful to collect data at a European level on these anomalies. Anomalies which are not always truly congenital in origin, sometimes associated with immaturity at birth are also excluded. In addition, poorly specified conditions are excluded and it is recommended that for any such cases more specific information be sought from medical records.

Please note that the list is not exhaustive and not all syndrome features are mentioned

EUROCAT Subgroups of Congenital Anomalies (Version 2014) EUROCAT Guide 1.4

EUROCAT Subgroups	ICD10-BPA	ICD9-BPA	Comments	Excluded minor anomalies post-2005	Excluded minor anomalies pre-2005	Subgroup binary variable number (al)
All anomalies *	Q-chapter, D215, D821, D1810^, P350, P351, P371	74, 75, 27910, 2281^, 76076, 76280, 7710, 7711, 77121		Exclude all minor anomalies as specified in Guide 1.4, section 3.2	Exclude all minor anomalies as specified in Guide 1.2 (ICD9 and ICD10)	al1
Nervous system	Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07	740, 741, 742		Q0461, Q0782		al2
Neural Tube Defects	Q00, Q01, Q05	740, 741, 7420				al3
Anencephalus and similar	Q00	740				al4
Encephalocele	Q01	7420	Exclude if associated with anencephalus			al5

			subgroup			
Spina Bifida	Q05	741	Exclude if associated with anencephalus or encephalocele subgroups			al6
Hydrocephalus	Q03	7423	Exclude hydranencephaly 74232. Exclude association with NTD subgroup			al7
Severe microcephaly	Q02	7421	Exclude association with NTD subgroup			al8
Arhinencephaly / holoprosencephaly	Q041, Q042	74226				al9
Eye	Q10-Q15	743		Q101-Q103, Q105, Q135	74365	al10
Anophthalmos / microphthalmos	Q110, Q111, Q112	7430, 7431				al11
Anophthalmos	Q110, Q111	7430				al12
Congenital cataract	Q120	74332				al13
Congenital glaucoma	Q150	74320				al14
Ear, face and neck	Q16, Q17, Q18	744		Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q1880, Q189	74411, 74412, 7443, 74491	al15
Anotia	Q160	74401				al16
Congenital Heart Defects	Q20-Q26	745, 746, 7470-7474	Exclude PDA with GA <37 weeks Exclude peripheral pulmonary artery stenosis with GA < 37 weeks	Q2111, Q250 if GA <37 weeks, Q2541, Q256 if GA<37 weeks, Q261	Q250, 7470 if GA <37 weeks **	al17
Severe CHD	Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262	74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742	ICD9-BPA has no code for HRH and double outlet right ventricle			al97
Common arterial truncus	Q200	74500				al18
Double outlet right ventricle	Q201	No code				al109
Transposition of great vessels	Q203	74510				al19
Single ventricle	Q204	7453				al20
VSD	Q210	7454				al21
ASD	Q211	7455		Q2111		al22
AVSD	Q212	7456				al23
Tetralogy of Fallot	Q213	7452				al24
Triscuspid atresia and stenosis	Q224	7461				al25
Ebstein's anomaly	Q225	7462				al26

Pulmonary valve Stenosis	Q221	74601				al27
Pulmonary valve Atresia	Q220	74600				al28
Aortic valve atresia/stenosis	Q230	7463	ICD9-BPA has no code for atresia			al29
Mitral valve anomalies	Q232, Q233	7465, 7466				al110
Hypoplastic left heart	Q234	7467				al30
Hypoplastic right Heart	Q226	No code				al31
Coarctation of aorta	Q251	7471				al32
Aortic atresia / interrupted aortic arch	Q252	74720				al111
Total anomalous pulm venous return	Q262	74742				al33
PDA as **only** CHD in term infants (GA +37 weeks)	Q250	7470	Livebirths only			al100
Respiratory	Q300, Q32-Q34	7480, 7484, 74850, 74852, 74858, 7486, 7488	Exclude Q336	Q314, Q315, Q320, Q331	Q309, 74819	al34
Choanal atresia	Q300	7480				al35
Cystic adenomatous malf of lung	Q3380	No code				al36
Oro-facial clefts	Q35-Q37	7490, 7491, 7492	Exclude association with holoprosencephaly or anencephaly subgroups			al101
Cleft lip with or without cleft palate	Q36, Q37	7491, 7492	Exclude association with holoprosencephaly or anencephaly subgroups			al102
Cleft palate	Q35	7490	Exclude association with cleft lip subgroup. Exclude association with holoprosencephaly or anencephaly subgroups			al103
Digestive system	Q38-Q45, Q790	750, 751, 7566		Exclude Q381, Q382, Q3850, Q400, Q401, Q4021, Q430, Q4320, Q4381, Q4382	Q381, Q401, 7500, 7506	al40
Oesophageal atresia with or without trachea-oesophageal fistula	Q390-Q391	75030-75031				al41
Duodenal atresia or stenosis	Q410	75110	Exclude if also annular pancreas subgroup			al42
Atresia or stenosis of other parts of small intestine	Q411-Q418	75111-75112				al43

Ano-rectal atresia and stenosis	Q420-Q423	75121-75124				al44
Hirschsprung's disease	Q431	75130-75133				al45
Atresia of bile ducts	Q442	75165				al46
Annular pancreas	Q451	75172				al47
Diaphragmatic hernia	Q790	75661				al48
Abdominal wall defects	Q792, Q793, Q795	75671, 75670, 75679				al49
Gastroschisis	Q793	75671				al50
Omphalocele	Q792	75670				al51
Urinary	Q60-Q64, Q794	75261, 753, 75672		Q610, Q627, Q633		al52
Bilateral renal agenesis including Potter syndrome	Q601, Q606	75300	Exclude unilateral			al53
Multicystic renal dysplasia	Q6140, Q6141	75316				al54
Congenital hydronephrosis	Q620	75320				al55
Bladder exstrophy and / or epispadia	Q640, Q641	75261, 7535				al56
Posterior urethral valve and / or prune belly	Q6420, Q794	75360, 75672				al57
Genital	Q50-Q52, Q54-Q56	7520-7524, 75260, 75262, 7527-7529		Q523, Q525, Q527, Q5520, Q5521	Q540, 75260#	al58
Hypospadias	Q54	75260			Q540, 75260	al59
Indeterminate sex	Q56	7527				al60
Limb	Q65-Q74	7543-7548, 755		Q653-Q656, Q662-Q669, Q670-Q678, Q680, Q6810, Q6821, Q683-Q685, Q7400	75432, 75452, 75460, 75473, 75481, 75560	al61
Limb reduction defects	Q71-Q73	7552-7554				al62
Club foot – talipes equinovarus	Q660	75450				al66
Hip dislocation and / or dyspasia	Q650-Q652, Q6580 Q6581	75430				al67
Polydactyly	Q69	7550				al68
Syndactyly	Q70	7551				al69
Other anomalies / syndromes						
Skeletal dysplasias	Q7402, Q77, Q7800, Q782-Q788	No code				al104
Craniosynostosis	Q750	75600				al75
Congenital constriction bands / amniotic band	Q7980	76280				al76
Situs inversus	Q893	7593				al79

Conjoined twins	Q894	7594				al80
Congenital skin disorders	Q80-Q82	7571, 7573		Q825, Q8280	Q825, Q8280, Q8281, 75731, 75738	al81
VATER/VACTERL	Q8726	759895				al112
Vascular disruption anomalies	Q0435, Q411, Q412, Q418, Q710, Q712, Q713, Q720, Q722, Q723, Q730, Q793, Q795, Q7980, Q7982, Q8706	No code				al113
Laterality anomalies	Q206, Q240, Q3381, Q890, Q893	No code				al114
Teratogenic syndromes with malformations	Q86, P350, P351, P371	No code				al82
Fetal alcohol syndrome	Q860	76076				al83
Valproate syndrome	Q8680	No code				al84
Maternal infections resulting in malformations	P350, P351, P371	7710, 7711, 77121				al86
Genetic syndromes + microdeletions	Q4471, Q6190, Q7484, Q751, Q754, Q7581, Q87, Q936, D821	75581, 75601, 75604, 7598, 27910	Exclude Associations and sequences Exclude Q8703, Q8704, Q8706, Q8708, Q8724, Q8726 Exclude 759801, 759844, 759895			al105
Chromosomal	Q90-Q92, Q93 , Q96-Q99	7580-7583, 7585-7589	Exclude microdeletions Q936			al88
Down syndrome	Q90	7580				al89
Patau syndrome / trisomy 13	Q914-Q917	7581				al90
Edwards syndrome / trisomy 18	Q910-Q913	7582				al91
Turner syndrome	Q96	75860, 75861, 75862, 75869				al92
Klinefelter syndrome	Q980-Q984	7587				al93

* All Anomalies = ALL cases of congenital anomaly, excluding cases with only minor anomalies as defined below. Cases with more than one anomaly are only counted once in the "All Anomalies" subgroup.
^ ICD10 code D1810 (ICD 9 code 2281) is the code for cystic hygroma
** The additional PDA exclusion (<2500 grams) listed in Guide 1.2 is not applied

EUROCAT Description of the Congenital Anomaly Subgroups (clinical definitions). EUROCAT Guide 1.4.

EUROCAT Subgroup	Description	Often diagnosed after one week of age
Nervous System		
Neural Tube Defects:	Neural tube defects inlcude anencephalus, encephalocele, spina bifida and iniencephalus	no
Anencephalus and similar	Total or partial absence of brain tissue and the cranial vault. The face and eyes are present. (incompatible with life)	no
Encephalocele	Cystic expansion of meninges and brain tissue outside the cranium. Covered by normal or atrophic skin.	no
Spina Bifida	Midline defect of the osseous spine usually affecting the posterior arches resulting in a herniation or exposure of the spinal cord and/or meninges	no
Hydrocephaly	Dilatation of ventricular system with impaired circulation and absorption of the cerebrospinal fluid. The dilatation should not be due to primary atrophy of the brain, with or without enlargement of the skull	no
Microcephaly	A reduction in the size of the brain with a skull circumference less than three standard deviations below the mean for sex, age and ethnic origin. Definitions known to vary between clinicians and regions.	yes
Arhinencephaly / holoprosencephaly	Absence of the first cranial (olfactory) nerve tract. There is a spectrum of anomalies from a normal brain, except for the first cranial nerve tract, to a single ventricle (holoprosencephaly)	yes
Eye		
Anophthalmos / microphthalmos	-	
Anophthalmos	Unilateral or bilateral absence of the eye tissue. Clinical diagnosis	no
Microphthalmos	Small eye/eyes with smaller than normal axial length. Clinical diagnosis	yes
Cataract	Alteration in the transparency of the crystalline lens	yes
Congenital glaucoma	Large ocular globe as a result of increased ocular pressure in fetal life	yes
Ear		
Anotia	Absent pinna, with or without atresia of ear canal	no
Congenital heart defects (CHD)		
Severe CHD	13 subgroups of severe CHD as defined below	yes
Common arterial truncus	Presence of a large single arterial vessel at the base of the heart (from which the aortic arch, pulmonary and coronary arteries originate), always accompanied by a large subvulvar septal defect.	yes
Double outlet right ventricle	Both aorta and the pulmonary artery connect to the right ventricle	yes
Transposition of great vessels, complete	Total separation of circulation with the aorta arising from the right ventricle and the pulmonary artery from the left ventricle	no
Single ventricle	Only one complete ventricle with an inlet valve and an outlet portion even though the outlet valve is atretic	no
VSD	Defect in the ventricular septum	yes
ASD	Defect in the atrial septum	yes
AVSD	Central defect of the cardiac septa and a	yes

	common atrioventricular valve, includes primum ASD defects	
Tetralogy of Fallot	VSD close to the aortic valves, infundibular and pulmonary valve stenosis and over-riding aorta across the VSD	yes
Tricuspid atresia and stenosis	Obstruction of the tricuspid valve and hypoplasia of the right ventricle	no
Ebstein's anomaly	Tricuspid valve displaced with large right atrium and small right ventricle	no
Pulmonary valve stenosis	Obstruction or narrowing of the pulmonary valves which may impair blood flow through the valves	yes
Pulmonary valve atresia	Lack of patency or failure of formation altogether of the pulmonary valve, resulting in obstruction of the blood flow from the right ventricle to the pulmonary artery	no
Aortic valve atresia/stenosis	Occlusion of aortic valve or stenosis of varying degree, often associated with bicuspid valves	yes for stenosis
Mitral valve anomalies	Atresia, stenosis or insufficiency of the mitral valve	Yes for stenosis and insufficiency
Hypoplastic left heart	Hypoplasia of the left ventricle, outflow tract and ascending aorta resulting from an obstructive lesion of the left side of the heart	no
Hypoplastic right heart	Hypoplasia of the right ventricle, always associated with other cardiac malformations	no
Coarctation of aorta	Constriction in the region of aorta where the ductus joins aorta	yes
Aortic atresia/interrupted aortic arch	Atresia or interrupted connection of the aorta	
Total anomalous pulmonary venous return	All four pulmonary veins drain to right atrium or one of the venous tributaries	No
PDA as only CHD in term infants	Open duct in infancy or later and requiring invasive treatment	yes
Respiratory		
Choanal atresia	Bony or membraneous choanae with no passage from nose to pharynx	Yes for unilateral
Cystic adenomatous malformation of lung	Cystic structures of the lung, usually unilateral	No
Orofacial clefts		
Cleft lip with and without cleft palate	Clefting of the upper lip with or without clefting of the maxillary alveolar process and hard and soft palate	
Cleft palate	Fissure defect of the soft and/or hard palate(s) or submucous cleft without cleft lip	No
Digestive system		
Oesophageal atresia with or without tracheo-oesophageal fistula	Occlusion or a long gap of the oesophagus with or without tracheo-oesophagael fistula	no
Duodenal atresia and stenosis	Occlusion or narrowing of duodenum	no
Atresia and stenosis of other parts of small intestine	Occlusion or narrowing of other parts of small intestine	no
Ano-rectal atresia and stenosis	Imperforate anus or absence or narrowing of the communication canal between the rectum and anus with or without fistula to neighbouring organs	no
Hirschsprung's disease	Absence of the parasympatic ganglion nerve cells (aganglionosis) of the wall of the colon or rectum. May result in congenital megacolon	yes
Atresia of bile ducts	Congenital absence of the lumen of the extrahepatic bile ducts	yes

Annular pancreas	pancreas surrounds the duodenum causing stenosis	yes
Diaphragmatic hernia	Defect in the diaphragm with protrusion of abdominal content into the thoracic cavity. Various degree of lung hypoplasia on the affected side	no
Abdominal wall defects		
Gastroschisis	Protrusion of abdominal contents through an abdominal wall defect lateral to an intact umbilical cord and not covered by a membrane	No
Omphalocele	Herniation of abdominal content through the umbilical ring, the contents being covered by a membrane sometimes ruptured at the time of delivery	No
Urinary		
Bilateral renal agenesis including Potter syndrome	Bilateral absence, agenesis, dysplasia or hypoplasia of kidneys including Potter's syndrome. Incompatible with life	no
Multi cystic renal dysplasia	Multiple, non-communicating cysts of varying size in the kidney without functional kidney tissue.	yes
Congenital hydronephrosis	Obstruction of the urinary flow from kidney to bladder. Report only major cases defined as a renal pelvis at or above 10 mm after birth.	yes
Bladder extrophy	Defect in the closure of the bladder and lower abdominal wall	no
Posterior urethral valve and/or prune belly	Urethral obstruction with dilatation of bladder and hydronephrosis. In severe cases also distended abdomen	no
Genital		
Hypospadias	The urethral meatus is abnormally located and is displaced proximally on the ventral surface of the penis	Yes
Indeterminate sex	Includes true and pseudohermaphroditism male or female	No
Limb		
Limb reduction	Total or partial absence or severe hypoplasia of skeletal structure of the limbs	no
Club foot - talipes equinovarus	Foot anomaly with equinus of the heel, varus of the hindfoot and adductus of the forefoot	no
Hip dislocation and/or dysplasia	Location of the head of the femur outside its normal position	no
Polydactyly	Extra digit or extra toe	no
Syndactyly	Partial or total webbing between 2 or more digits includes minor forms	yes
Other anomalies / syndromes		
Skeletal dysplasia	A large group of genetic diseases with developmental disorders of chondro-osseous tissue	Yes
Craniosynostosis	Premature closure of cranial sutures	Yes
Congenital constriction bands / Amniotic bands	Bands in the amniotic fluid that causes constriction of part of the brain, body or limbs, including limb-body-wall complex	No
Situs inversus	Inverse position of thoracic or abdominal organs or both	Yes
Conjoined twins	Siamese twins	No
Congenital skin disorders	A group of mainly genetic skin disorders in the newborn	No
VATER/VACTERL	Association with anomalies of Vertebra, anal atresia, cardiac, trachea- esophageal fistula, esophageal atresia, radial anomaly and limb defects	no
Vascular disruption anomalies (selected)	Anomalies likely to be due to vascular disruption	No
Laterality anomalies	Abnormal laterality mainly affecting heart and lungs	yes

Teratogenic syndromes with malformations	Congenital anomalies in pregnancies with known teratogenic exposure	Yes
Fetal alcohol syndrome	Fetal exposure to alcohol during pregnancy with following impact on fetal growth, facial appearance and development	Yes
Valproate syndrome	Fetal exposure to valproate during pregnancy with impact on fetal growth, facial appearance and development. Often associated with spina bifida	Yes
Maternal infections resulting in malformation	Specific maternal viral infections during pregnancy resulting in congenital anomalies in the fetus or infant	Yes
Genetic syndromes and microdeletions	Clinically or genetically diagnosed syndromes with dysmorphic features or congenital anomalies with or without a microdeletion	Yes
Chromosomal		
Down syndrome	karyotype 47,XX +21 or 47,XY +21 and translocations/mosaicism	no
Patau syndrome/trisomy 13	karyotype 47,XX +13 or 47,XY +13 and translocations/mosaicism	No
Edwards syndrome/trisomy 18	karyotype 47,XX +18 or 47,XY +18 and translocations/mosaicism	No
Turner syndrome	karyotype 45,X or structural anomalies of X chromosome	Yes
Klinefelter syndrome	karyotype 47,XXY or additional X-chromosomes	yes

"Non-congenital" anomalies

- Hydrocephaly where a result of preterm birth rather than congenital: all cases among preterm births should be thoroughly checked before registration.

EUROCAT List of minor anomalies. EUROCAT Guide 1.4. ICD10 codes marked in red: added in 2018 and 2019.

	Specified ICD10-BPA – if present
Head	
Aberrant scalp hair patterning	
Bony occipital spur	
Brachycephaly	
Compression facies	Q671
Depressions in skull, lacunar skull, temporal flattening	Q6740
Dolichocephaly	Q672
Dysmorphic face	Q189
Broad, prominent forehead	
Coarse facies	
Flattened face	
Frontal bossing / wide forehead	
Mid face hypoplasia	
Pointed facies	
Round head shape	
Sloping forehead	
Facial asymmetry	Q670
Flat occiput	
Macrocephalus	Q753
Metopic ridge, high metopic suture	
Other congenital deformities of skull, face and jaw	Q674
Plagiocephaly – head/skull asymmetry	Q673
Third fontanelle	
Skull, late closure	
Wormian bones	
Eyes	
Anisocoria	
Blue sclera	Q135
Congenital ectropion	Q101
Congenital entropion	Q102
Crocodile tears	Q0782
Dacryocystocele	H046
Downward slanting palpebral fissures	Q103
Dystopia canthorum	Q189
Epicanthic folds	Q189
Epicanthus inversus	Q189
Exophthalmos	H052
Hypertelorism	Q752
Hypotelorism	Q189
Other congenital malformations of eyelid	Q103
Oval shaped pupils	
Prominent/protruding eyes	H052
Short palpebral fissures	Q189
Stenosis or stricture of lacrimal duct	Q105

Synophrys	Q1880
Upward slanting palpebral fissures	Q103
Ears	
Absent tragus	
Accesorry auricle, preauricular appendage, tag or lobule	Q170
Asymmetric size	Q173
Auricular pit	
Bat ear, prominent, proturberant ear	Q175
Congenital absence of ear lobe	
Darwin's tubercle	
Double lobule	Q170
Lack of helical fold	Q173
Low set ears	Q174
Macrotia	Q171
Microtia/small ears	Q172
Narrow external auditory meatus	
Posterior angulation	Q173
Primitive shape	Q173
Pointed ear, Vulcan ear, simple ear	Q173
Unspecified and minor malformation of ear	Q179
Nose	
Anteverted nares	Q189
Bifid tip of nose	Q189
Broad nasal root, anomaly of nasal root	Q189
Depressed nasal bridge	Q189
Deviation of nasal septum	Q6741
Dysmorphic nose	Q189
Flat nose	Q189
Flattened nasal bridge	Q189
Notched alas	
Pinched nose	Q189
Prominent nasal bridge	Q189
Saddle nose	Q189
Small/hypoplastic nares	Q189
Small pointed nose	Q189
Underdeveloped nasal bones	Q189
Upturned nose	Q189
Wide nasal root	Q189
Oral regions	
Aberrant frenula	
Absent /hypoplasia depressor anguli oris (asymmetric crying	
Alveolar crest	
Anomalies of philtrum, elongated philtrum	Q189
Bifid uvula / cleft uvula	Q357
Borderline small mandible/ minor micrognathia	
Disturbances in tooth eruption	
Enamel hypoplasia	
Glossoptosis	
High arched palate	Q3850

Macrocheilia	Q186
Macroglossia / hemi-hypertrophy of tongue	Q382
Macrostomia	Q184
Malformed teeth	
Microcheilia	Q187
Microglossia	
Microstomia	Q185
Mid-oral tongue position	
Neonatal teeth	
Prominent jaw	Q189
Ranula	
Retrognathia/ receding chin	Q674
Short philtrum	Q189
Thin lips	Q189
Tongue tie or cyst of tongue	Q381
Neck	
Broad neck	Q189
Congenital malformation of face and neck, unspecified	Q189
Congenital thymic hypoplasia	
Mild webbed neck	
Other branchial cleft malformations	Q182
Preauricular sinus or cyst	Q181
Short neck	Q189
Sinus, fistula or cyst of branchial cleft	Q180
Thymus involution	
Thyreoglossal cyst	
Torticollis	Q680
Hands	
Accessorry carpal bones	Q7400
Arachnodactyly	
Clinodactyly (5th finger)	Q6810
Duplication of thumbnail	
Enlarged or hypertrophic nails	Q845
Other congenital malformations of nails	Q846
Overlapping fingers	
Short fingers (4. 5. th finger)	
Single/abnormal palmar crease	Q8280
Small fingers	
Subluxation of phalangeal bones	
Unusual dermatoglyphics	
Feet -Limb	
Bulbous toes	
Clicking hip, subluxation or unstable hip	Q653-Q656
Hip dysplasia and other specified/unspecified hip anomalies	Q658, Q659
Clubfoot of postural origin - other cong deformities of feet	Q668
Congenital deformity of feet, unspecified	Q669
Congenital pes planus	Q665
Enlarged or hypertrophic nails	Q845
Gap between toes (1st-2nd)	

Hallux varus – other congenital varus deformities of feet	Q663
Metatarsus varus – other congenital valgus deformities of feet	Q666
Metatarsus varus or metatarsus adductus	Q662
Overlapping toes	
Pes cavus	Q667
Prominent calcaneus	
Recessed toes (4th, 5th)	
Rocker bottom feet	Q6680
Short great toe	
Syndactyly (2nd-3rd toes)	
Talipes or pes calcaneovalgus	Q664
Talipes calcaneovarus	Q661
Skin	
Accessory nipples	Q833
Accessory skin tags	Q8281
Angioma	
Cafe-au-lait spot	
Depigmented spot	
Epibulbar dermoid	
Hemangioma if no treatment is required	
Heterochromia of hair	
Hypoplasia of toe nails	Q846
Lymphangioma if no treatment is required	
Mongoloid spot (whites)	Q8252
Neavus flammeus	Q8250
Persistent lanugo	
Pigmented naevus – congenital non-neoplastic naevus	Q825
Strawberry naevus	Q8251
Unusual placement of nipples/ wide spaced nipples	
Skeletal	
Abortive 12th rib	
Absence of rib/hypoplastic rib	Q7660
Accessory rib	Q7662
Bipartite vertebrae	
Bifid ribs	
Cervical rib	Q765
Congenital bowing of femur	Q683
Congenital bowing of fibula and tibia	Q684
Congenital bowing of long bones of leg, unspecified	Q685
Congenital bowing of upper limb	
Congenital deformity of spine	Q675
Congenital lordosis, postural	Q7643
Coronal clefts of vertebrae, incomplete	
Cubitus valgus	
Depressed sternum	
Duplication of ribs	
Fused rib, single	
Genu recurvatum	Q6821
Genua valgum	

Genua varum	
No ossification of os coccyx	
Ovoid configuration of vertebrae	
Prominent sternum	
Sacral dimple	L059
Shieldlike chest, other congenital deformities of chest	Q678
Spina bifida occulta	Q760
Sternum bifidum	Q7671
Depressed sternum / pectus excavatum	Q676
Prominent sternum / pectus carinatum	Q677
Brain	
Anomalies of septum pellucidum	
Arachnoid cysts	
Asymmetric ventricles, normal size	
Banana shaped cerebellum	
Cerebellar hypoplasia, mild	
Cerebral atrophy	
Choroid plexus cysts	
Cyst of septum pellucidum	
Enlarged cisterna magna, isolated	
Jaw-winking syndrome, Marcus Gunn's syndrome	Q0780
Periventricular leukomalacia	
Single congenital cerebral cyst	Q0461
Thin or hypoplastic corpus callosum	
Ventriculomegaly < 15 mm	
Cardiovascular	
Absence or hypoplasia of umbilical artery, single umbilical	Q270
Absence of vena cava superior	
Functional or unspecified cardiac murmur	R011
Cardiomegaly	I517
Cardiomyopathy	I429
Deviation of the heart axis	
Patent ductus arteriosus if GA < 37 weeks	Q250 if GA <37 weeks
Patent or persistent foramen ovale	Q2111
Peripheral pulmonary artery stenosis	Q256 if GA < 37 weeks
Persistent left superior vena cava	Q261
Persistent right aortic arch	Q2541
Persistent right umbilical vein	
Congenital heart block	Q246
Pulmonary	
Accessory lobe of lung	Q331
Azygos lobe of lung	Q3310
Bronchomalacia	Q322
Congenital laryngeal stridor	Q314
Single cyst of the lung	Q3300
Hyperplasia of thymus	
Laryngomalacia	Q3140
Pleural effusion	
Pulmonary hypoplasia, secondary	

Relaxation of diaphragm	
Thymus involution	
Tracheomalacia	Q320
Vocal cord palsy	
Gastro-intestinal	
Abdominal cyst not needing surgery	
Accessory spleen	
Anterior anus without surgery	
Choledochal cyst	Q444
Congenital adrenal hypoplasia	Q8911
Congenital cholestasis	
Congenital mesenteric cyst	Q4583
Cyst of spleen	
Diastasis recti	
Dilatation of intestine	
Functional gastro-intestinal disorders	Q4021, Q4320, Q4381, Q4382
Hepatomegaly	R160
Hiatus hernia	Q401
Inguinal hernia	K409
Liver cyst	
Meckel's diverticulum	Q430
Plica of anus	
Pyloric stenosis	Q400
Splenomegaly	R161
Transient choledochal cyst	
Umbilical hernia	
Renal	
Enlarged/thickened bladder	
Hydronephrosis with a pelvis dilatation less than 10 mm	
Hyperplastic and giant kidney	Q633
Single renal cyst	Q610
Vesico-ureteral-renal reflux	Q627
External genitals	
Bifid scrotum	Q5521
Buried penis	
Congenital chordee	Q544
Congenital adrenogenital disorders	E250
Congenital malformation of vulva	Q527
Congenital torsion of ovary	Q502
Curvature of penis	
Cysts of vulva	
Deficient or hooded foreskin/prepuce	N47
Developmental ovarian cyst(s)	Q501, Q5010, Q5011
Embryonic cyst of broad ligament	Q505
Enlarged clitoris	
Foreskin tethered to the scrotum	N47
Fusion of labia	Q525
Hydrocele of testis	P835
Hymen imperforate	Q523

Hypertrophy of hymen	
Hypoplasia of penis/micropenis	
Phimosis	N47
Prominent labia minora	
Retractile testis	Q5520
Seminal vesicle cyst	
Testicular torsion	N44
Transient ovarian cyst	
Undescended testicle	Q53
Unspecified ectopic testis	Q530
Vaginal skin tag	
Other	
Congenital malformation, unspecified	Q899
Chromosomal	
Balanced chromosomal rearrangements	Q95
Balanced translocations or inversions in normal individuals	
Balanced autosomal rearrangement in abnormal individual	Q952
Individuals with marker heterochromatin	
Individuals with autosomal fragile site	

Calculation of Prevalence Rates (Section 4.1. EUROCAT Guide 1.4)

In EUROCAT prevalence calculations, a baby/fetus with several anomalies is counted once within each class of anomaly. The number in different classes cannot be added to reach a total number of babies/fetuses. A baby is counted once only in any given prevalence.

EUROCAT prevalence is always cited as per 10,000 births.

Total prevalence =	$\frac{\text{No. Cases (LB + FD + TOPFA)}}{\text{No. Births (live and still)}} \times 10{,}000$
Livebirth prevalence =	$\frac{\text{No. Cases (LB)}}{\text{No. Births (live)}} \times 10{,}000$
Fetal death prevalence =	$\frac{\text{No. Cases (FD)}}{\text{No. Births (live and still)}} \times 10{,}000$
TOPFA prevalence =	$\frac{\text{No. Cases (TOPFA)}}{\text{No. Births (live and still)}} \times 10{,}000$
Cases =	Cases of congenital anomaly in population
LB =	Live birth
FD =	Fetal deaths from 20 weeks' gestation
TOPFA =	Termination of pregnancy for fetal anomaly after prenatal diagnosis, at any gestational age
Birth (live and still) =	All live and still births in the population as declared on official birth registrations

Note: Slight discrepancies are present between numerator and denominator as terminations of pregnancy for feta anomaly are included in the numerator but not the denominator, but are not great enough to have an important effect on prevalence.

It is very important **not** to include terminations done for other reasons than for fetal anomalies in either numerator or denominator. There may be large numbers of these terminations in some countries, and many are not examined for the presence or absence of congenital anomalies, nor recorded as such, so they can cause considerable bias in prevalence estimation.

Differences in total prevalence over time or between regions may reflect one or more of the following factors: genetic differences, environmental differences, differences in diagnostic services, differences in the methods of collecting epidemiological data, and even chance differences (see Interpretation of prevalence).

Differences in livebirth or fetal death prevalence over time or between regions may reflect the same factors as above, but also differences in prenatal screening policies and differences in frequency with which prenatal diagnosis is followed by termination of pregnancy.

See also section 4.2 in EUROCAT Guide 1.4 on Interpretation of Prevalence Rates.

Prevalence per 10,000 births (with 95%CI) of EUROCAT Congenital Anomaly subgroups. 2011 to 2017 - All full member registries combined. - Including genetic anomalies. www.eurocat-network.eu **accessed 20 April 2020;** last updated on: 10/12/2019

Anomaly group	Total Prevalence	Live	Still	TOPFA
All Anomalies	259.76 (258 - 261)	204.56 (203 - 205)	4.50 (4.32 - 4.69)	50.70 (50.08 - 51.33)
Nervous system	26.20 (25.75 - 26.65)	11.73 (11.44 - 12.04)	0.83 (0.75 - 0.91)	13.63 (13.31 - 13.96)
– Neural Tube Defects	10.08 (9.80 - 10.36)	2.03 (1.91 - 2.16)	0.31 (0.26 - 0.36)	7.74 (7.50 - 7.99)
– – *Anencephalus and similar*	4.05 (3.87 - 4.23)	0.20 (0.16 - 0.24)	0.18 (0.14 - 0.22)	3.67 (3.51 - 3.84)
– – *Encephalocele*	1.12 (1.03 - 1.22)	0.30 (0.25 - 0.35)	0.03 (0.02 - 0.05)	0.79 (0.71 - 0.87)
– – *Spina Bifida*	4.91 (4.72 - 5.11)	1.53 (1.43 - 1.64)	0.10 (0.07 - 0.13)	3.28 (3.12 - 3.44)
– Hydrocephalus	5.27 (5.07 - 5.47)	2.73 (2.59 - 2.88)	0.19 (0.15 - 0.23)	2.35 (2.21 - 2.48)
– Severe microcephaly	2.73 (2.59 - 2.88)	2.26 (2.13 - 2.39)	0.10 (0.07 - 0.13)	0.37 (0.32 - 0.43)
– Arhinencephaly/holoprosencephaly	1.58 (1.47 - 1.70)	0.25 (0.20 - 0.29)	0.06 (0.04 - 0.09)	1.28 (1.18 - 1.38)
Eye	4.01 (3.84 - 4.19)	3.62 (3.46 - 3.79)	0.04 (0.02 - 0.06)	0.35 (0.30 - 0.40)
– Anophthalmos/micropthalmos	0.89 (0.81 - 0.98)	0.65 (0.58 - 0.72)	0.02 (0.01 - 0.04)	0.22 (0.18 - 0.27)
– – *Anophthalmos*	0.20 (0.16 - 0.24)	0.12 (0.09 - 0.15)	0.01 (0.00 - 0.02)	0.07 (0.05 - 0.10)
– Congenital cataract	1.24 (1.15 - 1.34)	1.22 (1.12 - 1.32)	0.00 (0.00 - 0.01)	0.02 (0.01 - 0.04)
– Congenital glaucoma	0.31 (0.26 - 0.36)	0.31 (0.26 - 0.36)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Ear, face and neck	1.86 (1.74 - 1.98)	1.52 (1.42 - 1.64)	0.07 (0.05 - 0.09)	0.26 (0.22 - 0.31)
– Anotia	0.25 (0.21 - 0.29)	0.23 (0.19 - 0.28)	0.00 (0.00 - 0.01)	0.02 (0.01 - 0.03)
Congenital heart defects	79.17 (78.40 - 79.96)	69.31 (68.58 - 70.04)	1.25 (1.16 - 1.35)	8.61 (8.36 - 8.87)
– Severe CHD §	24.06 (23.63 - 24.49)	18.03 (17.66 - 18.41)	0.66 (0.59 - 0.73)	5.37 (5.16 - 5.57)
– Common arterial truncus	0.71 (0.64 - 0.79)	0.43 (0.37 - 0.49)	0.03 (0.02 - 0.05)	0.26 (0.21 - 0.30)
– Double outlet right ventricle §	1.62 (1.51 - 1.73)	1.11 (1.02 - 1.21)	0.07 (0.05 - 0.09)	0.44 (0.38 - 0.50)
– Transposition of great vessels	3.48 (3.32 - 3.65)	2.91 (2.76 - 3.06)	0.06 (0.04 - 0.09)	0.51 (0.45 - 0.58)
– Single ventricle	0.79 (0.71 - 0.87)	0.41 (0.35 - 0.47)	0.02 (0.01 - 0.04)	0.35 (0.30 - 0.41)
– Ventricular septal defect (VSD)	37.78 (37.25 - 38.33)	35.00 (34.49 - 35.52)	0.42 (0.36 - 0.48)	2.37 (2.23 - 2.51)
– Atrial septal defect (ASD)	16.56 (16.20 - 16.92)	16.07 (15.72 - 16.43)	0.09 (0.07 - 0.12)	0.39 (0.34 - 0.45)
– Atrioventricular septal defect	4.64 (4.46 - 4.84)	3.14 (2.99 - 3.30)	0.18 (0.14 - 0.22)	1.33 (1.23 - 1.43)

Anomaly group	Total Prevalence	Live	Still	TOPFA
(AVSD)				
– Tetralogy of Fallot	3.61 (3.44 - 3.78)	2.87 (2.72 - 3.02)	0.10 (0.08 - 0.13)	0.64 (0.57 - 0.71)
– Tricuspid atresia and stenosis	0.70 (0.63 - 0.78)	0.41 (0.36 - 0.47)	0.03 (0.02 - 0.05)	0.26 (0.22 - 0.31)
– Ebstein's anomaly	0.49 (0.43 - 0.55)	0.39 (0.34 - 0.45)	0.03 (0.02 - 0.05)	0.07 (0.05 - 0.09)
– Pulmonary valve stenosis	4.05 (3.87 - 4.23)	3.88 (3.71 - 4.06)	0.02 (0.01 - 0.03)	0.15 (0.12 - 0.19)
– Pulmonary valve atresia	1.13 (1.03 - 1.22)	0.81 (0.73 - 0.89)	0.02 (0.01 - 0.04)	0.30 (0.25 - 0.35)
– Aortic valve atresia/stenosis §	1.50 (1.39 - 1.61)	1.25 (1.16 - 1.36)	0.03 (0.01 - 0.04)	0.22 (0.18 - 0.26)
– Mitral valve anomalies	1.40 (1.30 - 1.51)	1.18 (1.08 - 1.27)	0.02 (0.01 - 0.03)	0.21 (0.17 - 0.26)
– Hypoplastic left heart	2.74 (2.60 - 2.89)	1.30 (1.20 - 1.40)	0.09 (0.06 - 0.12)	1.36 (1.26 - 1.47)
– Hypoplastic right heart §	0.65 (0.58 - 0.73)	0.33 (0.28 - 0.38)	0.03 (0.02 - 0.05)	0.29 (0.24 - 0.34)
– Coarctation of aorta	4.00 (3.82 - 4.18)	3.67 (3.51 - 3.84)	0.05 (0.04 - 0.08)	0.27 (0.23 - 0.32)
– Aortic atresia/interrupted aortic arch	0.53 (0.47 - 0.60)	0.41 (0.35 - 0.47)	0.01 (0.00 - 0.03)	0.12 (0.09 - 0.15)
– Total anomalous pulm venous return	0.71 (0.63 - 0.78)	0.66 (0.59 - 0.73)	0.00 (0.00 - 0.01)	0.04 (0.03 - 0.06)
– PDA as only CHD in term infants (>=37 weeks)	3.21 (3.05 - 3.37)	3.21 (3.05 - 3.37)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
Respiratory	4.16 (3.98 - 4.34)	3.32 (3.16 - 3.48)	0.14 (0.11 - 0.18)	0.71 (0.63 - 0.78)
– Choanal atresia	0.94 (0.85 - 1.03)	0.86 (0.79 - 0.95)	0.01 (0.00 - 0.02)	0.06 (0.04 - 0.09)
– Cystic adenomatous malf of lung §	1.12 (1.03 - 1.22)	1.01 (0.92 - 1.10)	0.02 (0.01 - 0.03)	0.10 (0.07 - 0.13)
Oro-facial clefts	14.26 (13.93 - 14.60)	12.57 (12.26 - 12.88)	0.21 (0.17 - 0.25)	1.49 (1.38 - 1.60)
– Cleft lip with or without palate	8.42 (8.17 - 8.68)	7.25 (7.01 - 7.49)	0.15 (0.11 - 0.18)	1.03 (0.94 - 1.12)
– Cleft palate	5.84 (5.63 - 6.05)	5.32 (5.12 - 5.53)	0.06 (0.04 - 0.09)	0.46 (0.40 - 0.52)
Digestive system	18.22 (17.85 - 18.60)	15.17 (14.83 - 15.51)	0.48 (0.42 - 0.54)	2.57 (2.44 - 2.72)
– Oesophageal atresia with or without tracheo-oesophageal fistula	2.65 (2.51 - 2.80)	2.36 (2.22 - 2.50)	0.09 (0.07 - 0.12)	0.21 (0.17 - 0.25)
– Duodenal atresia or stenosis	1.40 (1.30 - 1.51)	1.19 (1.10 - 1.29)	0.07 (0.05 - 0.10)	0.14 (0.11 - 0.18)
– Atresia or stenosis of other parts of small intestine	0.94 (0.86 - 1.03)	0.90 (0.82 - 0.98)	0.03 (0.01 - 0.04)	0.02 (0.01 - 0.03)

Anomaly group	Total Prevalence	Live	Still	TOPFA
– Ano-rectal atresia and stenosis	3.31 (3.15 - 3.47)	2.54 (2.40 - 2.69)	0.06 (0.04 - 0.08)	0.71 (0.64 - 0.78)
– Hirschsprung's disease	1.38 (1.28 - 1.49)	1.38 (1.28 - 1.49)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
– Atresia of bile ducts	0.35 (0.30 - 0.40)	0.35 (0.30 - 0.40)	0.00 (0.00 - 0.01)	0.00 (0.00 - 0.01)
– Annular pancreas	0.18 (0.14 - 0.22)	0.16 (0.13 - 0.20)	0.00 (0.00 - 0.01)	0.02 (0.01 - 0.03)
– Diaphragmatic hernia	2.87 (2.72 - 3.02)	2.03 (1.91 - 2.16)	0.10 (0.08 - 0.13)	0.73 (0.66 - 0.81)
Abdominal wall defects	6.48 (6.26 - 6.71)	3.36 (3.20 - 3.52)	0.26 (0.21 - 0.30)	2.87 (2.72 - 3.02)
– Gastroschisis	2.53 (2.40 - 2.68)	2.06 (1.93 - 2.19)	0.09 (0.07 - 0.12)	0.39 (0.33 - 0.44)
– Omphalocele	3.51 (3.35 - 3.68)	1.22 (1.12 - 1.32)	0.15 (0.12 - 0.19)	2.14 (2.02 - 2.28)
Urinary	35.32 (34.80 - 35.84)	29.99 (29.51 - 30.47)	0.56 (0.50 - 0.63)	4.76 (4.57 - 4.96)
– Bilateral renal agenesis including Potter syndrome	1.23 (1.14 - 1.33)	0.25 (0.20 - 0.29)	0.07 (0.05 - 0.09)	0.92 (0.84 - 1.01)
– Multicystic renal dysplasia	4.24 (4.06 - 4.42)	3.36 (3.20 - 3.52)	0.09 (0.06 - 0.12)	0.79 (0.72 - 0.87)
– Congenital hydronephrosis	13.20 (12.88 - 13.52)	12.63 (12.32 - 12.94)	0.10 (0.07 - 0.13)	0.47 (0.42 - 0.54)
– Bladder exstrophy and/or epispadia	0.63 (0.56 - 0.70)	0.43 (0.37 - 0.49)	0.01 (0.00 - 0.02)	0.19 (0.15 - 0.23)
– Posterior urethral valve and/or prune belly	1.26 (1.16 - 1.36)	0.99 (0.90 - 1.08)	0.02 (0.01 - 0.04)	0.25 (0.21 - 0.30)
Genital	21.87 (21.47 - 22.29)	21.01 (20.61 - 21.42)	0.12 (0.09 - 0.16)	0.74 (0.66 - 0.82)
– Hypospadias	18.12 (17.75 - 18.50)	17.97 (17.60 - 18.34)	0.04 (0.02 - 0.06)	0.12 (0.09 - 0.15)
– Indeterminate sex	0.55 (0.49 - 0.62)	0.39 (0.33 - 0.44)	0.02 (0.01 - 0.04)	0.14 (0.11 - 0.18)
Limb	42.86 (42.29 - 43.44)	37.14 (36.61 - 37.68)	0.67 (0.60 - 0.75)	5.04 (4.85 - 5.25)
– Limb reduction defects	5.37 (5.17 - 5.58)	3.47 (3.31 - 3.63)	0.17 (0.14 - 0.21)	1.74 (1.62 - 1.85)
– Club foot - talipes equinovarus	11.30 (11.01 - 11.60)	9.30 (9.04 - 9.58)	0.26 (0.22 - 0.31)	1.73 (1.62 - 1.85)
– Hip dislocation and/or dysplasia	10.55 (10.27 - 10.84)	10.53 (10.24 - 10.81)	0.01 (0.00 - 0.02)	0.02 (0.01 - 0.03)
– Polydactyly	9.63 (9.36 - 9.90)	8.91 (8.65 - 9.17)	0.08 (0.06 - 0.11)	0.64 (0.57 - 0.71)
– Syndactyly	4.20 (4.02 - 4.39)	3.76 (3.60 - 3.94)	0.07 (0.05 - 0.09)	0.37 (0.32 - 0.43)
Other anomalies/syndromes				
– Skeletal dysplasias §	1.99 (1.87 - 2.12)	0.97 (0.89 - 1.06)	0.04 (0.02 - 0.06)	0.98 (0.90 - 1.07)
– Craniosynostosis	2.88 (2.74 - 3.04)	2.67 (2.53 - 2.82)	0.06 (0.04 - 0.08)	0.16 (0.12 - 0.20)

Anomaly group	Total Prevalence	Live	Still	TOPFA
– Congenital constriction bands/amniotic band	0.56 (0.50 - 0.63)	0.25 (0.21 - 0.30)	0.07 (0.05 - 0.10)	0.24 (0.20 - 0.29)
– Situs inversus	0.80 (0.72 - 0.88)	0.59 (0.53 - 0.67)	0.01 (0.01 - 0.03)	0.19 (0.16 - 0.24)
– Conjoined twins	0.17 (0.14 - 0.21)	0.01 (0.00 - 0.02)	0.01 (0.00 - 0.03)	0.15 (0.12 - 0.19)
– Congenital skin disorders	1.66 (1.55 - 1.78)	1.56 (1.46 - 1.68)	0.02 (0.01 - 0.04)	0.08 (0.05 - 0.10)
– VATER/VACTERL	0.50 (0.44 - 0.57)	0.38 (0.32 - 0.43)	0.02 (0.01 - 0.03)	0.11 (0.08 - 0.14)
– Vascular disruption anomalies §	7.01 (6.78 - 7.24)	5.18 (4.98 - 5.38)	0.25 (0.21 - 0.30)	1.58 (1.47 - 1.69)
– Lateral anomalies §	2.06 (1.93 - 2.19)	1.37 (1.27 - 1.48)	0.09 (0.07 - 0.12)	0.59 (0.53 - 0.67)
– Teratogenic syndromes with malformations §	1.45 (1.34 - 1.56)	1.17 (1.07 - 1.27)	0.04 (0.03 - 0.06)	0.24 (0.20 - 0.28)
– Fetal alcohol syndrome	0.51 (0.45 - 0.58)	0.50 (0.44 - 0.56)	0.00 (0.00 - 0.01)	0.02 (0.01 - 0.03)
– Valproate syndrome §	0.03 (0.02 - 0.05)	0.03 (0.01 - 0.04)	0.00 (0.00 - 0.01)	0.01 (0.00 - 0.02)
– Maternal infections resulting in malformations	0.81 (0.73 - 0.89)	0.57 (0.51 - 0.64)	0.03 (0.02 - 0.05)	0.21 (0.17 - 0.25)
– Genetic syndromes + microdeletions	6.01 (5.80 - 6.23)	4.75 (4.56 - 4.94)	0.10 (0.08 - 0.13)	1.16 (1.07 - 1.26)
Chromosomal	43.84 (43.26 - 44.42)	16.80 (16.45 - 17.17)	1.49 (1.39 - 1.60)	25.54 (25.10 - 25.99)
– Down Syndrome	24.34 (23.91 - 24.77)	9.77 (9.50 - 10.05)	0.48 (0.43 - 0.55)	14.08 (13.75 - 14.41)
– Patau syndrome/trisomy 13	2.17 (2.04 - 2.30)	0.30 (0.25 - 0.35)	0.11 (0.08 - 0.14)	1.76 (1.64 - 1.88)
– Edward syndrome/trisomy 18	5.92 (5.71 - 6.14)	0.69 (0.62 - 0.77)	0.44 (0.38 - 0.50)	4.79 (4.60 - 4.99)
– Turner syndrome	2.45 (2.31 - 2.59)	0.58 (0.51 - 0.65)	0.15 (0.12 - 0.19)	1.72 (1.61 - 1.84)
– Klinefelter syndrome	0.66 (0.59 - 0.74)	0.44 (0.39 - 0.51)	0.01 (0.00 - 0.03)	0.21 (0.17 - 0.25)

Description of codes of CA according to Birth Defects Definitions Group (2017) – for comparison purposes. These are not EUROCAT groupings.

Description of codes	ICD-9-CM Codes	CDC/BPA Codes	ICD10-CM
Central Nervous System			
Anencephalus	740.0 – 740.1	740.00 – 740.10	Q00.0-Q00.1
Spina bifida without anencephalus	741.0, 741.9 w/o 740.0 - 740.10	741.00 – 741.99 w/o 740.0 – 740.10	Q05.0-Q05.9, Q07.01, Q07.03 w/o Q00.0 - Q00.1
Encephalocele	742.0	742.00 – 742.09	Q01.0 – Q01.9
Holoprosencephaly	742.2	742.26	Q04.2
Eye			
Anophthalmia microphthalmia	743.0, 743.1	743.00 – 743.10	Q11.0 – Q11.2
Congenital cataract	743.30 – 743.34	743.32	Q12.0
Ear			
Anotia/microtia	744.01, 744.23	744.01, 744.21	Q16.0, Q17.2
Cardiovascular			
Aortic valve stenosis	746.3	746.3	Q23.0
Atrial septal defect	745.5	745.51 – 745.59	Q21.1
Atrioventricular septal defect (Endocardial cushion defect)	745.60, .61, .69	745.60 – 745.69	Q21.2
Coarctation of the aorta	747.10	747.10 – 747.19	Q25.1
Common truncus (truncus arteriosus or TA)	747.10	747.10 – 747.19	Q20.0
Double outlet right ventricle (DORV)	745.11	745.13 – 745.15	Q20.1
Ebstein anomaly	746.2	746.20	Q22.5
Hypoplastic left heart syndrome	746.7	746.7	Q23.4
Interrupted aortic arch (IAA)	747.11	747.215 - 747.217, 747.285	Q25.2, Q25.4
Pulmonary valve atresia and stenosis	746.01 (pulmonary valve atresia), 746.02 (pulmonary valve stenosis) Note: for CCHD, 746.01 only (pulmonary atresia, intact ventricular septum)	746.00 (pulmonary valve atresia), 746.01 (pulmonary valve stenosis) Note: for CCHD, 746.00 only (pulmonary atresia, intact ventricular septum)	Q22.0, Q22.1 (Note: for CCHD, Q22.0 only (pulmonary atresia, intact ventricular septum))
Single Ventricle	745.3	745.3	Q20.4
Tetralogy of Fallot (TOF)	745.2	745.20 – 745.21, 747.31	Q21.3
Total anomalous pulmonary venous connection (TAPVC)	747.41	747.42	Q26.2
Transposition of the great arteries (TGA)	745.10, 745.12, 745.19 (Note: for CCHD, 745.10 only (d-TGA only))	745.10 – 745.12, 745.18 – 745.19 (Note: for CCHD, 745.10 (TGA complete, no VSD), 745.11 (TGA incomplete, with VSD), 749.18 (other specified TGA), 745.19 (unspecified TGA)	Q20.3, Q20.5 (Note: for CCHD, Q20.3 only)
Tricuspid valve atresia and stenosis	746.12	746.100 (tricuspid atresia), 746.106 (tricuspid stenosis) (excl. 746.105 – tricuspid insufficiency) Note: for CCHD, 746.100 only. Only tricuspid atresia is a CCHD. Many cases of tricuspid stenosis are not critical.	Q22.4
Ventricular septal defect	745.4	745.40 – 745.49 (excl. 745.487, 745.498)	Q21.0
Orofacial			
Choanal atresia	748.0	748.0	Q30.0
Cleft lip with cleft palate	749.2	749.20 – 749.29	Q37.0 – Q37.9

Cleft lip alone (without cleft palate)	749.1	749.10-749.19	Q36.0 – Q36.9
Cleft palate alone (without cleft lip)	749.0	749.00 – 749.09	Q35.1 – Q35.9
Gastrointestinal			
Biliary atresia	751.61	751.65	Q44.2 - Q44.3
Esophageal atresia/tracheoesophageal fistula	750.3	750.30 – 750.35	Q39.0 – Q39.4
Rectal and large intestinal atresia/stenosis	751.2	751.20 – 751.24	Q42.0 – Q42.9
Small intestinal atresia/stenosis	751.1	751.10-751.19	Q41.0 – Q41.9
Genitourinary			
Bladder exstrophy	751.1	751.10-751.19	Q64.10, Q64.19
Cloacal exstrophy	751.1	751.10-751.19	Q64.12
Congenital Posterior Urethral Valves	753.6	753.60	Q64.2
Hypospadias	752.61	752.60 – 752.62 (excluding 752.61 and 752.621)	Q54.0 – Q54.9 (excluding Q54.4)
Renal agenesis/hypoplasia	753.0	753.00 – 753.01	Q60.0 – Q60.6
Musculoskeletal			
Clubfoot	754.51, 754.70	754.50, 754.73	Q66.0, Q66.89
Craniosynostosis	No specific code	756.00-756.03	Q75.0
Diaphragmatic hernia	756.6	756.61	Q79.0, Q79.1
Gastroschisis	756.73 (as of 10/1/09; previously a shared code 756.79 with omphalocele)	756.71	Q79.3
Limb deficiencies (reduction defects)	755.2 – 755.4	755.20 – 755.49	Q71.0 – Q71.9, Q72.0 – Q72.9, Q73.0 – Q73.8
Omphalocele	756.72 (as of 10/1/09; previously a shared code 756.79 with gastroschisis)	756.70	Q79.2
Chromosomal			
Deletion 22 q11	758.32	758.37	Q93.81
Trisomy 13	758.1	758.10 – 758.19	Q91.4 – Q91.7
Trisomy 18	758.2	758.20 – 758.29	Q91.0 – Q91.3
Trisomy 21 (Down syndrome)	758.0	758.00 – 758.09	Q90.0 – Q90.9
Turner syndrome	758.6	758.60-758.69	Q96.0 – Q96.9

Annex 7. Diagnosis codes for long-term neurodevelopmental outcomes

ICD-11

Code	Description
06 Mental, behavioural or neurodevelopmental disorders	
6A00 Disorders of intellectual development	Disorders of intellectual development are a group of etiologically diverse conditions originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behavior that are approximately two or more standard deviations below the mean (approximately less than the 2.3rd percentile), based on appropriately normed, individually administered standardized tests. Where appropriately normed and standardized tests are not available, diagnosis of disorders of intellectual development requires greater reliance on clinical judgment based on appropriate assessment of comparable behavioural indicators.
6A00.0 Disorder of intellectual development, mild	A mild disorder of intellectual development is a condition originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately two to three standard deviations below the mean (approximately 0.1 – 2.3 percentile), based on appropriately normed, individually administered standardized tests or by comparable behavioural indicators when standardized testing is unavailable. Affected persons often exhibit difficulties in the acquisition and comprehension of complex language concepts and academic skills. Most master basic self-care, domestic, and practical activities. Persons affected by a mild disorder of intellectual development can generally achieve relatively independent living and employment as adults but may require appropriate support.

6A00.1 Disorder of intellectual development, moderate	A moderate disorder of intellectual development is a condition originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately three to four standard deviations below the mean (approximately 0.003 – 0.1 percentile), based on appropriately normed, individually administered standardized tests or by comparable behavioural indicators when standardized testing is unavailable. Language and capacity for acquisition of academic skills of persons affected by a moderate disorder of intellectual development vary but are generally limited to basic skills. Some may master basic self-care, domestic, and practical activities. Most affected persons require considerable and consistent support in order to achieve independent living and employment as adults.
6A00.2 Disorder of intellectual development, severe	A severe disorder of intellectual development is a condition originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately four of more standard deviations below the mean (less than approximately the 0.003rd percentile), based on appropriately normed, individually administered standardized tests or by comparable behavioural indicators when standardized testing is unavailable. Affected persons exhibit very limited language and capacity for acquisition of academic skills. They may also have motor impairments and typically require daily support in a supervised environment for adequate care, but may acquire basic self-care skills with intensive training. Severe and profound disorders of intellectual development are differentiated exclusively on the basis of adaptive behaviour differences because existing standardized tests of intelligence cannot reliably or validly distinguish among individuals with intellectual functioning below the 0.003rd percentile
6A00.3 Disorder of intellectual development, profound	A profound disorder of intellectual development is a condition originating during the developmental period characterized by significantly below average intellectual functioning and adaptive behaviour that are approximately four of more standard deviations below the mean (approximately less than the 0.003rd percentile), based on individually administered appropriately normed, standardized tests or by comparable behavioural indicators when standardized testing is unavailable. Affected persons possess very limited communication abilities and capacity for acquisition of academic skills is restricted to basic concrete skills. They may also have co-occurring motor and sensory impairments and typically require daily support

	in a supervised environment for adequate care. Severe and profound disorders of intellectual development are differentiated exclusively on the basis of adaptive behaviour differences because existing standardized tests of intelligence cannot reliably or validly distinguish among individuals with intellectual functioning below the 0.003rd percentile.
6A00.4 Disorder of intellectual development, provisional	Disorder of intellectual development, provisional is assigned when there is evidence of a disorder of intellectual development but the individual is an infant or child under the age of four or it is not possible to conduct a valid assessment of intellectual functioning and adaptive behaviour because of sensory or physical impairments (e.g., blindness, pre-lingual deafness), locomotor disability, severe problem behaviours or co-occurring mental and behavioural disorders.
6A00.Z Disorder of intellectual development, unspecified	This category is an 'unspecified' residual category

ICD-10

Code	Description
F70-F79 Mental retardation	
F70 Mild mental retardation	Approximate IQ range of 50 to 69 (in adults, mental age from 9 to under 12 years). Likely to result in some learning difficulties in school. Many adults will be able to work and maintain good social relationships and contribute to society.
F70.0 Mild mental retardation with the statement of no, or minimal, impairment of behaviour	Mild mental retardation with no or very minimal impairment to behaviour
F70.1 Mild mental retardation : significant impairment of behaviour requiring attention or treatment	Mild mental retardation plus a significant impairment of behaviour requiring attention or treatment
F70.8 Mild mental retardation : other impairments of behaviour	Mild mental retardation with other impairments of behaviour

F70.9 Mild mental retardation without mention of impairment of behaviour	Mild mental retardation without mention of impairment of behaviour
F71 Moderate mental retardation	Approximate IQ range of 35 to 49 (in adults, mental age from 6 to under 9 years). Likely to result in marked developmental delays in childhood but most can learn to develop some degree of independence in self-care and acquire adequate communication and academic skills. Adults will need varying degrees of support to live and work in the community.
F71.0 Moderate mental retardation with the statement of no, or minimal, impairment of behaviour	Moderate mental retardation with the statement of no, or minimal, impairment of behaviour
F71.1 Moderate mental retardation : significant impairment of behaviour requiring attention or treatment	Moderate mental retardation with a significant impairment of behaviour requiring attention or treatment
F71.8 Moderate mental retardation : other impairments of behaviour	Moderate mental retardation with other impairments of behaviour
F71.9 Moderate mental retardation without mention of impairment of behaviour	Moderate mental retardation without mention of impairment of behaviour
F72 Severe mental retardation	Approximate IQ range of 20 to 34 (in adults, mental age from 3 to under 6 years). Likely to result in continuous need of support.
F72.0 Severe mental retardation with the statement of no, or minimal, impairment of behaviour	Severe mental retardation with no or minimal impairment of behaviour
F72.1 Severe mental retardation : significant impairment of behaviour requiring attention or treatment	Severe metnal retardation with signficiant impairment of beahviour requiring attention or treatment
F72.8 Severe mental retardation : other impairments of behaviour	Severe mental retardation with other impairments
F72.9 Severe mental retardation without mention of impairment of behaviour	Severe mental retardation without mention of impairment of behaviour

F72 Severe mental retardation	Approximate IQ range of 20 to 34 (in adults, mental age from 3 to under 6 years). Likely to result in continuous need of support.
73.0 Profound mental retardation	IQ under 20 (in adults, mental age below 3 years). Results in severe limitation in self-care, continence, communication and mobility.
F73.0 Profound mental retardation with the statement of no, or minimal, impairment of behaviour	Profound mental retardation with no or minimal impairment of behaviour
F73.1 Profound mental retardation : significant impairment of behaviour requiring attention or treatment	Profound mental retardation with signficiant impairment of behaviour requiring attention or treatment
F73.8 Profound mental retardation : other impairments of behaviour	Proground mental retardation with other impairments of behaviour
F73.9 Profound mental retardation without mention of impairment of behaviour	Profound mental retardation without mention of impairment of behavior
F78 Other mental retardation	Other mental retardation; no further specfication given
F78.0 Other mental retardation with the statement of no, or minimal, impairment of behaviour	Other mental retardation with no or minimal impairment of behaviour
F78.1 Other mental retardation : significant impairment of behaviour requiring attention or treatment	Other mental retardation with significant impairment of behaviour requiring attention or treatment
F78.8 Other mental retardation : other impairments of behaviour	Other mental retardation: other impairments of behaviour
F78.9 Other mental retardation without mention of impairment of behaviour	Other mental retardsation without mention of impairment of behaviour
F79 Unspecified mental retardation	Including 'subnormality' and deficiency not otherwise specfied
F79.0 Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour	Unspecified mental retardation with the statement of no, or minimal, impairment of behaviour

F79.1 Unspecified mental retardation : significant impairment of behaviour requiring attention or treatment	Unspecified mental retardation : significant impairment of behaviour requiring attention or treatment
F79.8 Unspecified mental retardation : other impairments of behaviour	Unspecified mental retardation with other impairments of behaviour
F79.9 Unspecified mental retardation without mention of impairment of behaviour	Unspecified mental retardation without mention of impairment of behaviour

ICD-10

Code	Description
317-319 Intellectual Disabilities	
317 Mild intellectual disabilities*	Intellectual disability with IQ 50-70*
318 Other specified intellectual disabilities	None specified intellectual disabilities
318.0 Moderate intellectual disabilities	Intellectual disability with IQ 35-49
318.1 Severe intellectual disabilities	Severe intellectual disabilities IQ 20-34
318.3 Profound intellectual disabilities	Profound intellectual disability IQ less than 20
319 Unspecified intellectual disabilities	Subnormal intellectual functioning which originates during the developmental period; multiple potential etiologies, including genetic defects and perinatal insults; intelligence quotient (iq) scores are commonly used to determine whether an individual is mentally retarded; iq scores between 70 and 79 are in the borderline mentally retarded range and scores below 67 are in the retarded range

* US versions use the term mental retardation

Annex 8. Attention Deficit Hyperactivity Disorder (ADHD)

1. Synonyms / lay terms used

- ADHD
- Attention deficits disorder with hyperactivity
- Attention deficit hyperactivity disorder
- Attention deficit syndrome with hyperactivity
- Hyperkinetic disorder

2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out other conditions.

3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. Psychometic questionnaires may also be utilized and include the Child Behaviour Checklist (CBCL), Conner's Rating Scales or the Vanderbilt ADHD Rating Scale. Cognitive attention, IQ and other cognitive skills such as language functioning may also be assessed to determine any comorbid difficulties.

Diagnosis maybe based on the guidance in the Diagnostic and Statistical Manual of Mental Disorders, which is now on its 5th edition, rather than on ICD-11 categories.

4. Drugs used to treat

Attention Deficit Hyperactivity Disorder can be treated with stimulant medications which include: methylphenidate, dexmethylphenidate, lisdexamfetamine, atomoxetine and guanfacine. Stimulant medication is not always used and instead environmental or behavioural management techniques are utilised.

5. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /relaibly diagnosed

Specialist outpatient appointments. There is often an observation of the child in the home and/or school environment.

Annex 9. Autistic Spectrum Disorders

1. Synonyms / lay terms used

- Autism
- Autism syndrome
- Infantile autism
- 'ASD'
- Asperger's syndrome
- Pervasive developmental disorder
- Autistic disorder

2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out other conditions.

3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. Psychometic measurements may also be utilized and include the Modified Chekclist for Autism in Toddlers (MCAT), Screening Tool for Autism in Toddlers and Young Children (STAT), Autism Diagnostic Observation Schedule (ADOS), Autism Diagnostic Interview-Revised (ADI-R) or the Childhood Autism Rating Scale (CARS). IQ and other cognitive skills such as language may also be assessed to determine any comorbid difficulties.

Diagnosis maybe based on the guidance in the Diagnostic and Statistical Manual of Mental Disorders, which is now on its 5th edition, rather than on ICD-11 categories.

4. Drugs used to treat event

None. Certain medications may be used in the treatment of comorbid symptoms (e.g. melatonin for sleep difficulties), but none are specific enough to autism to be utilized as a proxy marker for this condition.

5. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /relaibly diagnosed

Specialist outpatient appointments. There may also be some observation of the child in the home and/or school environment.

Annex 10. Intellectual Disability

1. Synonyms / lay terms used

- Mental retardation (or 'retarded')
- Intellectual impairment
- Low IQ
- Incomplete development of the mind
- Feeble-mindedness
- Mental subnormality

2. Laboratory tests done specific for event

None. Genetic testing may be undertaken to rule out this as being part of a wider syndrome such as a genetic syndrome.

3. Diagnostic tests done specific for event

Diagnostic practices are variable across countries. Diagnosis may be made as part of a multidisciplinary team or by an individual clinician. Information collected to inform the diagnostic process also varies by what information is collected and who this information comes from. At a minimum there is a direct observation of the child by the diagnosing clinician/ team and information on early development and daily functioning collected from parents and educators. If the level of impairment is very obvious no psychometric assessments are utilized however other cases may require an assessment of intellectual functioning. The score from this assessment is called the intelligence quotient (IQ). Other cognitive skills are also likely to be assessed to inform on the extent of the difficulty across cognitive functioning. Learning disability is heterogenous in terms of presentation and etiologies. Whilst ICD codes are available for 'mild', 'moderate', 'severe' and 'profound' learning disability, these collectively only represent the most severe of cases (despite the utilization of the term 'mild') and a substantial impact on daily functioning can be found with IQ levels slightly above these cut offs.

4. Drugs used to treat event

None. Medications may be used to treat comorbidities but not this condition directly.

5. Procedures used specific for event treatment

Treatment will be non-medicinal in nature and will vary substantially between countries.

6. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /relaibly diagnosed

Specialist outpatient appointments. There is often an observation of the child in the home and/or school environment.

Annex 11. Bacterial infections

1. Event definition

Infectious disease is defined as an illness caused by a specific infectious agent or its toxic product that results from transmission of that agent or its products from an infected person, animal, or reservoir to a susceptible host, either directly or indirectly through an intermediate plant or animal host, vector or inanimate environment (Barreto, 2006).

Infectious diseases are caused by pathogenic microorganisms, such as bacteria, viruses, parasites or fungi; the diseases can be spread, directly or indirectly, from one person to another [World Health Organization]. Bacteria are single-celled organisms that can exist independently or as parasites. Bacterial infections could be divided according to the organ system which is affected.

Bacterial infections of Skin:

Epidermal infections, impetigo, ecthyma, Dermal infections, erysipelas, cellulitis, necrotizing fasciitis, Follicular infections, folliculitis, furunculosis, carbunculosis, Carbuncle: A network of furuncles connected by sinus tracts, Cellulitis: Painful, erythematous infection of deep skin with poorly demarcated borders, Erysipelas: Fiery red, painful infection of superficial skin with sharply demarcated borders: Papular or pustular inflammation of hair follicles, Furuncle: Painful, firm or fluctuant abscess originating from a hair follicle, Impetigo: Large vessicles and/or honey-crusted sores, abcess, lymphangitis, mastitis, onyxis, panaritium, septic thrombophlebitis (Pilly, 2016).

Table I. Bacterial skin residents and their associated dermatoses

Bacteria	Location	Distinguishing features	Skin pathology
Gram (+)			
Staphylococcus			
S. epidermidis	upper trunk	produce slime	
S. hominis	glabrous skin		
S. haemolyticus	produce slime		
S. capitis	head		
S. midis			
S. warneri			
S. saprophyticus	perineum	cause UTI	
S. cohnii			
S. xylosus			
S. simulans			
S. saccharolyticus	forehead/antecubital	anaerobic	
Micrococcus			
M. luteus			
M. varians			
M. lylae	in children/cold temp		
M. kristinae	in children		
M. nishinomiyaensis			
M. roseus			
M. sedentarius	pitted keratolysis		
M. agilis			
Corynebacterium			
C. minutissimum	intertriginous	lipophilic/porphyrin	erythrasma
C. tenuis	intertriginous	lipophilic	trichomycosis
C. xerosis	conjunctiva	lipophilic	conjunctivitis
C. jeikeium	intertriginous	lipophilic/antibiotic resistant	
Rhodococcus	lipophilic	granuloma in HIV	
Propionibacterium			
P. acnes	sebaceous gland	lipophilic/anaerobic	acne
P. granulosum	sebaceous gland	lipophilic/anaerobic	severe acne
P. avidum	axilla	lipophilic/anaerobic	
Brevibacterium	toe webs	nonlipophilic (large-colony)	foot odor, white piedra
Dermabacter	nonlipophilic (large-colony)	pitted keratolysis	
Gram (–)			
Acinetobacter	dry areas	gram-negative	burn wounds

From: Chiller, 2001.

Blood: Bacterial septicaemia, septic shock, or sepsis (Singer, 2016)

*Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection.

Organ dysfunction can be identified as an acute change in total SOFA score ≥2 points consequent to the infection.

Quick SOFA Criteria : respiratory rate > or = 22/min, altered mentation, systolic blood pressure < or = 100mmHg

SOFA SCORE:

System	Score 0	1	2	3	4
Respiration					
Pao_2/Fio_2, mm Hg (kPa)	≥400 (53.3)	<400 (53.3)	<300 (40)	<200 (26.7) with respiratory support	<100 (13.3) with respiratory support
Coagulation					
Platelets, $\times 10^3/\mu L$	≥150	<150	<100	<50	<20
Liver					
Bilirubin, mg/dL (μmol/L)	<1.2 (20)	1.2-1.9 (20-32)	2.0-5.9 (33-101)	6.0-11.9 (102-204)	>12.0 (204)
Cardiovascular	MAP ≥70 mm Hg	MAP <70 mm Hg	Dopamine <5 or dobutamine (any dose)[b]	Dopamine 5.1-15 or epinephrine ≤0.1 or norepinephrine ≤0.1[b]	Dopamine >15 or epinephrine >0.1 or norepinephrine >0.1[b]
Central nervous system					
Glasgow Coma Scale score[c]	15	13-14	10-12	6-9	<6
Renal					
Creatinine, mg/dL (μmol/L)	<1.2 (110)	1.2-1.9 (110-170)	2.0-3.4 (171-299)	3.5-4.9 (300-440)	>5.0 (440)
Urine output, mL/d				<500	<200

Abbreviations: Fio_2, fraction of inspired oxygen; MAP, mean arterial pressure; Pao_2, partial pressure of oxygen.

[a] Adapted from Vincent et al.[27]

[b] Catecholamine doses are given as μg/kg/min for at least 1 hour.

[c] Glasgow Coma Scale scores range from 3-15; higher score indicates better neurological function.

* Septic shock is defined as a subset of sepsis in which underlying circulatory and cellular metabolism abnormalities are profound enough to substantially increase mortality

Nervous system: Bacterial meningitis, meningococcal meningitis, Pneumococcal meningitis, Haemophilus influenzae Type b, Neonatal Meningitis, Tetanus, Botulism, Listeriosis, encephalitis, cerebral abscess.

Table 3. Proposed definitions of bacterial meningitis and other central nervous system infections

Bacterial meningitis in children and infants >8 wks old
- Definite bacterial meningitis
  - Compatible clinical syndrome, plus
    - All ages: fever, 94%
    - 1–5 mos: irritability, 85%
    - 6–11 mos: impaired consciousness, 79%
    - >12 mos: vomiting, 82%; neck rigidity, 78%
      - (note: many other compatible signs and symptoms) plus
  - Positive culture of cerebrospinal fluid (CSF), or positive CSF Gram stain or bacterial antigen, or
- Probable bacterial meningitis
  - Compatible clinical syndrome, plus
  - Positive culture of blood, plus
  - One of the following CSF changes
    - >5 leukocytes
    - Glucose of ≤40 or 0.5 CSF/serum ratio
    - Protein of ≥100 mg/dL
- Possible bacterial meningitis
  - Compatible clinical syndrome, plus
  - One of the following CSF changes
    - >100 leukocytes
    - Glucose of ≤40 or CSF/serum glucose ratio ≤0.5
    - Protein of ≥100 mg/dL plus
  - Negative cultures or antigen for bacteria, viral, fungal, or mycobacteria

Neonatal meningitis (<8 wks of age)
- Compatible clinical syndrome, plus
- Isolation of likely pathogenic organism from CSF, or positive specific bacterial antigen, or
- Abnormal CSF consistent with bacterial infection

Shunt infection or device associated ventriculitis
- Definite shunt infection
  - Compatible clinical signs and symptoms, plus
  - Isolation of bacterial pathogen from device puncture, lumbar puncture or other significant site (e.g., overlying shunt wound, cellulites, or shunt tubing)
- Probable shunt infection
  - Compatible clinical signs and symptoms
  - CSF consistent with bacterial infection
  - Negative blood, CSF and device cultures for bacteria

Intracranial or extracranial (spinal) infection
- Compatible neurologic signs and symptoms, plus
- Acceptable radiologic imaging or surgical/anatomic evidence or positive cultures or histology from site, or
- Autopsy confirmation

From: (Overturf, 2005)

Table 1. Bacterial Infections of the Nervous System

Disease	Pathogen	Signs and Symptoms	Transmission	Antimicrobial Drugs	Vaccine
Botulism	*Clostridium botulinum*	Blurred vision, drooping eyelids, difficulty swallowing and breathing, nausea, vomiting, often fatal	Ingestion of preformed toxin in food, ingestion of endospores in food by infants or immunocompromised adults, bacterium introduced via wound or injection	Antitoxin; penicillin (for wound botulism)	None
Hansen's disease (leprosy)	*Mycobacterium leprae*	Hypopigmented skin, skin lesions, and nodules, loss of peripheral nerve function, loss of fingers, toes, and extremities	Inhalation, possible transmissible from armadillos to humans	Dapsone, rifampin, clofazimin	None
Haemophilus influenzae type b meningitis	*Haemophilus influenza*	Nausea, vomiting, photophobia, stiff neck, confusion	Direct contact, inhalation of aerosols	Doxycycline, fluoroquinolones, second- and third-generation cephalosporins, and carbapenems	Hib vaccine
Listeriosis	*Listeria monocytogenes*	Initial flu-like symptoms, sepsis and potentially fatal meningitis in susceptible individuals, miscarriage in pregnant women	Bacterium ingested with contaminated food or water	Ampicillin, gentamicin	None
Meningococcal meningitis	*Neisseria meningitidis*	Nausea, vomiting, photophobia, stiff neck, confusion; often fatal	Direct contact	Cephalosporins or penicillins	Meningococcal conjugate
Neonatal meningitis	*Streptococcus agalactiae*	Temperature instability, apnea, bradycardia, hypotension, feeding difficulty, irritability, limpness, seizures, bulging fontanel, stiff neck, opisthotonos, hemiparesis, often fatal	Direct contact in birth canal	Ampicillin plus gentamicin, cefotaxime, or both	None
Pneumococcal meningitis	*Streptococcus pneumoniae*	Nausea, vomiting, photophobia, stiff neck, confusion, often fatal	Direct contact, aerosols	Cephalosporins, penicillin	Pneumococcal vaccines
Tetanus	*Clostridium tetani*	Progressive spasmatic paralysis starting with the jaw, often fatal	Bacterium introduced in puncture wound	Penicillin, antitoxin	DTaP, Tdap

https://courses.lumenlearning.com/microbiology/chapter/bacterial-diseases-of-the-nervous-system/

Respiratory tract, ears, nose, and throat: Sinusitis, Otitis, Stomatitis, Parotiditis, Epiglottitis

Bacterial sore throat, Bronchitis, Pneumonia, Diphtheria, tuberculosis, pertussis

Table 1. Bacterial Infections of the Respiratory Tract

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs	Vaccine
Acute otitis media (AOM)	*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*, others	Earache, possible effusion; may cause fever, nausea, vomiting, diarrhea	Often a secondary infection; bacteria from respiratory tract become trapped in eustachian tube, cause infection	None	Cephalosporins, fluoroquinolones	None
Diphtheria	*Corynebacterium diphtheria*	Pseudomembrane on throat, possibly leading to suffocation and death	Inhalation of respiratory droplets or aerosols from infected person	Identification of bacteria in throat swabs; PCR to detect diphtheria toxin in vitro	Erythromycin, penicillin, antitoxin produced in horses	DtaP, Tdap, DT, Td, DTP
Legionnaires disease	*Legionella pneumophila*	Cough, fever, muscle aches, headaches, nausea, vomiting, confusion; sometimes fatal	Inhalation of aerosols from contaminated water reservoirs	Isolation, using Warthin-Starry procedure, of bacteria in sputum	Fluoroquinolones, macrolides	None
Pertussis (whooping cough)	*Bordetella pertussis*	Severe coughing with "whoop" sound; chronic cough lasting several months; can be fatal in infants	Inhalation of respiratory droplets from infected person	Direct culture of throat swab, PCR, ELISA	Macrolides	DTaP, Tdap
Q fever	*Coxiella burnetii*	High fever, coughing, pneumonia, malaise; in chronic cases, potentially fatal endocarditis	Inhalation of aerosols of urine, feces, milk, or amniotic fluid of infected cattle, sheep, goats	PCR, ELISA	Doxycycline, hydroxychloroquine	None
Streptococcal pharyngitis, scarlet fever	*Streptococcus pyogenes*	Fever, sore throat, inflammation of pharynx and tonsils, petechiae, swollen lymph nodes; skin rash (scarlet fever), strawberry tongue	Direct contact, inhalation of respiratory droplets or aerosols from infected person	Direct culture of throat swab, rapid enzyme immunoassay	β-lactams	None
Tuberculosis	*Mycobacterium tuberculosis*	Formation of tubercles in lungs; rupture of tubercles, leading to chronic, bloody cough; healed tubercles (Ghon complexes) visible in radiographs; can be fatal	Inhalation of respiratory droplets or aerosols from infected person	Mantoux tuberculin skin test with chest radiograph to identify Ghon complexes	Isoniazid, rifampin, ethambutol, pyrazinamide	BCG

https://courses.lumenlearning.com/microbiology/chapter/bacterial-infections-of-the-respiratory-tract/

Table 2. Bacterial Causes of Pneumonia

Disease	Pathogen	Signs and Symptoms	Transmission	Diagnostic Tests	Antimicrobial Drugs	Vaccine
Chlamydial pneumonia	*Chlamydophila pneumoniae*, *C. psittaci*, *Chlamydia trachomatis*	Bronchitis; mild to severe respiratory distress	Inhalation of respiratory droplets or aerosols from infected person (*C. pneumoniae*); exposure to infected bird (*C. psittaci*); exposure in the birth canal (*Chlamydia trachomatis*)	Tissue culture, PCR	Tetracycline, macrolides	None
Haemophilus pneumonia	*Haemophilus influenza*	Cough, fever or low body temperature, chills, chest pain, headache, fatigue	Inhalation of respiratory droplets or aerosols from infected person or asymptomatic carrier	Culture on chocolate agar, serotyping of blood or cerebrospinal fluid samples	Cephalosporins, fluoroquinolones	Hib
Klebsiella pneumonia	*Klebsiella pneumoniae*, others	Lung necrosis, "currant jelly" sputum; often fatal	Health care associated; bacteria introduced via contaminated ventilators, intubation, or other medical equipment	Culture, PCR	Multidrug resistant; antibiotic susceptibility testing necessary	None
Mycoplasma pneumonia (walking pneumonia)	*Mycoplasma pneumoniae*	Low fever, persistent cough	Inhalation of respiratory droplets or aerosols from infected person	Culture with penicillin, thallium acetate	Macrolides	None
Pneumococcal pneumonia	*Streptococcus pneumoniae*	Productive cough, bloody sputum, fever, chills, chest pain, respiratory distress	Direct contact with respiratory secretions	Gram stain, blood agar culture with optichin and sodium deoxycholate, quellung reaction	β-lactams, macrolides or cephalosporin, fluoroquinolones	Pneumococcal conjugate vaccine (PCV13), pneumococcal polysaccharide vaccine (PPSV23)
Pseudomonas pneumonia	*Pseudomonas aeruginosa*	Viscous fluid and chronic inflammation of lungs; often fatal	Health care associated; bacteria introduced via contaminated ventilators; also frequently affects patients with cystic fibrosis	Culture from sputum or other body fluid	Multidrug resistant; antibiotic susceptibility testing necessary	None

https://courses.lumenlearning.com/microbiology/chapter/bacterial-infections-of-the-respiratory-tract/

Urinary tract: Bacterial UTIs can involve the urethra, prostate, bladder, or kidneys. Symptoms may be absent or include urinary frequency, urgency, dysuria, lower abdominal pain, and flank pain. Systemic symptoms and even sepsis may occur with kidney infection. Diagnosis is based on analysis and culture of urine. Treatment is with antibiotics and removal of any urinary tract catheters and obstructions. Includes Urethritis, Cystitis, Acute urethral syndrome, Acute pyelonephritis.

2. Synonyms / lay terms used

Skin:

Epidermal infections (impetigo, ecthyma), Dermal and hypodermal infections (erysipelas, cellulitis, necrotizing fasciitis), Follicular infections, folliculitis, furunculosis, carbunculosis, Carbuncle: A network of furuncles connected by sinus tracts, Cellulitis: Painful, erythematous infection of deep skin with poorly demarcated borders, Erysipelas: Fiery red, painful infection of superficial skin with sharply demarcated borders, Folliculitis: Papular or pustular inflammation of hair follicles, Furuncle: Painful, firm or fluctuant abscess originating from a hair follicle, Impetigo: Large vessicles and/or honey-crusted sores.

Blood: Sepsis, Septicaemia, Septic Shock (these are other terms but not synonyms)

Nervous System: Bacterial meningitis, meningococcal meningitis, Pneumococcal meningitis, Haemophilus influenzae Type b, Neonatal Meningitis, Tetanus, Botulism, Listeriosis, meningitis

Respiratory System, ear, nose, and throat: Streptococcal infections, Strep throat, Otitis media, Ear infection, Bacterial Rhinosinusitus, Diphtheria, Bacteria pneumonia, Haemophilus pneumonia, tuberculosis, TB, pertussis, whooping cough

Urinary Tract: Urethritis, Cystitis, Acute urethral syndrome, Asymptomatic bacteriuria, Acute pyelonephritis, urinary tract infection, UTI

3. Laboratory tests done specific for event

Peripheral white cell count, culture-based tests, c-reactive protein, procalcitonin, rapid antigen tests, stool antigen test, blood antigen test, cerebrospinal antigen test, serological tests, nucleic acid amplification test, polymerase chain reaction, peptide nucleic acid fluorescent in situ hybridisation,

4. Diagnostic tests done specific for event

Bacteriological determination, chest radiograph, urine dipstick, wet prep microscopy, gram stain, radiograph, magnetic resonance imaging (MRI)

5. Drugs used to treat event

Antibiotics

Classe ATC J01 (systemic antibacterials)

A01AB13 (tetracycline)

A01AB21 chlortetracycline

A01AB22 doxycycline

A01AB23 minocycline

D06 antibiotics for topical use

R02AB antibiotics for throat preparations

S01A/CEyepreparationsS02A/CEarpreparationsS03 Eye and ear preparations with antiinfectives

The anti-infective drugs (and their respective ATC codes) considered as markers for infections were: anti-infectives and antiseptics for local oral treatment (A01AB); intestinal anti-infectives (A07A); antifungals, antibiotics and chemotherapeutics for dermatological use (D01, D06); antibacterials, antimycotics, antiinfectives, antimycobacterials, and antivirals for systemic use (J01–J05); immune sera

and immunoglobulins (J06); antiparasitic products, insecticides and repellents (P), mupirocin (R01AX06), antiseptics and antibiotics throat preparations (R02A); ophthalmological and otological antiinfectives alone or in combination (S01A, S01C, S02A, S02C) (Palosse-Cantaloube, 2016).

6. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Outpatient specialist, in-hospital, GP, emergency room

7. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA

ICD-10 label	ICD-10 code
Certain infectious diseases	A00-B99
Nervous system infections	G00-G07, G53.0, G53.1, G63.0, G73.4, G94.0
Ophthalmological infections	H00, H05.0, H06.1, H10.0, H13.0, H13.1, H19.0-H19.2, H22.0, H32.0, H44.0, H44.1, H45.1, H58.8, H59.8
Ear, nose and throat infections	H60.0-H60.3, H62.0-H62.4, H66.0-H66.4, H67.0, H67.1, H70, H75.0, H94.0, J32, J34.0, J36, J37.8, J39.0, J39.1, K04.0, K04.1, K04.4, K04.6, K04.7, K05.2, K11.3, K11.2
Cardiovascular system infections	I30.1, I32.0, I32.1, I33, I38, I40.0, I41.0-I41.2, I98.0, I98.1
Upper respiratory tract	J00-J06
Lung infections	J09-J18, J20-J22, J85.0-J85.2, J86
Gastro-intestinal infections	D73.3, K23.0, K23.1, K35-K37, K57, K61, K63.0, K63.1, K65, K67, K75.0, K77.0, K80.0, K80.1, K80.3, K81, K87.1, K93.0, K93.1
Dermatological infections	L00-L08
Musculoskeletal system infections	M00, M01, M60.0, M63.0-M63.2, M65.0, M65.1, M68.0, M71.0, M71.1, M73.0, M73.1, M86, M90.0-M90.2
Urinary and gynecologic tract infections	N08.0, N10, N12, N13.6, N15.1, N16.0, N22.0, N29.0, N29.1, N30.0, N33, N34, N39.0, N41, N43.1, N45, N48.1, N48.2, N49, N51, N61, N70-N76, N77.0, N77.1
Infections during pregnancy (mother)	O23, O75.3, O85, O86, O91, O98
Others	U80, U81, U88, U89

(Sahli, 2016)

8. Proposed codes by Codemapper

ICD10CM	A00	Cholera
ICD10CM	A15	Respiratory tuberculosis

ICD10CM	A15.0	Tuberculosis of lung
ICD10CM	A15.4	Tuberculosis of mediastinal lymph nodes
ICD10CM	A15.4	Tuberculosis of tracheobronchial lymph nodes
ICD10CM	A15.8	Mediastinal tuberculosis
ICD10CM	A18.01	Tuberculous arthritis
ICD10CM	A18.2	Tuberculous adenitis
ICD10CM	A18.31	Tuberculous ascites
ICD10CM	A18.4	Tuberculosis of skin and subcutaneous tissue
ICD10CM	A18.7	Tuberculosis of adrenal glands
ICD10CM	A18.81	Tuberculosis of thyroid gland
ICD10CM	A18.84	Tuberculous pericarditis
ICD10CM	A18.85	Tuberculosis of spleen
ICD10CM	A19	tuberculous polyserositis
ICD10CM	A23	Brucellosis
ICD10CM	A23.9	Brucellosis, unspecified
ICD10CM	A28.0	Pasteurellosis
ICD10CM	A30-A49	Other bacterial diseases (A30-A49)
ICD10CM	A31.9	Mycobacterial infection, unspecified
ICD10CM	A32	Listeriosis
ICD10CM	A32.9	Listeriosis, unspecified
ICD10CM	A35	Tetanus NOS
ICD10CM	A36	Diphtheria
ICD10CM	A36.9	Diphtheria, unspecified
ICD10CM	A37	Whooping cough
ICD10CM	A37.0	Whooping cough due to Bordetella pertussis
ICD10CM	A39	Meningococcal infection
ICD10CM	A39.1	Waterhouse-Friderichsen syndrome
ICD10CM	A39.9	Meningococcal infection, unspecified
ICD10CM	A41.50	Gram-negative sepsis, unspecified
ICD10CM	A42	Actinomycosis
ICD10CM	A42.1	Abdominal actinomycosis
ICD10CM	A42.2	Cervicofacial actinomycosis
ICD10CM	A42.9	Actinomycosis, unspecified
ICD10CM	A43	Nocardiosis
ICD10CM	A43.9	Nocardiosis, unspecified
ICD10CM	A44	Bartonellosis
ICD10CM	A44.0	Systemic bartonellosis
ICD10CM	A44.9	Bartonellosis, unspecified
ICD10CM	A48	Other bacterial diseases, not elsewhere classified
ICD10CM	A48.0	Gas gangrene
ICD10CM	A48.3	Toxic shock syndrome
ICD10CM	A48.4	Brazilian purpuric fever
ICD10CM	A48.8	Other specified bacterial diseases
ICD10CM	A49	Bacterial infection of unspecified site
ICD10CM	A49.0	Staphylococcal infection, unspecified site
ICD10CM	A49.1	Streptococcal infection, unspecified site
ICD10CM	A49.2	Hemophilus influenzae infection, unspecified site
ICD10CM	A49.3	Mycoplasma infection, unspecified site
ICD10CM	A49.8	Other bacterial infections of unspecified site

ICD10CM	A49.9	Bacterial infection, unspecified
ICD10CM	A51.49	Secondary syphilitic lymphadenopathy
ICD10CM	A52.00	Cardiovascular syphilis, unspecified
ICD10CM	A54	Gonococcal infection
ICD10CM	A54.9	Gonococcal infection, unspecified
ICD10CM	A56.3	Chlamydial infection of anus and rectum
ICD10CM	A66.6	Yaws goundou
ICD10CM	A66.7	Mucosal yaws
ICD10CM	A69.1	Necrotizing ulcerative (acute) gingivitis
ICD10CM	A69.9	Spirochetal infection, unspecified
ICD10CM	A74.9	Chlamydial infection, unspecified
ICD10CM	A75-A79	Rickettsioses (A75-A79)
ICD10CM	A77.4	Ehrlichiosis
ICD10CM	A77.40	Ehrlichiosis, unspecified
ICD10CM	A78	Q fever
ICD10CM	A79.9	Rickettsiosis, unspecified
ICD10CM	B47.1	Actinomycetoma
ICD10CM	B96.20	Unspecified Escherichia coli [E. coli] as the cause of diseases classified elsewhere
ICD10CM	E06.0	Suppurative thyroiditis
ICD10CM	G00	bacterial meningitis
ICD10CM	G00.9	Bacterial meningitis, unspecified
ICD10CM	I01	Rheumatic fever with heart involvement
ICD10CM	J15.9	Unspecified bacterial pneumonia
ICD10CM	K65.2	Spontaneous bacterial peritonitis
ICD10CM	K65.9	Bacterial peritonitis NOS
ICD10CM	K83.0	Ascending cholangitis
ICD10CM	K90.81	Whipple's disease
ICD10CM	L02.92	Furuncle, unspecified
ICD10CM	N49.3	Fournier gangrene
ICD10CM	P36	Bacterial sepsis of newborn
ICD10CM	P36.8	Other bacterial sepsis of newborn
ICD10CM	P36.9	Bacterial sepsis of newborn, unspecified
ICD10CM	P39.4	Neonatal pyoderma
ICD10CM	R65.10	Systemic inflammatory response syndrome (SIRS) NOS
ICD10CM	R78.81	Bacteremia
ICD9CM	001	Cholera
ICD9CM	001.0	Cholera due to vibrio cholerae
ICD9CM	001.9	Cholera, unspecified
ICD9CM	003.9	Salmonella infection, unspecified
ICD9CM	004	Shigellosis
ICD9CM	004.9	Shigellosis, unspecified
ICD9CM	008.1	Intestinal infection due to arizona group of paracolon bacilli
ICD9CM	008.2	Intestinal infection due to aerobacter aerogenes
ICD9CM	008.5	Bacterial enteritis, unspecified
ICD9CM	010.1	Tuberculous pleurisy in primary progressive tuberculosis
ICD9CM	011	Pulmonary tuberculosis
ICD9CM	011.9	Unspecified pulmonary tuberculosis
ICD9CM	011.90	Pulmonary tuberculosis, unspecified, unspecified

ICD9CM	017.5	Tuberculosis of thyroid gland
ICD9CM	017.6	Tuberculosis of adrenal glands
ICD9CM	017.60	Tuberculosis of adrenal glands, unspecified
ICD9CM	017.7	Tuberculosis of spleen
ICD9CM	020	Plague
ICD9CM	020.0	Bubonic plague
ICD9CM	020.9	Plague, unspecified
ICD9CM	020-027.99	ZOONOTIC BACTERIAL DISEASES
ICD9CM	023	Brucellosis
ICD9CM	023.9	Brucellosis, unspecified
ICD9CM	026	Rat-bite fever
ICD9CM	026.9	Unspecified rat-bite fever
ICD9CM	027.0	Listeriosis
ICD9CM	027.1	Erysipelothrix infection
ICD9CM	027.2	Pasteurellosis
ICD9CM	027.9	Unspecified zoonotic bacterial disease
ICD9CM	030-041.99	OTHER BACTERIAL DISEASES
ICD9CM	031.9	Unspecified diseases due to mycobacteria
ICD9CM	032	Diphtheria
ICD9CM	032.9	Diphtheria, unspecified
ICD9CM	033	Whooping cough
ICD9CM	033.0	Whooping cough due to bordetella pertussis [B. pertussis]
ICD9CM	033.9	Whooping cough, unspecified organism
ICD9CM	036	Meningococcal infection
ICD9CM	036.3	Waterhouse-Friderichsen syndrome, meningococcal
ICD9CM	036.9	Meningococcal infection, unspecified
ICD9CM	037	Tetanus
ICD9CM	038.40	Septicemia due to gram-negative organism, unspecified
ICD9CM	039	Actinomycotic infections
ICD9CM	039.2	Abdominal actinomycotic infection
ICD9CM	039.3	Cervicofacial actinomycotic infection
ICD9CM	039.9	Actinomycotic infection of unspecified site
ICD9CM	040	Other bacterial diseases
ICD9CM	040.0	Gas gangrene
ICD9CM	040.2	Whipple's disease
ICD9CM	040.3	Necrobacillosis
ICD9CM	040.8	Other specified bacterial disease
ICD9CM	040.82	Toxic shock syndrome
ICD9CM	040.89	Other specified bacterial diseases
ICD9CM	041	Bacterial infection in conditions classified elsewhere and of unspecified site
ICD9CM	041.49	Other and unspecified Escherichia coli [E. coli]
ICD9CM	041.8	Other specified bacterial infections in conditions classified elsewhere and of unspecified site
ICD9CM	041.89	Other specified bacterial infections in conditions classified elsewhere and of unspecified site, other specified bacteria
ICD9CM	041.9	Bacterial infection, unspecified, in conditions classified elsewhere and of unspecified site
ICD9CM	082.4	Ehrlichiosis

ICD9CM	082.40	Ehrlichiosis, unspecified
ICD9CM	083.0	Q fever
ICD9CM	083.9	Rickettsiosis, unspecified
ICD9CM	088.0	Bartonellosis
ICD9CM	091.4	Adenopathy due to secondary syphilis
ICD9CM	093	Cardiovascular syphilis
ICD9CM	093.9	Cardiovascular syphilis, unspecified
ICD9CM	095.3	Syphilis of liver
ICD9CM	098	Gonococcal infections
ICD9CM	099.52	Other venereal diseases due to chlamydia trachomatis, anus and rectum
ICD9CM	104.9	Spirochetal infection, unspecified
ICD9CM	137.0	Late effects of respiratory or unspecified tuberculosis
ICD9CM	320	Bacterial meningitis
ICD9CM	320.9	Meningitis due to unspecified bacterium
ICD9CM	380.12	Acute swimmers' ear
ICD9CM	391	Rheumatic fever with heart involvement
ICD9CM	482.9	Bacterial pneumonia, unspecified
ICD9CM	510	Empyema
ICD9CM	567.23	Spontaneous bacterial peritonitis
ICD9CM	680	Carbuncle and furuncle
ICD9CM	790.7	Bacteremia
ICD9CM	995.9	Systemic inflammatory response syndrome (SIRS)
ICD9CM	995.90	Systemic inflammatory response syndrome, unspecified

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Annex 12. Digestive disorders

1. Synonyms / lay terms used

Irregularity, hard stools

2. Laboratory tests done specific for event

None.

3. Diagnostic tests done specific for event

There is no diagnostic test done specific for event.

Diagnosis is based on a careful examination that should explore the patient's symptoms and confirm whether he or she is indeed constipated based on frequency (e.g, fewer than three bowel movements per week), consistency (lumpy/hard), excessive straining, prolonged defecation time, or need to support the perineum or digitate the anorectum. In the vast majority of cases (probably >90%), there is no underlying cause (e.g, cancer, depression or hypothyroidism), and constipation responds to ample hydration, exercise and supplementation of dietary fiber. Physical examination and, particularly, a rectal examination should exclude fecal impaction and most of the important diseases that present with constipation and possibly indicate features suggesting an evacuation disorder (e.g, high anal sphincter tone).

The presence of serious symptoms (weight loss, rectal bleeding or anemia) mandates specific diagnostic tests:

- Colonoscopy
- Sigmoidoscopie +/- biopsy of mucosal lesions
- Colonic radiography
- Measurement of serum calcium, potassium and thyroid-stimulating hormone levels

A small minority (probably <5%) of patients have severe or "intractable" constipation. Further observation of the patient may occasionally reveal a previously unrecognized cause, such as an evacuation disorder, laxative abuse, malingering, or psychological disorder. In these patients, evaluation of the physiologic function of the colon and pelvic floor and of psychological status aid in the rational choice of treatment:

- Measurement of colonic transit (radiopaque marker transit tests, radioscintigraphy)
- Anorectal and pelvic floor tests (balloon expulsion test, anorectal manometry, defecography…)

4. Drugs used to treat event

- A06AA Softeners, emollients: Liquid paraffin, ...
- A06AB Contact laxatives: Bisacodyl, Senna glycosides, Cascara, Sodium picosulfate, ...
- A06AC Bulk-forming laxatives: Ispaghula (psylla seeds), Sterculia, Methylcellulose, ...
- A06AD Osmotically acting laxatives: Magnesium, Lactulose, Lactitol, Sodium sulfate, Macrogol, Mannitol, Sodium phosphate, Sorbitol, Sodium tartrate
- A06AG Enemas: Glycerol, Sorbitol, ...
- A06AX Other drugs for constipation: Glycerol, Carbon dioxide producing drugs, ...

5. Procedures used specific for event treatment

None.

6. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

GP and outpatient specialist (pediatrician and gastroenterologist).

7. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA

ICD-10:

- K59.0: Constipation
- F45.3: Somatoform autonomic dysfunction (psychogenic form of constipation

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Annex 13. Hearing Loss

1. Event definition

Hearing loss, also known as hearing impairment, is a partial or total inability to hear. Hearing loss exists when there is diminished acuity to sounds normally heard. Hearing loss often happens gradually over time. However, it can also appear suddenly. Hearing loss is often permanent, but can sometimes be temporary. Hearing loss may occur in one or both ears.

Causes

Hearing loss may be caused by a number of factors, including: genetics, ageing, exposure to noise, some infections, birth complications, trauma to the ear, and certain medications or toxins.

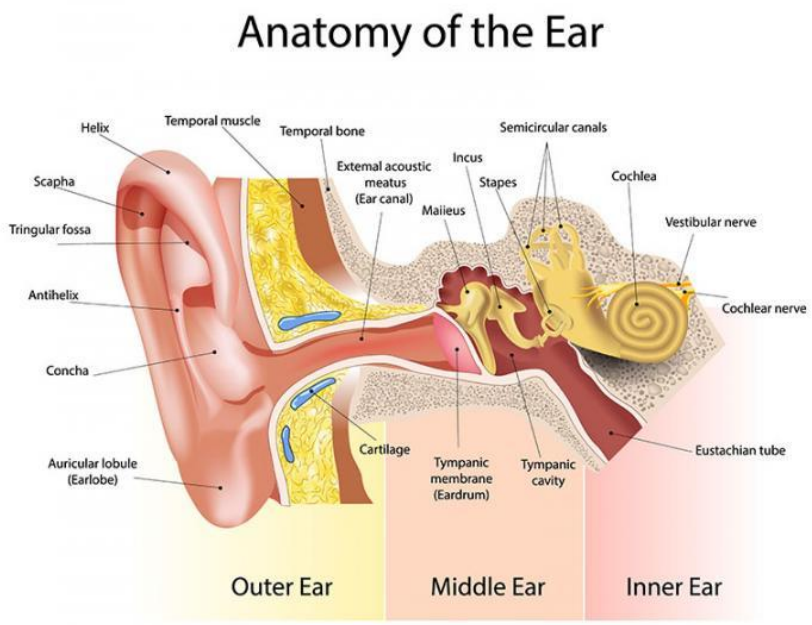
More than half of childhood hearing impairment is thought to be hereditary but hereditary hearing impairment (HHI) can also manifest later in life.

Disorders of the sense of hearing

Hearing loss can result from disorders of the auricle, external auditory canal, middle ear, inner ear, or central auditory pathways. In general, lesions in the auricle, external auditory canal, or middle ear that impede the transmission of sound from the external environment to the inner ear cause *conductive hearing loss*, whereas lesions that impair mechanotransduction in the inner ear or transmission of the electrical signal along the eighth nerve to the brain cause *sensorineural hearing loss*. Combinations of conductive and sensorineural hearing losses are called a *mixed hearing loss*.

1a. Supporting information Physiology of the ear and in utero development

The ear is composed of three parts: the outer ear (pinna, ear canal), middle ear (tympanic cavity, three ossicles), and inner ear (cochlea containing the organ of Corti and hair cells).



The inner ear is the first to develop *in utero*. The cochlea starts to grow around the 5th pregnancy week and has completed two and a half turns at the 10th week. Ciliated sensory cells of the organ of Corti develop from the 12th to the 20th weeks. At the 22nd week, the inner ear has reached its adult size and shape. In the middle ear, the ossicles start to differentiate around the 8th week. The ossicles and the tympanic cavity have reached their full size at the 26th and 30th week, respectively. In the outer ear, pinna development extends from the 5th to the 10th week, and ear cannel development ends around the 16th week.

In short, the ear development extends from the 4th to the 30th week of pregnancy; after this, the fetus is able to react to external auditory stimuli.

Therefore, in utero exposure to ototoxic drugs could lead to hearing impairment. Certain infections during pregnancy, such as cytomegalovirus, syphilis and rubella, may also cause hearing loss in the child.

Epidemiology

Hearing loss is one of the most common sensory disorders in humans and can be present at any age. Nearly 10 % of the adult population has some hearing loss. In France, 0.13% of infants suffer from severe deafness.

Consequences of hearing disorder in childhood

Hearing loss in infants, even mild, negatively impacts language and speech development, and delays social-emotional development. Evidence tends to indicate that the earlier an intervention is performed

(before 3 or 6 months-old), the more the language skills improve.

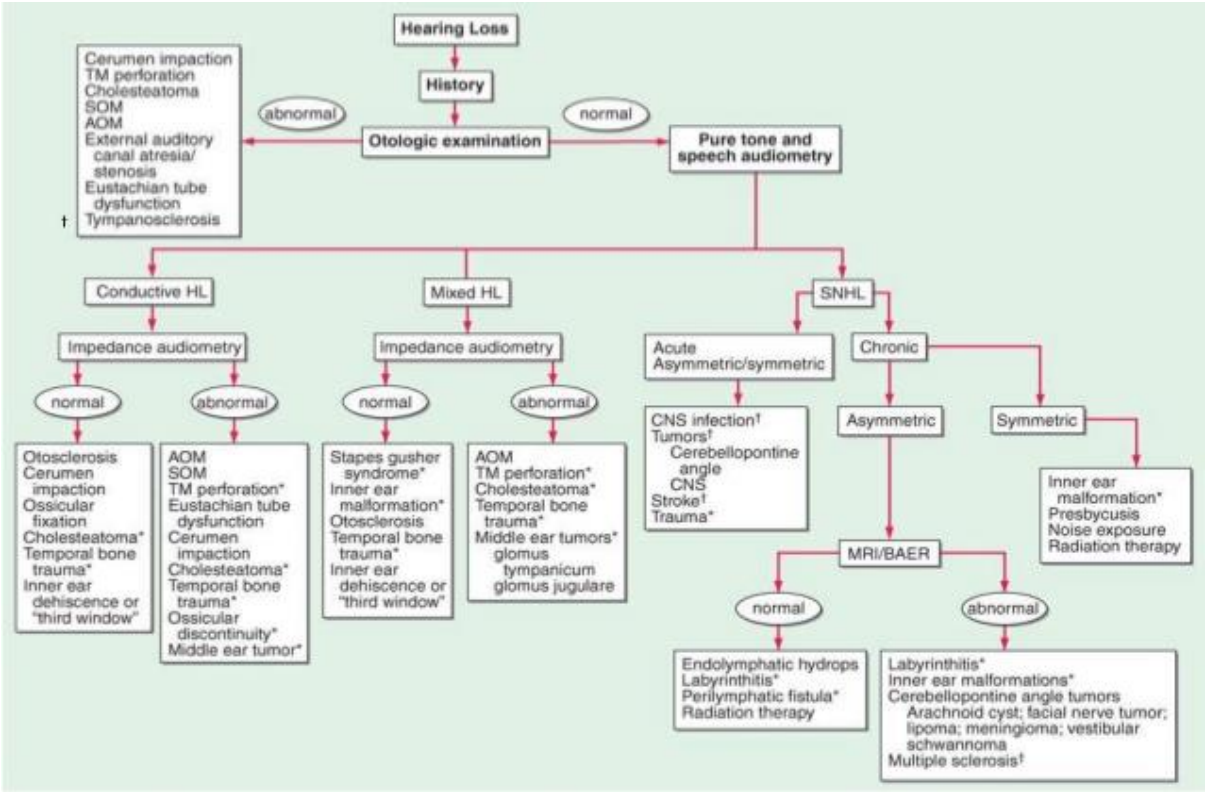
2. Synonyms / lay terms used

- Hearing disorder
- Hearing impairment
- Hearing loss
- Deafness
- Congenital hearing disorder
- Conductive hearing loss
- Sensorineural hearing loss
- Mixed hearing loss

3. Diagnostic tests done specific for event

- **Audiologic assessment**: the minimum audiologic assessment for hearing loss should include the measurement of pure tone air-conduction and bone conduction thresholds, speech reception threshold, word recognition score, tympanometry, acoustic-reflex decay. This test battery provides a screening evaluation of the entire auditory system. The responses are measured in decibels.
    - The Rinne and Weber tuning fork tests are used to screen for hearing loss, differentiate conductive from sensorineural hearing losses, and to confirm the findings of audiologic evaluation.
- **Evoked responses:** several test can be used:
    - *Electrocochleography* measures the earliest evoked potentials generated in the cochlea and the auditory nerve
    - *Brainstem auditory evoked responses (BAERs)*, also known as *auditory brainstem responses (ABRs)* are useful in differentiating the site of sensorineural hearing loss.
        - The *vestibular-evoked myogenic potential (VEMP)* test elicits a vestibulocollic reflex.
- **Imaging studies:** the test of the radiologic tests is largely determined by whether the goal is to evaluate the bony anatomy of the external, middle and inner ear or to image the auditory nerve and brain.

  Several algorithms for the approach to hearing loss were proposed. In the Harrisson's book, principles of internal medicine, the algorithm propose is:



*HL: hearing loss
*SNHL: sensorineural hearing loss
*TM: tympanic membrane
*SOM: serous otitis media
*AOM: acute otitis media
*BAER: brainstem auditory evoked response
*CT: scan of temporal bone
MRI: scan

4. Drugs used to treat event

To our knowledge, currently, no drugs are used to treat hearing disorders.

5. Procedures used specific for event treatment

In general, conductive hearing losses are amenable to **surgical correction**, while sensorineural hearing losses are more difficult to manage. Patients with mild, moderate and severe sensorineural hearing losses are regularly rehabilited with **hearing aids** of varying configuration and strength.

6. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /relaibly diagnosed

Hearing losses can be diagnosed by a GP but hearing specialists must be consulted in order to confirm the diagnosis.

7. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA

ICD10 codes:

- H91 Other hearing loss
  - H91.0 Ototoxic hearing loss
  - H91.2 Sudden idiopathic hearing loss
  - H91.8 Other specified hearing loss
  - H91.9 Hearing loss, unspecified
- H90 Conductive and sensorineural hearing loss
  - H90.0 Conductive hearing loss, bilateral
  - H90.1 Conductive hearing loss, unilateral with unrestricted hearing on the contralateral side
  - H90.2 Conductive hearing loss, unspecified
  - H90.3 Sensorineural hearing loss, bilateral
  - H90.4 Sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side
  - H90.5 Sensorineural hearing loss, unspecified
  - H90.6 Mixed conductive and sensorineural hearing loss, bilateral
  - H90.7 Mixed conductive and sensorineural hearing loss, unilateral with unrestricted hearing on the contralateral side
  - H90.8 Mixed conductive and sensorineural hearing loss, unspecified
- Z01.1 Examination of ears and hearing
- Z97.4 Presence of external hearing-aid
- Z46.1 Fitting and adjustment of hearing aid
- Z45.3 Adjustment and management of implanted hearing device

- Z82.2 Family history of deafness and hearing loss
- Q16 Congenital malformations of ear causing impairment of hearing

8. Experience of participating datasources to extract the events prior to Conception

The CHUT of Toulouse especially studied this event in the publication "C. Foch et al., In utero druf exposure and hearing impairment in 2-year-old children, A case-control study using the EFEMERIS database, International Journal of Pediatric Otorhinolaryngology, 113 (2018) 192-197."

The main study objective was to assess the association between in utero drug exposure and the occurrence of hearing impairment in 2-year-old children. A case-control study was carried out using the EFEMERIS database, recording medications dispensed during pregnancy and the compulsory health certificates for child at 8 days, 9 and 24 months.

Any hearing loss is routinely reported in the child's health certificates. Cases were defined as children with an abnormal hearing examination recorded on the 24-month certificate. Gene-related deafness was excluded. Controls were defined as children with a normal hearing examination recorded on the 24-month certificate and no abnormal hearing examination recorded on the 9-month or the 8-day certificate.

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Annex 14. Maternal gestational diabetes mellitus

1. Event definition

Gestational diabetes mellitus (GDM), defined as glucose intolerance with onset or first recognition in pregnancy (Alberti, 1998), affect as many as 5% of pregnant women in Europe (Eades, 2017; FHI, 2017). Across continents, the prevalence of GDM varies more markedly (from 1% to <30%), owing to lack of consensus on diagnostic criteria, differing antenatal screening practices, genetic variation, as well as to differences in maternal correlates such as ethnicity and life-style (McIntyre, 2019).
Efforts have been made to harmonize these clinical definitions, for instance by the Brighton Collaboration Gestational Diabetes Working Group (GAIA) (Kachikis , 2017).

The GAIA case definitions are outlined below (Kachikis , 2017):

GDM is a clinical syndrome characterized by:
-The absence of a pre-gestational diabetes diagnosis which per se is defined by:
i) Previous diagnosis of diabetes while not pregnant, OR
ii) First trimester hemoglobin A1c level of ⩾ 6.5% (47.5 mmol/mol), OR
iii) First trimester fasting blood glucose 126 mg/dL/⩾7 mmol/L

AND

-Identification of sustained hyperglycaemia during pregnancy not due to other known causes (i.e. corticosteroids, beta-mimetic, etc.).

The major criteria used to identify GDM is via administration of the “Glucose Challenge Test” which comprises of a blood test two hours after a liquid containing 75 g glucose (or 100 g, depending on the guideline) has been administered. The diagnostic criteria for GDM based on fasting plasma glucose level and levels after glucose challenge test vary across country guidelines, as outlines in the Table below - extracted from the GAIA guidelines (Kachikis , 2017).

Table 1
Diagnostic oral glucose tolerance tests based on organization or country guidelines.

Test	Guidelines	Number of abnormal values necessary for diagnosis	Fasting plasma glucose mmol/l (mg/dl)	1-h plasma glucose mmol/l (mg/dl)	2-h plasma glucose mmol/l (mg/dl)	3-h plasma glucose mmol/l (mg/dl)	Timing
75 g OGTT							
	WHO 2013 [1]	1	⩾5.1–6.9 (92–125)	⩾10.0 (180)	⩾8.5–11.0 (153–199)	N/A	24–28 wks
	IADPSG [25]	1	⩾5.1 (92)	⩾10.0 (180)	⩾8.5 (153)	N/A	
	NICE (UK) [26]	1	⩾5.6 (101)	Not required	⩾7.8 (140)	N/A	24–28 wks
100 g OGTT							
	Carpenter Coustan [27]	2	⩾5.3 (95)	⩾10.0 (180)	⩾8.6 (155)	⩾7.8 (140)	24–28 wks
	NDDG [27]	2	⩾5.8 (105)	⩾10.6 (190)	⩾9.2 (165)	⩾ 8.0 (145)	

OGTT (Oral glucose tolerance test); IADPSG (International Association of Diabetes and Pregnancy Study Groups); WHO (World Health Organization); NICE (The National Institute for Health and Care Excellence, UK); NDDG (National Diabetes Data Group).

2. Synonyms / lay terms used

Diabetes of pregnancy.

According to GAIA definition, alternate terminology for GDM includes "pregnancy-induced hyperglycemia." Diabetes in pregnancy is frequently used to describe pregestational diabetes or is used as an umbrella term for pregestational diabetes and GDM.

ICD-10 synonyms: «Antepartum diabetes mellitus», «Gestational diabetes (diabetes of pregnancy)", "Gestational diabetes mellitus complicating pregnancy", "Gestational diabetes mellitus in pregnancy".

3. Laboratory tests done specific for event

Fasting plasma glucose level ≥ 7.0 mmol/l; or ii) two hours after glucose challenge test glucose level ≥ 11.1 mmol/l (Helsedirektorate, 2018) These levels may vary according to country-specific guidelines, see the Table above (Kachikis , 2017).

4. Diagnostic tests done specific for event

Administration of the "Glucose Challenge Test" and blood test two hours after the 75 g glucose containing liquid.

5. Drugs used to treat event

Metformin, insulin or oral antidiabetics. Below is an overview of recommended pharmacological treatment of GDM across guidelines (reference lacking).

Pharmacologic management of GDM.

ACOG [1]	ADA [2,3]	CDA [4]	IDF [5]	NICE [6]
No conclusive evidence of glucose threshold to start therapy Insulin and oral agents are equally efficacious, either are appropriate first-line agents	If targets not met with lifestyle modifications, initiate pharmacotherapy Insulin preferred Short term data support glyburide and metformin; no long term data (2015 SOC)	If targets not met within 2 weeks of lifestyle modifications, initiate pharmacotherapy Insulin preferred (multiple daily injections) If nonadherent to or refuse insulin, initiate glyburide or metformin	If targets not met with lifestyle modifications, initiate pharmacotherapy Insulin preferred Metformin and glyburide are safe and effective alternatives	If fasting glucose <126 mg/dL at diagnosis, trial of lifestyle modifications If targets not met within 1–2 weeks of lifestyle modifications, initiate metformin. Insulin is recommended if metformin is contraindicated, fasting glucose at diagnosis >126 mg/dL, or fasting glucose at diagnosis 108–125 mg/dL and complications (e.g., macrosomia or hydramnios). Insulin can also be used as add-on therapy Initiate glibenclamide (glyburide) if targets not met with metformin and patient declines insulin or if patient cannot tolerate metformin

ACOG, American College of Obstetricians and Gynecologists; ADA, American Diabetes Association; CDA, Canadian Diabetes Association; GDM, gestational diabetes mellitus; IDF, International Diabetes Federation; NICE, National Institute for Health and Care Excellence.

According to two recent Cochrane meta-analyses, insulin and oral anti-diabetic pharmacological therapies have similar effects on key health outcomes. The available evidence suggests that there are minimal harms associated with the effects of treatment with either insulin or oral anti-diabetic pharmacological therapies. The choice to use one or the other may be down to physician or maternal preference, availability or severity of GDM (Brown, 2017). However, data comparing oral anti-diabetic pharmacological therapies with placebo/standard care (lifestyle advice) remain insufficient to inform clinical practice (Brown, 2017b).

6. Procedures used specific for event treatment

Not applicable.

It is generally recommended that patients self-monitor fasting glucose (goal <95 mg/dL) and postprandial glucose 1 hour (goal <140 mg/dL) or 2 hours (goal <120 mg/dL) after eating.

7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

GP, prenatal check-ups by GP and/or midwives, measurement of glucose done at home or at GP.

8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA

ICD-9 (2015 ICD-9-CM Diagnosis Code)	
648.0	Diabetes mellitus complicating pregnancy childbirth or the puerperium
648.00	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, unspecified as to episode of care or not applicable (convert 648.00 to ICD-10-CM)
648.01	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with or without mention of antepartum condition (convert 648.01 to ICD-10-CM)
648.02	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, delivered, with mention of postpartum complication (convert 648.02 to ICD-10-CM)
648.03	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, antepartum condition or complication (convert 648.03 to ICD-10-CM)
648.04	Diabetes mellitus of mother, complicating pregnancy, childbirth, or the puerperium, postpartum condition or complication
648.8	Abnormal glucose tolerance of mother complicating pregnancy childbirth or the puerperium
648.80	Abnormal glucose tolerance of mother, unspecified as to episode of care or not applicable convert 648.80 to ICD-10-CM
648.81	Abnormal glucose tolerance of mother, delivered, with or without mention of antepartum condition (convert 648.81 to ICD-10-CM)
648.82	Abnormal glucose tolerance of mother, delivered, with mention of postpartum complication (convert 648.82 to ICD-10-CM)
648.83	Abnormal glucose tolerance of mother, antepartum condition or complication (convert 648.83 to ICD-10-CM)
648.84	Abnormal glucose tolerance of mother, postpartum condition or complication (convert 648.84 to ICD-10-CM)

ICD-10 (2017 version)	
O24	Diabetes mellitus in pregnancy, childbirth, and the puerperium
O24.4	Gestational diabetes mellitus
O24.41	Gestational diabetes mellitus in pregnancy
O24.410	…… diet controlled
O24.414	…… insulin controlled
O24.415	…… controlled by oral hypoglycemic drugs
O24.419	…… unspecified control
O24.42	Gestational diabetes mellitus in childbirth
O24.420	…… diet controlled
O24.424	…… insulin controlled
O24.425	…… controlled by oral hypoglycemic drugs
O24.43	Gestational diabetes mellitus in the puerperium
O24.430	…… diet controlled
O24.434	…… insulin controlled
O24.435	Gestational diabetes mellitus in puerperium, controlled by oral hypoglycemic drugs
O24.439	…… unspecified control

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Annex 15. Preeclampsia

1. Event definition

Hypertensive disorders of pregnancy are leading cause of maternal and infant morbidity and mortality, and they complicate up to 10% of the pregnancies. However, the aetiology of these disorders, in particular of preeclampsia, remains not fully understood.

Hypertensive disorders is an umbrella term that includes pre-existing and gestational hypertension, preeclampsia, and eclampsia.

Braunthal and Brateanu have recently shown that differences in case definition of hypertensive disorders of pregnancy do exist across guidelines (Braunthal, 2019). However, efforts have been made to harmonise these clinical definitions, for instance by the Brighton Collaboration Preeclampsia Working Group (GAIA) (Rouse, 2016).

The GAIA case definitions are outlined below (Rouse, 2016):

PREECLAMPSIA

Preeclampsia is defined as development of new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND new onset proteinuria after 20 weeks gestation.

Level 1 of diagnostic certainty: proteinuria diagnosed with ≥300 mg of protein on 24 h urine collection OR ≥0.3 on spot protein:creatinine ratio.

Level 2 of diagnostic certainty: proteinuria diagnosed with ≥1+ protein on urine dipstick.

Insufficient evidence: blood pressure cannot be measured OR no proteinuria evaluation is available (note diagnosis of preeclampsia with severe features does not require proteinuria, see definition below).

PREECLAMPSIA WITH SEVERE FEATURES

For all levels of diagnostic certainty, preeclampsia with severe features is a clinical syndrome characterized by pregnancy ≥20 weeks AND new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h AND at least one of the criteria for severe disease:

Level 1 of diagnostic certainty

At least one of the following: Systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only minutes OR

Development of severe, persistent headache OR

Development of visual changes OR

Eclampsia OR

New onset thrombocytopenia (platelets <100,000/µL) OR

New onset unremitting epigastric pain OR

AST and ALT elevated to twice upper limit of normal OR

Evidence of liver capsular hematoma or liver rupture (diagnosed on clinical exam or with imaging) OR

Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease) or oliguria (<500 cc/24 h) OR

Pulmonary edema (confirmed on imaging with chest X-ray, or on clinical exam).

Level 2 of diagnostic certainty: new onset nausea and vomiting.

Insufficient evidence: blood pressure cannot be measured.

GESTATIONAL HYPERTENSION

For all levels of diagnostic certainty, gestational hypertension is a clinical syndrome characterized by pregnancy ≥20 weeks AND new onset hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg) sustained on two measurements over a minimum of 1 h WITHOUT severe features (see preeclampsia with severe features category) and WITHOUT proteinuria.

Level 1 of diagnostic certainty: no proteinuria (as defined by 24 h urine collection < 300 mg, spot protein:creatinine ratio <0.3).

Level 2 of diagnostic certainty: no proteinuria (as defined by urine dipstick negative or trace).

Insufficient evidence: blood pressure cannot be measured OR no proteinuria evaluation is available.

Blood pressure is considered elevated if the systolic blood pressure is ≥140 mmHg or the diastolic blood pressure is ≥90 mmHg, sustained over time. A diagnosis of hypertension be made if the systolic blood pressure is ≥140 mmHg or the diastolic blood pressure is ≥90 mmHg on two measurements at a minimum of one hour apart. The length of time that the blood pressure should remain elevated varies as well, from 15 min to 4 h depending on which organization guidelines are followed.

TIMING

Preeclampsia and gestational hypertension are conventionally defined as developing after 20 weeks

gestation, but there can be great variability in exact timing of presentation of the disease. In one study (Lisonkova, 2013), approximately 10% of the preeclampsia diagnoses were made before 34 weeks gestation. Preeclampsia can develop up to 6 weeks postpartum and, in fact, 20–50% of eclampsia occurs in the postpartum period. The progression from normal blood pressure to hypertension to preeclampsia can proceed rapidly, gradually, or not at all.

Symptoms

Vascular: Severely elevated blood pressures, with systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥110 mmHg, which is confirmed after only minutes (to facilitate timely antihypertensive treatment).

Neurologic: Development of a severe headache (which can be diffuse, frontal, temporal or occipital) that generally does not improve with over the counter pain medications (such as acetaminophen/paracetamol).

Development of visual changes: including photopsia, scotomata, cortical blindness (Roos, 2012).

Eclampsia, or new-onset grand mal seizures in a patient with preeclampsia, without other provoking factors (such as evidence of cerebral malaria or preexisting seizure disorder). Seizures are often preceded by headaches, visual changes or altered mental status (Cooray, 2011).

Hematologic: New onset thrombocytopenia, with platelet count <100,000/μL.

Gastrointestinal: New onset of nausea, vomiting, epigastric pain, Transaminitis (AST and ALT elevated to twice the upper limit of normal), Liver capsular hemorrhage or liver rupture

Renal: Worsening renal function, as evidenced by serum creatinine level greater than 1.1 mg/dL or a doubling of the serum creatinine (absent other renal disease), oliguria (urine output <500 mL/24 h).

Respiratory: Pulmonary edema (confirmed on clinical exam or imaging).

2. Synonyms used

"New onset hypertension in pregnancy with proteinuria", "eclampsia," "preeclampsia," "gestational hypertension" and "pregnancy-induced hypertension" are commonly used in clinical practice. The terms "eclampsia," "preeclampsia," "gestational hypertension" and "pregnancy-induced hypertension" are commonly used in clinical practice. "Pregnancy-induced hypertension" is a term referring to hypertensive disorders of pregnancy in general, but lacks the specificity of the other terms, and so the Brighton definitions (Rouse, 2016) will refer only to "eclampsia," "preeclampsia," and "gestational

hypertension." All of these disorders are characterized by elevations in blood pressure.

Preeclampsia and eclampsia have additional diagnostic criteria based on laboratory findings by clinical physical exam or patient reported symptoms reflecting the systemic nature of the disease.

The diagnosis of gestational hypertension is provisional, in that every woman with new blood pressure elevation in pregnancy should be further evaluated for the development of preeclampsia. It is possible to move from a diagnosis of gestational hypertension to preeclampsia or eclampsia, but not from preeclampsia to gestational hypertension (Rouse, 2016).

3. Laboratory tests done specific for event

Proteinuria in urine by 24 h urine collection, a spot protein:creatinine ratio, or with urinary dipstick.

4. Diagnostic tests done specific for event

Systolic and diastolic blood pressure, urinalysis.

According to GAIA definition (Rouse, 2016), blood pressure is considered elevated if the systolic blood pressure is ≥140 mmHg or the diastolic blood pressure is ≥90 mmHg, sustained over time. A diagnosis of hypertension be made if the systolic blood pressure is ≥140 mmHg or the diastolic blood pressure is ≥90 mmHg on two measurements at a minimum of one hour apart.

Proteinuria can be quantified by 24 h urine collection, a spot protein:creatinine ratio, or with urinary dipstick. Proteinuria of ≥300 mg in a 24 h urine specimen (the gold standard for measurement of proteinuria), or ≥0.30 on a spot protein:creatinine ratio, or ≥1+ on a dipstick meets the criteria for preeclampsia (Rouse, 2016).

5. Drugs used to treat event

Metyldopa, labetalol, nifedipine (Other antihypertensives may also be used occationally). This is supported by the recent study by Braunthal et al (Braunthal, 2019); see an extract of Table 3 from this article below:

Table 3. Common antihypertensive medications used in pregnancy.

	Urgent BP lowering		Outpatient BP control	
Labetalol	Intravenous	10–20 mg, then 20–80 mg every 10–30 min, maximum 300 mg OR 1–2 mg/min infusion	Oral	200–2400 mg/day, divided into two to three doses
Hydralazine	Intravenous	5 mg, then 5–10 mg every 20–40 min, maximum 20 mg OR 0.5–10 mg/h infusion	Not commonly used first-line	
Nifedipine	Oral *Immediate release*	10–20 mg every 2–6 h*, maximum 180 mg/day *May repeat initial dose after 20 min if needed	Oral *Extended Release*	30–120 mg/day
Methyldopa	Not commonly used first-line		Oral	500–3000 mg/day, divided into two to four doses

Adapted from the American College of Obstetricians and Gynecologists Practice Bulletin Number 2019.[3,12]

6. Procedures used specific for event treatment

Termination of pregnancy, induced delivery if preeclampsia is near to term.

7. Setting (outpatient specialist, in-hospital, GP, emergency room) where condition will be most frequently /reliably diagnosed

Obstetrician/gynaecologist and if severe hospitalization.

8. Diagnosis codes or algorithms used in different papers to extract the events in Europe/USA

See an overview from the NVPO project (evaluation of GAIA definitions)

ICD-10 (2017 version)	ICD-9 (2015 ICD-9-CM Diagnosis Code)
O14 Pre-eclampsia	**642.4 Mild or unspecified pre-eclampsia** 642.40 - Mild/NOS preeclampsia-unspecified 642.41 - Mild/NOS preeclampsia-delivery 642.42 - Mild preeclampsia-delivery w p/p 642.43 - Mild/NOS preeclampsia-antepartum
O14.* (that is with any digit after the decimal point)	**642.7 Pre-eclampsia or eclampsia superimposed on pre-existing hypertension** 642.70 - Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, unspecified as to episode of care or not applicable 642.71 - Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, delivered, with or without mention of antepartum condition 642.72 - Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, delivered, with mention of postpartum complication 642.73 - Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, antepartum condition or complication 642.74 - Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, postpartum condition or complication

	642.5 Severe pre-eclampsia 642.50 - Severe preeclampsia-unspecified 642.51 - Severe preeclampsia-delivery 642.52 - Severe pre-eclampsia, delivered, with mention of postpartum complication 642.53 - preeclampsia-antepartum 642.54 - Severe preeclampsia-postpartum

MEDDRA	
10040446	Severe pre-eclampsia, postpartum
10040445	Severe pre-eclampsia, antepartum
10040449	Severe pre-eclampsia, with delivery, with mention of postpartum complication
10040448	Severe pre-eclampsia, with delivery
10040447	Severe pre-eclampsia, unspecified as to episode of care
10040444	Severe pre-eclampsia
10036489	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, postpartum
10036487	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, antepartum
10036490	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension, with delivery
10036486	Pre-eclampsia or eclampsia superimposed on pre-existing hypertension
10027622	Mild or unspecified pre-eclampsia, postpartum
10027621	Mild or unspecified pre-eclampsia, antepartum
10027625	Mild or unspecified pre-eclampsia, with delivery, with mention of postpartum complication
10027624	Mild or unspecified pre-eclampsia, with delivery
10027623	Mild or unspecified pre-eclampsia, unspecified as to episode of care
10027620	Mild or unspecified pre-eclampsia
10036485	Pre-eclampsia
10036492	Pre-eclampsia toxemia
10036493	Pre-eclamptic toxaemia
10044130	Toxaemia of pregnancy
10044133	Toxemia of pregnancy
10074050	Pre-eclampsia toxaemia

READ	
L1250	Severe pre-eclampsia unspecified.
L125z	Severe pre-eclampsia NOS
L125.	Severe pre-eclampsia
L1240	Mild pre-eclampsia unspecified
L124.	Mild/unspecified pre-eclampsia
L124z	Mild/unspec.pre-eclampsia NOS
L1245	Mild pre-eclampsia
L124.	Mild/unspecified pre-eclampsia
L1246	Pre-eclampsia, unspecified
L12B.	Protein hypertens of pregnancy

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Annex 16. Advantages and Disadvantages of the Main Data Sources

Data Source	Quality of outcome data	Quality of exposure data	Quality of confounder data	Comments
Healthcare databases	Variable, often limited to livebirths	High coverage of prescriptions, but not of compliance or OTC drugs	Variable	May need considerable prior validation work to use for research
Birth cohorts	Good for perinatal and childhood outcomes, variable for congenital anomalies and rare outcomes, may not include terminations of pregnancy	High coverage of both prescribed and OTC drugs, including compliance	Usually extensive confounder information available	Limited population size/statistical power; research-ready
Congenital Anomaly registries	High quality diagnostic information, terminations of pregnancy for fetal anomaly included	May be incomplete unless linked to prescription data, OTC available but incomplete, compliance available	Tends to be limited to maternal age, comedications and comorbidities	Research-ready
Primary care databases	Incomplete information on pregnancy timing so estimation needed. Variable information on congenital anomalies and rare outcomes	High coverage of prescribed drugs but not of drugs administered in hospital or OTC drugs	Extensive confounder information available regarding data available to general practitioner	Limited population size/statistical power; Research-ready

*For more detailed information on particular data sources, see the ConcePTION Data Catalogue. There is no "ideal" observational data source. An appropriate data source for the study question should be found according to a balance of advantages and disadvantages, and the quality of the data source MUST be taken into account in the interpretation of results.

Annex 17. Analytical methods

Table 1. Analytical methods for testing a hypothesis on observational data

Model	Outcome type	Exposure type	Advantages	Disadvantages	References
T-test	Continuous	Binary	Simple to run	Cannot adjust for confounders Would not recommend for use in final analysis	
Linear regression	Continuous	Continuous, Binary, Categorical	Can adjust for confounders	Observations must be independent of each other. (i.e. not measurements over time)	
Chi-Squared test	Binary	Binary, Categorical	Simple to run	Cannot adjust for confounders Cannot be used for small counts Would not recommend for use in final analysis	(Crijns, Jentink et al. 2011)
Fisher's exact test	Binary	Binary, Categorical	Simple to run Works well for small counts	Cannot adjust for confounders Would not recommend for use in final analysis	(Interrante, Ailes et al. 2017)
Logistic regression	Binary	Continuous, Binary, Categorical	Can adjust for confounders	Observations must be independent of each other.	(Interrante, Ailes et al. 2017)
Ordinal logistic regression	Categorical – Ordered	Continuous, Binary, Categorical	Can adjust for confounders	Observations must be independent of each other.	
Multinomial logistic regression	Categorical – Unordered	Continuous, Binary, Categorical	Can adjust for confounders	Observations must be independent of each other.	
Poisson regression	Counts/Rates	Continuous, Binary, Categorical	Can adjust for confounders	Can experience overdispersion*	
Negative binomial regression	Counts/Rates	Continuous, Binary, Categorical	Can adjust for confounders Accounts for overdispersion*	Will have lower precision than the Poisson model	

Kaplan-Meier survival analysis	Time to event/Survival	Binary, Categorical	Quick and simple	Cannot adjust for confounders	
Parametric survival analysis (Exponential, Weibull)	Time to event/Survival	Continuous, Binary, Categorical	Can adjust for confounders	Data must fit the specified distribution	
Semi-Parametric survival analysis (Cox proportional hazards regression)	Time to event/Survival	Continuous, Binary, Categorical	Can adjust for confounders Do not need to specify the distribution of the baseline hazard	Will have lower precision than a parametric survival analysis	(Richardson, Stephens et al. 2017)
Longitudinal models	Repeat measures	Continuous, Binary, Categorical	Accounts for between measure correlations eg over time	Requires large sample sizes for reasonable precision	
Hierarchical models	Continuous, Binary, Categorical,	Continuous, Binary, Categorical	Can be used when independence of patients seems unlikely e.g. within a hospital	Requires large sample sizes for reasonable precision	
Fixed effect meta-analysis			Does not over-weight small studies	Does not account for between study estimate variation	
Random effect meta-analysis			Accounts for between study variation	Gives more weight to smaller studies than fixed effect method Has lower precision than the fixed effect method	(Garne, Vinkel Hansen et al. 2016)

**overdispersion is the presence of greater variability than expected in any given statistical model.*

Note: All of the methods listed above are frequentist statistical methods. Alternatively, similar Bayesian approaches are available.

Annex 18. Statistical power and sample size considerations

Number of patients needed

Cohort study sample sizes

Table 1. The number of patients needed to be a) on treatment X and b) in the study, when **0.1% of the study population are on treatment X**

a) The number of patients needed to be on treatment X

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	8,088,321	808,081	80,057	15,344	7,255
	1.2	2,078,386	207,640	20,565	3,936	1,857
	1.5	358,172	35,779	3,540	674	316
	2	99,366	9,924	980	185	86
	5	9,247	922	90	16	6

b) The number of patients needed to be in the study

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	8,088,321,488	808,081,490	80,057,486	15,344,223	7,255,043
	1.2	2,078,385,997	207,639,542	20,564,892	3,936,015	1,857,381
	1.5	358,172,230	35,779,422	3,540,137	674,401	316,157
	2	99,366,025	9,924,276	980,096	185,033	85,616
	5	9,246,765	922,213	89,749	15,708	6,378

Table 2. The number of patients needed to be a) on treatment X, b) in the study, when **1% of the study population are on treatment X**

a) The number of patients needed to be on treatment X

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	8,164,841	815,726	80,815	15,489	7,323
	1.2	2,098,840	209,683	20,767	3,975	1,876
	1.5	362,119	36,174	3,579	682	320
	2	100,659	10,053	993	187	87
	5	9,468	944	92	16	7

b) The number of patients needed to be in the study

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	816,484,080	81,572,607	8,081,460	1,548,911	732,340
	1.2	209,883,964	20,968,283	2,076,714	397,462	187,553
	1.5	36,211,891	3,617,363	357,910	68,179	31,960
	2	10,065,884	1,005,338	99,283	18,742	8,672
	5	946,776	94,426	9,191	1,609	655

Table 3. The number of patients needed to be a) on treatment X, b) in the study, when **5% of the study population are on treatment X**

a) The number of patients needed to be on treatment X

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	8,522,435	851,451	84,353	16,166	7,643
	1.2	2,194,402	219,229	21,712	4,155	1,960
	1.5	380,536	38,013	3,761	716	336
	2	106,674	10,654	1,052	199	92
	5	10,476	1,045	102	18	7

b) The number of patients needed to be in the study

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	170,448,707	17,029,023	1,687,055	323,324	152,857
	1.2	43,888,044	4,384,587	434,241	83,099	39,206
	1.5	7,610,713	760,263	75,218	14,324	6,713
	2	2,133,487	213,082	21,041	3,971	1,836
	5	209,512	20,896	2,035	357	146

Table 4. The number of patients needed to be a) on treatment X, b) in the study, when **10% of the study population are on treatment X**

a) The number of patients needed to be on treatment X

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	9,014,049	900,565	89,217	17,097	8,082
	1.2	2,325,725	232,348	23,011	4,403	2,077
	1.5	405,789	40,536	4,010	763	358
	2	114,882	11,474	1,133	214	99
	5	11,808	1,178	115	20	8

b) The number of patients needed to be in the study

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	90,140,492	9,005,652	892,169	170,970	80,820
	1.2	23,257,250	2,323,482	230,106	44,028	20,768
	1.5	4,057,893	405,356	40,101	7,634	3,576
	2	1,148,824	114,738	11,329	2,137	988
	5	118,080	11,778	1,147	201	82

Table 5. The number of patients needed to be a) on treatment X, b) in the study, when **25% of the study population are on treatment X**

a) The number of patients needed to be on treatment X

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	10,881,552	1,087,136	107,694	20,633	9,750
	1.2	2,824,148	282,140	27,939	5,343	2,519
	1.5	501,208	50,066	4,952	942	440
	2	145,590	14,540	1,435	270	125
	5	16,535	1,649	161	28	12

b) The number of patients needed to be in the study

		Outcome prevalence in unexposed				
		0.01%	0.1%	1%	5%	10%
Risk Ratio	1.1	43,526,208	4,348,544	430,777	82,532	39,000
	1.2	11,296,591	1,128,559	111,755	21,373	10,075
	1.5	2,004,831	200,264	19,808	3,767	1,761
	2	582,360	58,160	5,740	1,081	499
	5	66,139	6,596	643	113	47

Case-control samples sizes

Matching ratios of cases to controls from 1:1 up to 1:9 are reported, with three tables produced for each ratio; the number of cases required, the total number of patients required, and the number of patients required to be on treatment.

The columns in each table express a range of treatment exposures within the controls and the rows express a range of expected odds ratios.

Table 6. The total number of a) cases, b) patients, c) patients on treatment X (Controls/Cases), needed in the study when **cases and controls are matched 1:1**

a) The total number of cases needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	1,648,956	166,545	34,851	18,485	9,005
	1.2	431,133	43,584	9,157	4,881	2,412
	1.5	77,656	7,872	1,674	905	466
	2	22,791	2,321	503	278	152
	5	2,523	264	64	40	27

b) The total number of patients needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	3,297,912	333,090	69,702	36,970	18,010
	1.2	862,266	87,168	18,314	9,762	4,824
	1.5	155,312	15,744	3,348	1,810	932
	2	45,582	4,642	1,006	556	304
	5	5,046	528	128	80	54

c) . The total number of patients on treatment X (Controls/Cases) needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	1,649/1,814	1,665/1,830	1,743/1,907	1,848/2,013	2,251/2,416
	1.2	431/517	436/522	458/544	488/574	603/689
	1.5	78/116	79/117	84/122	90/129	116/155
	2	23/46	23/46	25/48	28/51	38/61
	5	3/13	3/13	3/13	4/14	7/17

Table 7. The total number of a) cases, b) patients, c) patients on treatment X (Controls/Cases), needed in the study when **cases and controls are matched 1:2**

a) The total number of cases needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	1,228,910	124,135	25,990	13,794	6,733

	1.2	319,455	32,302	6,793	3,626	1,799
	1.5	56,686	5,749	1,225	665	345
	2	16,310	1,663	362	202	112
	5	1,684	177	43	27	20

b) The total number of patients needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	3,686,767	372,409	77971	41383	20200
	1.2	958,375	96,907	20380	10879	5398
	1.5	170,060	17,248	3676	1996	1036
	2	48,931	4,990	1087	607	337
	5	5,053	532	130	82	61

c) . The total number of patients on treatment X (Controls/Cases) needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	2,458/1,352	2,483/1,364	2,599/1,422	2,759/1,502	3,367/1,806
	1.2	639/383	646/387	679/404	725/427	900/514
	1.5	113/85	115/86	123/90	133/95	173/115
	2	33/33	33/33	36/35	40/37	56/45
	5	3/8	4/9	4/9	5/10	10/13

Table 8. The total number of a) cases, b) patients, c) patients on treatment X (Controls/Cases), needed in the study when cases and controls are **matched 1:4**

a) The total number of cases needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	1,018,931	102,934	21,560	11,449	5,597
	1.2	263,653	26,664	5,612	2,998	1,492
	1.5	46,235	4,691	1,002	545	285
	2	13,099	1,336	292	163	92
	5	1,278	135	33	21	16

b) The total number of patients needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	5,094,655	514,670	107,800	57,245	27,985
	1.2	1,318,265	133,320	28,060	14,990	7,460
	1.5	231,175	23,455	5,010	2,725	1,425
	2	65,495	6,680	1,460	815	460
	5	6,390	675	165	105	80

c) . The total number of patients on treatment X (Controls/Cases) needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	4,076/1,121	4,117/1,131	4,312/1,180	4,580/1,247	5,597/1,502
	1.2	1,055/316	1,067/319	1,122/333	1,199/353	1,492/426
	1.5	185/69	188/70	200/73	218/78	285/95

	2	52/26	53/26	58/28	65/30	92/37
	5	5/6	5/6	7/7	8/8	16/10

Table 9. The total number of a) cases, b) patients, c) patients on treatment X (Controls/Cases), needed in the study when cases and controls are **matched 1:9**

a) The total number of cases needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	902,291	91,157	19,099	10,146	4,965
	1.2	232,671	23,534	4,956	2,650	1,321
	1.5	40,449	4,105	878	478	251
	2	11,336	1,157	253	142	80
	5	1,068	113	28	18	14

b) The total number of patients needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	9,022,910	911,570	190,990	101,460	49,650
	1.2	2,326,710	235,340	49,560	26,500	13,210
	1.5	404,490	41,050	8,780	4,780	2,510
	2	113,360	11,570	2,530	1,420	800
	5	10,680	1,130	280	180	140

c) . The total number of patients on treatment X (Controls/Cases) needed in the study

		Expected proportion exposed in the controls				
		0.1%	1%	5%	10%	25%
Odds ratio	1.1	8,121/992	8,204/1002	8,595/1,045	9,131/1,105	11,171/1,332
	1.2	2,094/279	2,118/282	2,230/294	2,385/312	2972/377
	1.5	364/61	369/61	395/64	430/68	565/84
	2	102/23	104/23	114/24	128/26	180/32
	5	10/5	10/5	13/6	16/6	32/9

Table 10. The total number of patients and treated patients required for a range of treatment prevalence's and effect sizes.

Treatment prevalence	Effect size	Total number of patients needed	Number of patients needed to be treated
1%	10% of SD	79,300	793
	25% of SD	12,700	127
	50% of SD	3,200	32
	100% of SD	800	8
5%	10% of SD	16,540	827
	25% of SD	2,660	133
	50% of SD	680	34
	100% of SD	180	9
10%	10% of SD	8,730	873

	25% of SD	1,400	140
	50% of SD	360	36
	100% of SD	90	9
25%	10% of SD	4,188	1,047
	25% of SD	672	168
	50% of SD	172	43
	100% of SD	44	11

**SD – Standard deviation*

To put the above table in context, we can look at an example concerning IQ testing. IQ's are known to vary with a standard deviation of around 15 points. Therefore, if we were to look for an effect size after treatment of 15 points, this would fall under the 100% of the standard deviation category. This would mean, if the treatment prevalence was 5% within your population, then the required sample size would be 180 patients, 9 of which would need to be on treatment.

Annex 19: Note on Heckman model to address selection bias

Selection bias: The Heckman Method

Selection bias arises in many settings in case of observation studies. Examples of common mechanisms of selection bias is non-participation of subjects in surveys or evaluations because they refuse to participate in the study or because they are difficult to reach or due to non-response to key questions regarding outcomes or predictors. Other examples of selection bias are survival and/or transfer bias where patients that are transferred to specialized services must have survived their initial hospitalizations to be "eligible for transfer", or patients who are transferred to specialized centers tend to have more severe disease.

Another common mechanism for selection bias is loss to follow-up (attrition) in prospective cohort studies, especially those that are population-based and have a long period of follow-up. This type of selection bias may result in a cohort with less severe disease than that of the initial cohort when subjects lost to follow-up tend to be those with more severe disease ("favourable selection bias") or, conversely, in a cohort with more severe disease if those lost to follow-up are subjects with less severe disease ("adverse selection").

The Heckman Model

The Heckman model can reduce or eliminate the bias due to selection in the estimates of regression models (linear regression for continuous outcomes and the probit model for binary outcomes). It was developed in econometrics by James Heckman in order to address the problem of selection bias that occurs in several contexts in econometrics, in particular in the so-called "evaluation problems". It is still infrequently used in epidemiology in part due to less familiarity of epidemiologists with econometrics methods and in particular the Heckman model. Nevertheless, especially in cases where the mechanism of selection, or more empirically speaking, the factors related to the presence of absence of subjects in the study population are known, the Heckman method can be very useful for addressing the bias in the estimates of regression models that is due to adverse or favourable selection in the study population.