Electronic Supplementary Material: Drug Safety

Signal detection in EUROmediCAT: Identification and evaluation of medication-congenital anomaly associations and use of VigiBase as a complementary source of reference

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List of supplementary tables and figures

Supplementary Table 1. Congenital anomaly counts in EUROmediCAT and VigiBase analysis datasets

Congenital anomaly [a]	EUROmediCAT		VigiBase	
	N	%	N	%
All non-chromosomal anomalies	**21,636**	**100**	**45,749**	**100**
All fetuses with a congenital anomaly [b] not in the 61 subgroups below (i.e. only included as controls)	**3,721**	**17.2**	**24,818**	**54.25**
Neural Tube Defects	**837**	**3.87**	**1,607**	**3.51**
Anencephalus	273	1.26	319	0.70
Encephalocele	110	0.51	101	0.22
Spina Bifida	454	2.10	1,066	2.33
Hydrocephalus	463	2.14	267	0.58
Microcephaly	236	1.09	546	1.19
Arhinencephaly / holoprosencephaly	75	0.35	61	0.13
Anophthalmos	25	0.12	24	0.05
Congenital cataract	118	0.55	100	0.22
Congenital glaucoma	41	0.19	21	0.05
Anotia	32	0.15	50	0.11
Congenital heart defects (CHD)	**7,571**	**34.99**	**11,243**	**24.57**
Severe CHD	**1,893**	**8.75**	**2,656**	**5.81**
Common arterial truncus	63	0.29	66	0.14
Transposition of great vessels	340	1.57	485	1.06
Double outlet right ventricle	83	0.38	169	0.37
Single ventricle	83	0.38	56	0.12
Ventricular septal defect	3,650	16.87	2,847	6.22
Atrial septal defect	1,940	8.97	4,165	9.10
Atrioventricular septal defect	206	0.95	170	0.37
Tetralogy of Fallot	304	1.41	600	1.31
Tricuspid atresia and stenosis	77	0.36	105	0.23
Ebstein's anomaly	44	0.20	89	0.19
Pulmonary valve stenosis	488	2.26	518	1.13
Pulmonary valve atresia	98	0.45	115	0.25
Aortic valve atresia/stenosis	155	0.72	107	0.23
Mitral valve anomalies	126	0.58	149	0.33
Hypoplastic left heart	210	0.97	432	0.94
Hypoplastic right heart	31	0.14	102	0.22
Coarctation of aorta	321	1.48	555	1.21
Total anomalous pulmonary venous return	41	0.19	150	0.33
Aortic atresia/interrupted aortic arch	24	0.11	73	0.16
Patent ductus arteriosus as only CHD in term infants	350	1.62	1,986 [c]	4.34
Choanal atresia	77	0.36	61	0.13
Cleft lip with or without cleft palate	993	4.59	1,156	2.53
Cleft palate	682	3.15	1,222	2.67
Oesophageal atresia with or without tracheo-oesophageal fistula	299	1.38	237	0.52

Duodenal atresia or stenosis	94	0.43	42	0.09
Atresia or stenosis of other parts of small intestine	96	0.44	14	0.03
Ano-rectal atresia and stenosis	346	1.60	261	0.57
Hirschsprung's disease	90	0.42	41	0.09
Atresia of bile ducts	29	0.13	66	0.14
Annular pancreas	24	0.11	5	0.01
Diaphragmatic hernia	266	1.23	170	0.37
Gastroschisis	234	1.08	204	0.45
Omphalocele	214	0.99	307	0.67
Bilateral renal agenesis including Potter syndrome	105	0.49	633	1.38
Multicystic renal dysplasia	323	1.49	418	0.91
Congenital hydronephrosis	1,180	5.45	208	0.45
Bladder exstrophy and/or epispadia	61	0.28	38	0.08
Posterior urethral valve and/or prune belly	112	0.52	72	0.16
Hypospadia	1,887	8.72	1,016	2.22
Limb reduction	608	2.81	273	0.60
Club foot - talipes equinovarus	1,137	5.26	1,712	3.74
Polydactyly	893	4.13	488	1.07
Syndactyly	515	2.38	383	0.84
Craniosynostosis	200	0.92	465	1.02
Congenital constriction bands/amniotic band	46	0.21	44	0.10
Situs inversus	76	0.35	71	0.16
Conjoined twins	7	0.03	16	0.03
Lateral anomalies	140	0.65	71	0.16

[a] *For details on coding of congenital anomalies in EUROCAT data, including detailed ICD mapping, see the EUROCAT coding guide 1.4 [1]; mapping to MedDRA® terms for the VigiBase-congenital anomaly data are described in Supplementary table 4*

[b] *Only major congenital anomalies are included in EUROmediCAT data*

[c] *VigiBase data includes all reports on Patent ductus arteriosus, irrespective of other CHDs or preterm fetus*

Supplementary Table 2. MedDRA® High Level Terms in the System Organ Class *Congenital, familial and genetic disorders* describing hereditary/genetic disorders and infections excluded from the VigiBase-congenital anomaly dataset

MedDRA® High Level Term [a]
Abnormal gene carriers
Anaemias congenital (excl haemoglobinopathies)
Autosomal chromosomal abnormalities
Bacterial infections congenital
Chromosomal abnormalities NEC
Coagulation disorders congenital
Connective tissue disorders congenital
Genetic mitochondrial abnormalities NEC
Haematological disorders congenital NEC
Haemoglobinopathies congenital
Immune system abnormalities congenital
Inborn errors of amino acid metabolism
Inborn errors of bilirubin metabolism
Inborn errors of carbohydrate metabolism (excl glucose)
Inborn errors of lipid metabolism
Inborn errors of metabolism NEC
Inborn errors of porphyrin metabolism
Inborn errors of steroid synthesis
Infections congenital NEC
Lysosomal storage disorders
Mycobacterial infections congenital
Neurological disorders congenital NEC
Non-site specific bone disorders congenital
Non-site specific cartilage disorders congenital
Non-site specific muscle disorders congenital
Peripheral nervous system disorders congenital NEC
Protozoal infections congenital
Purine metabolism disorders congenital
Pyrimidine metabolism disorders congenital
Sex chromosomal abnormalities
Viral infections congenital

[a] *Medical Dictionary for Regulatory Activities (MedDRA®) version 20.1*

Supplementary Table 3. Definitions of exclusion criteria applied to the VigiBase reports describing a chromosomal anomaly, skeletal dysplasia, genetic syndrome, microdeletion or an isolated congenital dislocation of the hip

Exclusion criterion	**Definition** [a]
Exclusion of reports with a chromosomal disorder	MedDRA® High Level Terms: Autosomal chromosomal abnormalities, Chromosomal abnormalities NEC, Sex chromosomal abnormalities
Exclusion of reports with a skeletal dysplasia	MedDRA® High Level Terms: Non-site specific bone disorders congenital, Non-site specific cartilage disorders congenital
Exclusion of reports with a genetic syndrome/microdeletion	MedDRA® High Level Terms: Abnormal gene carriers, Genetic mitochondrial abnormalities NEC
Exclusion of reports with isolated hip dislocations	MedDRA® Preferred Term "Developmental hip dysplasia" being the only reported adverse event term in the MedDRA® System Organ Class "Congenital, familial and genetic disorders"

[a] *Medical Dictionary for Regulatory Activities (MedDRA®) version 20.1*

Supplementary Table 4. Mapping of EUROCAT congenital anomaly subgroups to MedDRA®

EUROCAT Congenital anomaly subgroup	**MedDRA® Terms included** [a]
Anencephalus and similar	Anencephaly (PT)
Annular pancreas	Congenital pancreatic anomaly (PT)
Anophthalmos	Anophthalmos (PT)
Anorectal atresia and stenois	Anal atresia (PT),Rectal atresia (PT)
Anotia	Anotia (PT)
Aortic atresia/interrupted aortic arch	Congenital aortic atresia (PT),Interruption of aortic arch (PT)
Aortic valve atresia/stenosis	Aortic valve atresia (PT),Congenital aortic valve stenosis (PT)
Arhinencephaly/holoprosencephaly	Holoprosencephaly (PT)
Atresia of bile ducts	Congenital absence of bile ducts (PT)
Atresia or stenosis of other parts of small intestine	Congenital small intestinal atresia (PT)
Atrial septal defect	Atrial septal defect (PT)
Atrioventricular septal defect	Atrioventricular septal defect (PT)
Bilateral renal agenesis including Potter syndrome	Potter's syndrome (PT),Renal aplasia (PT)
Bladder exstrophy and/or epispadia	Congenital ectopic bladder (PT)
Choanal atresia	Choanal atresia (PT)
Cleft lip with or without palate	Cleft lip (PT),Cleft lip and palate (PT)
Cleft palate	Cleft palate (PT)
Club foot talipes equinovarus	Talipes (PT)
Coarctation of aorta	Coarctation of the aorta (PT)
Common arterial truncus	Truncus arteriosus persistent (PT)
Congenital cataract	Cataract congenital (PT)
Congenital constriction bands/amniotic band	Amniotic band syndrome (PT)
Congenital glaucoma	Developmental glaucoma (PT)
Congenital heart defects	Arterial disorders congenital (HLT),Cardiac disorders congenital NEC (HLT),Cardiac hypoplasias congenital (HLT),Cardiac malpositions congenital (HLT),Cardiac septal defects congenital (HLT),Cardiac valve disorders congenital (HLT),Cardiovascular disorders congenital NEC (HLT),Great vessel disorders congenital (HLT),Multiple cardiac abnormalities congenital (HLT)
Congenital hydronephrosis	Congenital hydronephrosis (PT)
Conjoined twins	Conjoined twins (PT)
Craniosynostosis	Craniosynostosis (PT)
Diaphragmatic hernia	Congenital diaphragmatic hernia (PT)
Double outlet right ventricle	Double outlet right ventricle (PT)
Duodenal atresia or stenosis	Duodenal atresia (PT)
Ebsteins anomaly	Ebstein's anomaly (PT)
Encephalocele	Encephalocele (PT)
Gastroschisis	Gastroschisis (PT)
Hirschsprungs disease	Congenital megacolon (PT)
Hydrocephalus	Congenital hydrocephalus (PT)

Hypoplastic left heart	Hypoplastic left heart syndrome (PT)
Hypoplastic right heart	Hypoplastic right heart syndrome (PT)
Hypospadias	Hypospadias (PT)
Lateral anomalies	Heterotaxia (PT)
Limb reduction	Limb reduction defect (PT)
Microcephaly	Microcephaly (PT)
Mitral valve anomalies	Congenital mitral valve incompetence (PT),Congenital mitral valve stenosis (PT),Mitral valve atresia (PT)
Neural tube defects	Anencephaly (PT),Encephalocele (PT),Neural tube defect (PT),Spina bifida (PT),Spina bifida cystica (PT)
Oesophageal atresia with or without tracheo-oesophageal fistula	Oesophageal atresia (PT)
Omphalocele	Exomphalos (PT)
PDA as only CHD in term infant	Patent ductus arteriosus (PT)
Polydactyly	Polydactyly (PT)
Posterior urethral valve and/or prune belly	Congenital ectopic bladder (PT),Urethral valves (PT)
Pulmonary valve atresia	Congenital pulmonary valve atresia (PT)
Pulmonary valve stenosis	Pulmonary valve stenosis congenital (PT)
Multicystic renal dysplasia	Congenital cystic kidney disease (PT),Renal dysplasia (PT)
Severe CHD	Anomalous pulmonary venous connection (PT),Aortic valve atresia (PT),Atrioventricular septal defect (PT),Coarctation of the aorta (PT),Congenital aortic valve stenosis (PT),Congenital mitral valve incompetence (PT),Congenital mitral valve stenosis (PT),Congenital pulmonary valve atresia (PT),Congenital tricuspid valve atresia (PT),Congenital tricuspid valve stenosis (PT),Double outlet right ventricle (PT),Ebstein's anomaly (PT),Fallot's tetralogy (PT),Hypoplastic left heart syndrome (PT),Hypoplastic right heart syndrome (PT),Mitral valve atresia (PT),Transposition of the great vessels (PT),Truncus arteriosus persistent (PT),Univentricular heart (PT)
Single ventricle	Univentricular heart (PT)
Situs inversus	Heterotaxia (PT)
Spina bifida	Spina bifida (PT),Spina bifida cystica (PT)
Syndactyly	Syndactyly (PT)
Tetralogy of fallot	Fallot's tetralogy (PT)
Total anomalous pulmonary venous return	Anomalous pulmonary venous connection (PT)
Transposition of great vessels	Transposition of the great vessels (PT)
Tricuspid atresia and stenosis	Congenital tricuspid valve atresia (PT),Congenital tricuspid valve stenosis (PT)
Ventricular septal defect	Ventricular septal defect (PT)

[a] Preferred term (PT) or High Level Term (HLT); Medical Dictionary for Regulatory Activities (MedDRA®) version 20.1

Supplementary Table 5. Number of cases exposed to at least one medication in each class of drug in the EUROmediCAT signal detection and the VigiBase-congenital anomaly datasets

Class of drug (ATC-1)	Anatomical System	EUROmediCAT [a]		VigiBase [b]	
		N	%	N	%
A	Alimentary tract and metabolism	2,969	13.7	4,916	10.7
B	Blood and blood forming organs	726	3.4	4,165	9.1
C	Cardiovascular system	1,363	6.3	3,208	7.0
D	Dermatologicals	23	0.1	2,608	5.7
G	Genito-urinary system and sex hormones	5,299	24.5	3,557	7.8
H	Systemic hormonal preparations, excluding sex hormones and insulins	3,256	15.0	2,108	4.6
J	Anti-infectives for systemic use	4,021	18.6	7,773	17.0
L	Antineoplastic and immunomodulating agents	141	0.7	6,164	13.5
M	Musculo-skeletal system	666	3.1	2,385	5.2
N	Nervous system	5,694	25.9	18,673	40.8
P	Antiparasitic products, insecticides and repell ents	125	0.6	453	1.0
R	Respiratory system	3,365	15.6	2,234	4.9
S	Sensory Organs	0	0.0	2,122	4.6
V	Various	188	0.9	1,008	2.2
	Total	21,636	-	45,749	-

[a] After excluding cases with exposures only to: medication of unknown timing, folic acid, minerals and/or vitamins, ATC codes with less than 5 digits, topical medications; [b] VigiBase data accounts only for drugs characterized as suspected of interacting in the individual case safety reports

Supplementary Table 6. Details of 49 medication-congenital anomaly associations from signal detection analysis in EUROmediCAT and evaluation in VigiBase; information for eight signals recommended for further investigation are highlighted with grey shading

EUROmediCAT analysis		**EUROmediCAT results**			**VigiBase results**			
ATC Code Chemical subgroup/ Substance name	**Congenital Anomaly**	N [a]	PRR (95% CI) adjusted for registry	Cases with exposure to only this medication; NONE(n) Concurrent medications with at least 2 exposures (n)	Substance name	N	PRR (95% CI) *[$PRR_{unmasked}$ (99% CI)]* [a]	Case series review
A02AA Magnesium compounds	Coarctation of aorta	3	11.75 (4.25 - 32.51)	NONE(2)	-	0	-	-
A02AB04 Dihydroxialumini sodium carbonate	Polydactyly	3	7.71 (3.27 - 18.14)	NONE(3)	Dihydroxyaluminium sodium carbonate	0	-	-
A02AD01 Ordinary salt combinations	Cleft lip ± palate	38	1.82 (1.31 - 2.52)	NONE(10) N02BE01(11), G01AF04(3), A06AC01(2), A02BX13(2)	-	0	-	-
A02BA02 Ranitidine	Craniosynostosis	5	2.91 (1.22 - 6.92)	NONE(2)	Ranitidine	0	-	-
A02BB Prostaglandins	Limb reduction	3	4.68 (1.61 - 13.6)	NONE(1)	Misoprostol	4	5.9 (2.24 - 15.57)	*Reasonably supportive* Two well documented reports describing unsuccessful medical termination with misoprostol in first trimester and no other comedication reported
A02BB01/ G02AD06 Misoprostol	Anencephalus	5	12.11 (5.33 - 27.53)	NONE(1) N02BE01(3)	Misoprostol	3	3.77 (1.23 - 11.57)	*Reasonably supportive* Two well documented reports describing unsuccessful medical termination with misoprostol in first trimester. Mifepristone in 2 cases
A02BX02 Sucralfate	Hypospadias	6	4.26 (2.24 - 8.10)	NONE(2)	Sucralfate	1	15.02 (3.03 - 74.52)	*Inconclusive* Polypharmacy and high chromium and cobalt levels in mother (hip arthroplasty)
A10AB Insulins and analogues for injection, fast-acting	Single ventricle	8	5.44 (2.42 - 12.21)	NONE(1) A10AC01(2), A10AE04(2)	-	0	-	-
A10AB01/ A10AC01/ A10AD01/ A10ACE01 Insulin - human	Aortic valve atresia/ stenosis	7	5.1 (2.24 - 11.61)	NONE(2)	-	0	-	-
	Atrial septal defect	41	1.86 (1.40 - 2.47)	NONE(9) A10AC01(9), C02AB01(3), N02BA01(3), A10BA02(2), G03DB01(2), J01CA04(2)	Insulin human	7	0.85 (0.42 - 1.74)	*Inconclusive* Confounding factors such as maternal diabetes (poorly controlled) and comedications (e.g. valproic acid, antiretrovirals), and sparse doc cases

	Patent ductus arteriosus as only CHD in term infants	15	3.26 (1.97 - 5.37)	NONE(1)	-	0	-	-
A10AB04/ A10AC04/ A10AD04 Insulin lispro	Patent ductus arteriosus as only CHD in term infants	8	3.76 (1.95 - 7.26)	NONE(0) A10AC01(5)	Insulin lispro	1	0.19 (0.03 - 1.32)	*Inconclusive* Sparse doc
A10AB05/ A10AD05 Insulin aspart	Common arterial truncus	4	9.19 (3.15 - 26.84)	NONE(0)	Insulin aspart	0	-	-
	Hypoplastic left heart	7	3.81 (1.80 - 8.07)	NONE(1) A10AC01(3), H03AA01(2)		0	-	-
	Lateral anomalies	5	3.86 (1.59 - 9.35)	NONE(0) A10AE04(3)		1	8.36 (1.18 - 59.47)	*Inconclusive* Anomaly (*Situs inversus*) precedes exposure (from gestational week 8)
	Transposition of great vessels	10	3.62 (1.94 - 6.75)	NONE(1) A10AE04(3), A10AC01(2)		1	1.21 (0.17 - 8.50)	*Inconclusive* Sparse doc
	Ventricular septal defect	44	1.57 (1.21 - 2.04)	NONE(7) A10AC01(15), A10AE04(6), H03AA01(4), A10AE05(4), H01AB01(4), A10BA02(4), C07AG01(2), J01CA08(2), A10AD05(2), M01AE01(2), C02AB01(2)		4	0.82 (0.32 - 2.14)	*Inconclusive* Confounding factors such as maternal diabetes (poorly controlled), sepsis, and comedications (e.g. sertraline, antihypertensives, amoxicillin), and sparse doc
A10AE Insulins and analogues for injection, long-acting	Congenital heart defects	42	1.35 (1.08 - 1.67)	NONE(5) A10AB05(28), H03AA01(8), A10AB04(6), A10BA02(4), A10AB01(4), A10AC01(3), N02BA01(2), C07AG01(2), N02BE01(2), A10AB(2)	Insulin detemir	14	1.36 (0.88 - 2.08) *[1.98 (1.12 - 3.47)]*	*Inconclusive* Wide range of different and non-specific cardiac defects. Maternal diabetes (poorly controlled) and majority not exposed in first trimester, or sparse doc cases
		-	-		Insulin glargine	24	1.14 (0.81 - 1.6) *[1.65 (1.06 - 2.59)]*	*Inconclusive* Wide range of different and non-specific cardiac defects. Maternal diabetes and variable times of exposure (different types of diabetes)
		-	-		Insulin degludec	1	0.68 (0.11 - 4.06)	*Inconclusive* Confounding factors such as maternal diabetes and polypharmacy
		-	-		Insulin human	22	0.99 (0.69 - 1.43)	*Inconclusive* Non-eligible reports (all but one did not refer to a long-acting human insulin)
		-	-		Insulin porcine	4	0.96 (0.41 - 2.26)	*Inconclusive* Non-eligible reports (no case referred to porcine insulin)

C01BC Antiarrhythmics, class IC	Patent ductus arteriosus as only CHD in term infants	3	32.99 (16.75 - 64.99)	NONE(0) C01AA05(2) digoxin	Flecainide	3	5.32 (1.97 - 14.37)	*Inconclusive* Two foetuses were treated with flecainide for pre-existing cardiac disorder
C09CA03 Valsartan	Bilateral renal agenesis including Potter syndrome	3	84.36 (25.28 - 281.48)	NONE(0)	Valsartan	8	6.22 (3.19 - 12.12)	*Inconclusive (for exposure in first trimester)* Renal agenesis (1 case), renal dysgenesis (7). Renal agenesis case the only with exposure limited to 1st trimester, however mother with systemic lupus erythematosus and exposure to another powerful teratogen (myelophenolic acid)
G03DA Pregnen (4) derivatives	Limb reduction	60	1.31 (1.00 - 1.71)	NONE(28) N02BA01(6), G03DB01(4), N02BE01(4), G03GA08(3), B01AB05(2), C02AB01(2), H03AA01(2), G03CA03(2)	Progesterone	1	1.65 (0.23 - 11.61)	*Inconclusive* Sparse doc
G03DA03 Hydroxyprogesterone	Atrial septal defect	28	1.41 (1.01 - 1.97)	NONE(5) G03DB01(11), G03DA04(5), G03DC01(3), C08DA01(2), A03AD02(2)	Hydroxyprogesterone	1	0.37 (0.05 - 2.51)	*Inconclusive* Sparse doc
G03DB Pregnadien derivatives	Hypospadias	119	1.38 (1.11 - 1.70)	NONE(76) A03AD02(9), G03DA03(6), B01AC06(6), G03DA04(6), G03GA01(2), G03GA01(2), B01AA03(2), N05BA01(2)	Chlormadinone	1	15.02 (3.03 - 74.52)	*Inconclusive* Sparse doc
					Megestrol	1	45.07 (42.41 - 47.90)	*Inconclusive* Sparse doc
					Dydrogesterone	3	4.23 (1.44 - 12.45)	*Inconclusive* One case (in-vitro fertilization) with obesity and gestational diabetes and two sparse doc cases
H03AA01 Levothyroxine sodium	Ventricular septal defect	388	1.18 (1.07 - 1.30)	NONE(271) G03DA04(18), N02BA01(13), G03DB01(7), R03AC02(6), N02BE01(5), J01CR02(5), G03GA01(5), A10AB05(4), B01AB05(4), H03BA02(3), A10AC01(3), J01CE02(3), G02CA(3), B01AB04(3), C02AB01(3), M01AE01(3), H03CA(3), C07AB02(3), G03GA08(3), R03DA02(3) +20 further medications with 2 exposures	Levothyroxine	16	1.67 (1.05 - 2.66)	*Inconclusive* Confounding factors such as threatening abortion (antithyroid antibodies), epileptic seizures, thyroid malignancy and polypharmacy or sparse doc cases

J01XE Nitrofuran derivatives	Cleft palate	20	1.76 (1.14 - 2.73)	NONE(10) J01CA04(3), N02BE01(2), J01CA08(2)	Nitrofurantoin	5	2.72 (1.17 - 6.34)	*Inconclusive* Sparse doc cases with no specified time of exposure or polypharmacy
	Patent ductus arteriosus as only CHD in term infants	13	2.41 (1.40 - 4.17)	NONE(5) J01CA08(3)		6	2.01 (0.93 - 4.31)	*Inconclusive* Non-eligible reports (all but one did not meet the case definition due to prematurity or other congenital heart defects)
J01XX Other antibacterials	Pulmonary valve stenosis	12	2.68 (1.50 - 4.79)	NONE(4) G03DA04(2), N02BE01(2)	Fosfomycin	1	8.04 (1.24 – 52.22)	*Inconclusive* One case with several antibiotics used for urinary tract infection. Fosfomycin used for one day in first trimester, co-suspect drugs (clotrimazole, sulfamethotaxole/trimethoprim, norfloxacin) used for 4-11 days in first trimester
	Tetralogy of Fallot	8	2.25 (1.09 - 4.61)	NONE(4)	-	0	-	-
N02BA Salicylic acid and derivatives	Atresia or stenosis of other parts of small intestine	9	2.09 (1.04 - 4.20)	NONE(3) H02AB06(2), H03AA01(2), C08CA05(2)	-	0	-	-
	Tetralogy of Fallot	21	1.57 (1.01 - 2.46)	NONE(10) B01AB05(3), A10BA02(2), G03DA04(2), C02AB01(2)	Acetylsalicylic acid	2	0.25 (0.06 – 1.00)	*Inconclusive* Sparse doc
N02BB Pyrazolones	Cleft lip ± palate	7	2.82 (1.37 - 5.79)	NONE(2) G03DA04(2), N02BE01(2)	-	0	-	-
N03AA Barbiturates and derivatives	Microcephaly	4	6.64 (2.39 - 18.49)	NONE(2) N03AG01(2)	Phenobarbital	11	6.65 (3.75 - 11.80)	*Inconclusive* Concomitant use of other confounding antiepileptics or sparse doc
					Primidone	2	4.67 (1.21 – 18.00)	*Inconclusive* Concomitant use of other confounding antiepileptics or sparse doc
N03AA02 Phenobarbital	Cleft lip ± palate	7	3.81 (1.90 - 7.66)	NONE(6)	Phenobarbital	25	7.15 (4.99 - 10.25)	*Inconclusive* Concomitant use of other confounding antiepileptics or sparse doc
N03AF Carboxamide derivatives	Patent ductus arteriosus as only CHD in term infants	9	3.08 (1.61 - 5.89)	NONE(4)	Carbamazepine	15	0.46 (0.28 - 0.75)	*Inconclusive* Six non-eligible reports (did not meet the case definition due to prematurity or other congenital heart defects) or confounding factors such as alcohol use (incl. fetal alcohol syndrome) and comedications (e.g. antiepileptics, paroxetine), or sparse doc cases
					Oxcarbazepine	5	1.25 (0.53 - 2.94)	*Inconclusive* Non-eligible reports (all but one did not meet the case definition due to prematurity or other congenital heart defects)

N03AF01 Carbamazepine	Atrioventricular septal defect	7	3.76 (1.78 - 7.93)	NONE(5)	Carbamazepine	1	0.35 (0.05 - 2.52)	*Inconclusive* One case, co-medicated with topiramate
	Severe CHD	30	1.67 (1.20 - 2.34)	NONE(24)		29	0.66 (0.46 - 0.95)	*Reasonably supportive* One third of cases report monotherapy or comedication of drugs with no known teratogenicity in first trimester and few other obvious alternative explanations. One third with monotherapy but sparse doc cases. One third comedication with valproic acid or topiramate. Reporting spread over time and countries
	Spina Bifida	14	2.99 (1.78 - 5.01)	NONE(5) N03AG01(4), N03AX09(3), N03AX14(2)		29	1.67 (1.17 - 2.4)	*Reasonably supportive* Majority of cases report monotherapy or comedication with lamotrigine or levetiracetam. Reporting widely spread over time
N03AG01 Valproic acid	Atrial septal defect	49	1.63 (1.27 - 2.11)	NONE(22) N03AF01(5), N03AX11(5), N03AE01(3), R03AC02(2), N05BA09(2), N03AX09(2), N03AA03(2)	Valproic acid	159	0.77 (0.66 - 0.89) *[1.73 (1.32 - 2.28)]*	*Reasonably supportive* Valproic acid is a powerful teratogen. The general pattern for all five case series is similar*: majority of cases report valproic acid as the sole suspected drug with no concomitant antiepileptic drugs. Cases present multiple congenital anomalies including fetal valproate syndrome. Reporting is widely spread over time and countries *Valproic acid – Spina bifida case series: Excluding legal cases and suspected duplicates
	Cleft palate	24	2.30 (1.55 - 3.40)	NONE(13) N03AF01(3), N03AX14(2), N03AX09(2)		83	1.4 (1.13 - 1.75)	
	Craniosynostosis	8	2.39 (1.17 - 4.91)	NONE(5) N03AX11(2)		25	1.1 (0.73 - 1.64	
	Hypospadias	52	1.9 (1.47 - 2.45)	NONE(30) N03AF01(4), N03AX11(3), H03AA01(2), N03AX09(2), N03AE01(2)		134	2.93 (2.45 - 3.50)	
	Spina Bifida	39	5.59 (4.08 - 7.66)	NONE(18) N03AX09(7), N03AF01(4), N03AX14(2), N05BA06(2), N03AE01(2)		512	17.82 (15.92 - 19.94)	
N03AX09 Lamotrigine	Spina Bifida	13	3.41 (1.99 - 5.83)	NONE(2) N03AG01(7), N03AF01(3), N03AX14(2)	Lamotrigine	42	1.57 (1.16 - 2.13)	*Inconclusive* Majority of cases exposed to multiple antiepileptics or valproic acid, or sparse doc cases
R03AC Selective beta-2-adrenoreceptor agonists	Cleft palate	55	1.5 (1.12 - 2.01)	NONE(28) R03DA01(7), R03AK06(5), R03DA02(5), J01CA04(2), R03DA05(2)	Salmeterol	3	4.69 (1.62 - 13.53)	*Inconclusive* One case co-medicated with fluticasone and cetirizine, two sparse doc cases
					Salbutamol	14	4.56 (2.78 - 7.47)	*Inconclusive* One non-eligible case (chromosomal syndrome). Polypharmacy or sparse doc cases
					Terbutaline	2	1.47 (0.38 - 5.72)	*Inconclusive* One non-eligible case (genetic syndrome), one case indicated exposure only in third trimester

	Posterior urethral valve and/or prune belly	14	1.83 (1.02 - 3.28)	NONE(4) R03DA01(2), R03AK06(2)	-	0	-	-
R03AK Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	Multicystic renal dysplasia	11	2.39 (1.32 - 4.31)	NONE(3) R03AC02(4), G01AF02(2)	Budesonide; Formoterol	2	5.11 (1.32 - 19.84)	*Inconclusive* One non-eligible case (adult), one sparse doc
R03CA02 Ephedrine	Congenital hydronephrosis	4	9.82 (4.83 - 19.96)	NONE(2)	Ephedrine	0	-	-
	Multicystic renal dysplasia	3	39.35 (14.99 - 103.30)	NONE(1)	Ephedrine	0	-	-
R03CC13 Clenbuterol	Cleft lip ± palate	3	8.93 (3.88 - 20.53)	NONE(1)	Clenbuterol	0	-	-

***ATC**, Anatomical Therapeutic Chemical classification; **PRR**, Proportional Reporting Ratio; the proportion of exposures to each specific medication in cases with a specific anomaly, compared to the proportion of exposures to that medication in the anomaly comparison group.*

[a] $PRR_{unmasked}$ values shown if lower limit of PRR 95% CI (PRR_{025}) <1 and lower limit of $PRR_{unmasked}$ 99% CI (PRR_{005}) >1; unmasked PRRs exclude reports containing influential outliers (defined as medication-CA pairs which, upon removal, decreased the expected value of the anomaly or medication by more than 10%)

Supplementary Table 7. Literature and product labelling review and overall evaluation for all medication-CA associations; information for eight signals recommended for further investigation are highlighted with grey shading

ATC Code Chemical subgroup/ Substance name	Congenital Anomaly	Information from previous EUROmediCAT studies and review of existing evidence for new associations	Product labelling information [a]	Rating of evidence from literature/ regulatory labelling [b]	Overall evaluation, combining existing evidence ratings and EUROmediCAT and VigiBase data [c]
A02AA Magnesium compounds	Coarctation of aorta	Non-specific ATC group	Non-specific ATC group	-	Non-specific medication group
A02AB04 Dihydroxialumini sodium carbonate	Polydactyly	Case-control study of Peptic ulcer disease did find increased risk polydactyly, but not necessarily from aluminium compounds [2].	No label in eMC or Dailymed	*	Insufficient evidence
A02AD01 Ordinary salt combinations	Cleft lip ± cleft palate	Non-specific ATC group. Included in previous EUROmediCAT review [3], with no evidence of teratogenicity found. Only 1 case-control study was found, which found no increases in CAs for those treated with aluminium magnesium hydrocarbonate/hydroxide [2].	Non-specific ATC group	-	Non-specific medication group
A02BA02 Ranitidine	Craniosynostosis	Several studies have analysed ranitidine use in first trimester of pregnancy including over 1,200 exposed pregnancies, with no reports of any increase in malformations [4-8].	"There are no adequate and well-controlled studies in pregnant women." [9].	*	Insufficient evidence
A02BB Prostaglandins	Limb reduction	Increased risk of vascular disruption anomalies including limb defects is acknowledged [10-12].	"Congenital anomalies sometimes associated with fetal death have been reported subsequent to the unsuccessful use of misoprostol as an abortifacient, but the drug's teratogenic mechanism has not been demonstrated. Several reports in the literature associate the use of misoprostol during the first trimester of pregnancy with skull defects, cranial nerve palsies, facial malformations, and limb defects." (misoprostol) [9].	***	Established teratogen
A02BB01/ G02AD06 Misoprostol	Anencephalus	High risk of teratogenicity due to fetal vascular disruption has been noted [13], with increased risk of anencephaly in 1 study [12].	"Misoprostol induces uterine contractions and is associated with abortion, premature birth, foetal death and foetal malformations. Approximately a 3-fold increased risk of malformations was reported in pregnancies exposed to misoprostol during the first trimester, compared to a control group incidence of 2%." The label lists anencephalus [14].	***	Established teratogen

A02BX02 Sucralfate	Hypospadias	A case-control study of peptic ulcer disease found no increased risk of hypospadias [2], and absorption from gastro-intestinal tract is negligible [15]. A Cochrane review of treatments for heartburn in pregnancy found no evidence of harm, but included very few studies, of which none reported on CAs [16].	Safety in pregnant women has not been established [9, 14].	*	Insufficient evidence
A10AB Insulins and analogues for injection, fast-acting	Single ventricle	Women with pre-gestational diabetes have a higher risk of major congenital anomalies, particularly heart defects, than women without diabetes [17-19]. In this analysis no distinction can be made between women taking insulin having a higher risk of specific anomalies due to the insulin or due to the fact that they have diabetes. A more detailed analysis of insulin and congenital anomalies using the EUROmediCAT data compared human insulin to insulin analogues and found no increased risk of the insulin analogues [20].	See individual insulins below.	*	Maternal disease
A10AB01/ A10AC01/ A10AD01/ A10AE01 Insulin - human	Aortic valve atresia/ stenosis Atrial septal defect Patent ductus arteriosus as only CHD in term infants	See above	"Available data from published studies over decades have not established an association with human insulin use during pregnancy and major birth defects, miscarriage or adverse maternal fetal outcomes." [9].	* * *	Maternal disease Maternal disease Maternal disease
A10AB04/ A10AC04/ A10AD04 Insulin lispro	Patent ductus arteriosus as only CHD in term infants	See above	"Data on a large number of exposed pregnancies do not indicate any adverse effect of insulin lispro on pregnancy or on the health of the foetus/newborn." [14].	*	Maternal disease
A10AB05/ A10AD05 Insulin aspart	Common arterial truncus Hypoplastic left heart Lateral anomalies Transposition of great vessels Ventricular septal defect	See above	"Data from two randomised controlled clinical trials (322 + 27 exposed pregnancies) do not indicate any adverse effect on pregnancy or on the health of the foetus/new born when compared to soluble human insulin." [14].	* * * * *	Maternal disease Maternal disease Maternal disease Maternal disease Maternal disease

A10AE Insulins and analogues for injection, long-acting	Congenital heart defects	See above	"For insulin glargine no clinical data on exposed pregnancies from controlled clinical studies are available. A large amount of data on pregnant women (more than 1000 pregnancy outcomes) indicate no specific adverse effects of insulin glargine on pregnancy and no specific malformative nor feto/neonatal toxicity of insulin glargine." [14]. For insulin detemir, "A randomised controlled clinical trial of pregnant women with type I diabetes using [insulin detemir] during pregnancy did not show an increase in the risk of fetal abnormalities." [9].	*	Maternal disease
C01BC Antiarrhythmics, class IC	Patent ductus arteriosus as only CHD in term infants	Flecainide and digoxin combination treatment is recommended in the third trimester for foetal supraventricular tachycardia, with fast restoration of sinus rhythm [21]. It is likely these are not first trimester exposures.	Safety of flecainide in pregnant women has not been established. Flecainide has been shown to cause fetal abnormalities in one breed of rabbit [14].	*	Insufficient evidence
C09CA03 Valsartan	Bilateral renal agenesis including Potter syndrome	Valsartan is known to adversely affect kidney function when taken in the second or third trimester [22, 23], but studies have failed to find evidence of first trimester teratogenicity [24-26]. It is likely the first trimester medications reported in EUROmediCAT continued into the second trimester, and that it is the harmful effects of the second trimester we are detecting. As such the EUROmediCAT data do not provide evidence that there is harm in the first trimester. All cases come from one registry.	"The use of Angiotensin II Receptor Antagonists (AIIRAs) is not recommended during the first trimester of pregnancy. The use of AIIRAs is contra-indicated during the second and third trimester of pregnancy." [14]. "AIIRAs therapy exposure during the second and third trimesters is known to induce human fetotoxicity (decreased renal function, oligohydramnios, skull ossification retardation) and neonatal toxicity (renal failure, hypotension, hyperkalemia)." [14].	*	Insufficient evidence
G03DA Pregnen (4) derivatives	Limb reduction	In previous EUROmediCAT review [3] and previous EUROmediCAT study found increased risk for complete absence of a limb with Pregnen derivatives; previous studies have found a significant association between "sex hormones" and certain CAs. However, poor methodology and a lack of consistent results have resulted in the conclusion that there is no evidence that sex hormones produced nongenital organ teratogenesis [27].	"Data on a large number of exposed pregnancies indicate no adverse effects of progesterone on the foetus." [14]. "There is limited and inconclusive data on the risk of congenital anomalies, including genital abnormalities in male or female infants, following intrauterine exposure during pregnancy." (progesterone) [14].	*	**Signal recommended for further investigation**

G03DA03 Hydroxyprogesterone	Atrial septal defect	In previous EUROmediCAT review in relation to association with limb reduction defects [3]. As above, previous studies have found a significant association between "sex hormones" and certain CHDs. However, there has been poor methodology and a lack of consistent results. A large proportion of the cases in EUROmediCAT were taking co-medications and there is some uncertainty as to whether these medications were actually taken in the first trimester as they are indicated to reduce the risk of preterm birth.	Indicated to reduce the risk of preterm birth. Clinical trial data are "insufficient to determine a drug-associated risk of adverse developmental outcomes as none of the [hydroxyprogesterone] treated women received the drug during the first trimester of pregnancy." [9].	*	Insufficient evidence
G03DB Pregnadien derivatives	Hypospadias	In previous EUROmediCAT review [3]; progestogens have been associated with hypospadias [28-30] but with inconsistent findings [29, 31, 32]. No increase in all CAs combined with dydrogesterone (G03DB01) was found in 3 very small trials or a review of case reports [33-36].	"Several reports suggest an association between intrauterine exposure to progestational drugs in the first trimester of pregnancy and genital abnormalities in male and female foetuses. The risk of hypospadias, 5 to 8 per 1,000 male births in the general population, may be approximately doubled with the exposure to progestational drugs." (megestrol) [14].	***	Established teratogen
H03AA01 Levothyroxine sodium	Ventricular septal defect	Three studies reported no evidence of an association with thyroid medications with ventricular septal defects [37-39]. The modest association of 1.18 compared with the known benefits of treating hypothyroidism to the fetus promotes caution in declaring this a signal.	Around 2-3% of women have hypothyroidism [37] and are recommended to take levothyroxine to prevent the harmful effects of hypothyroidism to the fetus. "Experience with levothyroxine use in pregnant women, including data from post-marketing studies have not reported increased rates of major birth defects or miscarriages." [9].	*	Insufficient evidence
J01XE Nitrofuran derivatives	Cleft palate	Case-control studies have reported increased risk of clefts, but this was based on self-reports after birth [40-42] and cohort studies have lacked the power to confirm this [43-45]. ACOG opinion was that the evidence regarding an association of nitrofuran class of antibiotics and birth defects was mixed [46].	"Extensive clinical use since 1952, suitability in pregnancy has been well documented." (nitrofurantoin) [14]. Animal study 68x human dose observed growth retardation and a low incidence of minor and common malformations. No adequate and well-controlled studies in pregnant women (nitrofurantoin) [9].	**	**Signal recommended for further investigation**
	Patent ductus arteriosus as only CHD in term infants	An association of cardiovascular malformations and nitrofuran derivatives has not been reported as consistently as that for clefts.		**	**Signal recommended for further investigation**
J01XX Other antibacterials	Pulmonary valve stenosis Tetralogy of Fallot	Non-specific ATC group	Non-specific ATC group	- -	Non-specific medication group Non-specific medication group

N02BA Salicylic acid and derivatives	Atresia or stenosis of other parts of small intestine	An association with gastroschisis has been recorded [47-51], but no association atresia or stenosis of other parts of small intestine have been found.	"Data from epidemiological studies suggest an increased risk of miscarriage and of cardiac malformation and gastroschisis after use of a prostaglandin synthesis inhibitor in early pregnancy." (acetylsalicylic acid) [14].	**	**Signal recommended for further investigation**
	Tetralogy of Fallot	One study that noted a non-significant association between conal malformations of the heart and acetylsalicylic acid 8.5% vs 7.8% [52]. Other studies have not found an increased association [47, 49].		**	**Signal recommended for further investigation**
N02BB Pyrazolones	Cleft lip ± cleft palate	One prospective cohort study of 446 exposed women in the first trimester found no increased risks of major birth defects and none of the defects that did occur were an oro-facial cleft [53].	No label in eMC or Dailymed	*	Insufficient evidence
N03AA Barbiturates and derivatives	Microcephaly	Three of the 4 EUROmediCAT cases were listed as phenobarbital, an anti-epileptic that was not previously investigated in EUROmediCAT due to a well-established association with microcephaly [54].	"Phenobarbital therapy in epileptic pregnant women presents a risk to the fetus in terms of major and minor congenital defects such as congenital craniofacial, digital abnormalities and, less commonly, cleft lip and palate." (phenobarbital). "Primidone is suspected to have caused serious birth defects when administered during pregnancy. There have been reports of congenital abnormalities including congenital heart disease, cleft palate and conditions associated with maternal folate deficiency, including spina bifida, microencephaly and anencephaly." (primidone) [14].	***	Established teratogen
N03AA02 Phenobarbital	Cleft lip ± cleft palate	See above; an association with clefts has also been well-established previously [54].	See above	***	Established teratogen
N03AF Carboxamide derivatives	Patent ductus arteriosus as only CHD in term infants	Carbamazepine previously investigated in EUROmediCAT [55] and increased risk of spina bifida identified. Possibility of bias in diagnosing PDA amongst women taking Carbamazepine.	"Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. There have also been reports that associate with developmental disorders and congenital anomalies (e.g., craniofacial defects, cardiovascular malformations and anomalies involving various body systems)." [9]. For oxcarbazepine, "there is moderate amount of data on pregnant women (300-1000 pregnancy outcomes). However, the data on oxcarbazepine associated with congenital malformation is limited." [14].	**	Insufficient evidence

N03AF01 Carbamazepine	Atrioventricular septal defect Severe CHD Spina Bifida	Carbamazepine previously investigated in EUROmediCAT [55] and increased risk of Spina Bifida observed in other studies confirmed. Exploratory analysis suggested a higher risk of single ventricle and atrioventricular septal defect.	See above	** ** ***	**Signal recommended for further investigation** **Signal recommended for further investigation** Established teratogen
N03AG01 Valproic acid	Atrial septal defect Cleft palate Craniosynostosis Hypospadias Spina Bifida	Valproic acid previously investigated in a EUROmediCAT study, with increased risks for ASD, Hypospadias, Cleft palate and Spina bifida confirmed [56].	Contraindicated; prescribed and dispensed according to the Valproate Pregnancy Prevention Programme [14]. "Pregnancy registry data show that maternal valproate use can cause neural tube defects and other structural abnormalities (e.g., craniofacial defects, cardiovascular malformations, hypospadias, limb malformations)." [9].	*** *** *** *** ***	Established teratogen Established teratogen Established teratogen Established teratogen Established teratogen
N03AX09 Lamotrigine	Spina Bifida	Lamotrigine previously investigated in EUROmediCAT and increased risk for Spina Bifida was shown for Lamotrigine Polytherapy, but not monotherapy [57]. 11 out of 13 cases in EUROmediCAT were taking other AEDS.	"A large amount of data on pregnant women exposed to lamotrigine monotherapy during the first trimester of pregnancy (more than 8700) do not suggest a substantial increase in the risk for major congenital malformations, including oral clefts." [14].	*	Insufficient evidence
R03AC Selective beta-2-adrenoreceptor agonists	Cleft palate Posterior urethral valve and/or prune belly	Inhaled beta-2-agonists investigated in a previous EUROmediCAT analysis showed an increased odds for cleft palate, which was interpreted as being of concern, but with no association for Posterior urethral valve and/or prune belly [58].	"A moderate amount of clinical data on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or feto/ neonatal toxicity of salmeterol." [14]. "Safety in pregnant women has not been established. Rare reports of various congenital anomalies following intrauterine exposure to salbutamol (including cleft palate, limb defects and cardiac disorders) have been received." [14]. "Although no teratogenic effects have been observed in animals or in patients, [terbutaline] should only be administered with caution during the first trimester of pregancy." [14].	** *	Previously recommended for further investigation **Signal recommended for further investigation**
R03AK Adrenergics in combination with corticosteroids or other drugs, excl. anticholinergics	Multicystic renal dysplasia	Long acting beta-2-agonists investigated in EUROmediCAT with an increased association, previously interpreted as a potential new signal requiring further attention [58], with only two new additional cases in the current EUROmediCAT analysis.	"There are no adequate data from use of formoterol in pregnant women. In animal studies formoterol has caused adverse effects in reproduction studies at very high systemic exposure levels. Data on approximately 2000 exposed pregnancies indicate no increased teratogenic risk associated with the use of inhaled budesonide. In animal studies glucocorticosteroids have been shown to induce malformations." (budesonide;formoterol) [14].	**	Previously recommended for further investigation

R03CA02 Ephedrine	Congenital hydronephrosis Multicystic renal dysplasia	Ephedrine and Clenbuterol were included in previous EUROmediCAT studies, but no evidence of any significant associations were observed [59, 60].	"Limited published data on the use of ephedrine sulfate are insufficient to determine a drug associated risk of major birth defects or miscarriage." [9].	* *	Insufficient evidence Insufficient evidence
R03CC13 Clenbuterol	Cleft lip ± cleft palate	See above	No label in eMC or Dailymed	*	Insufficient evidence

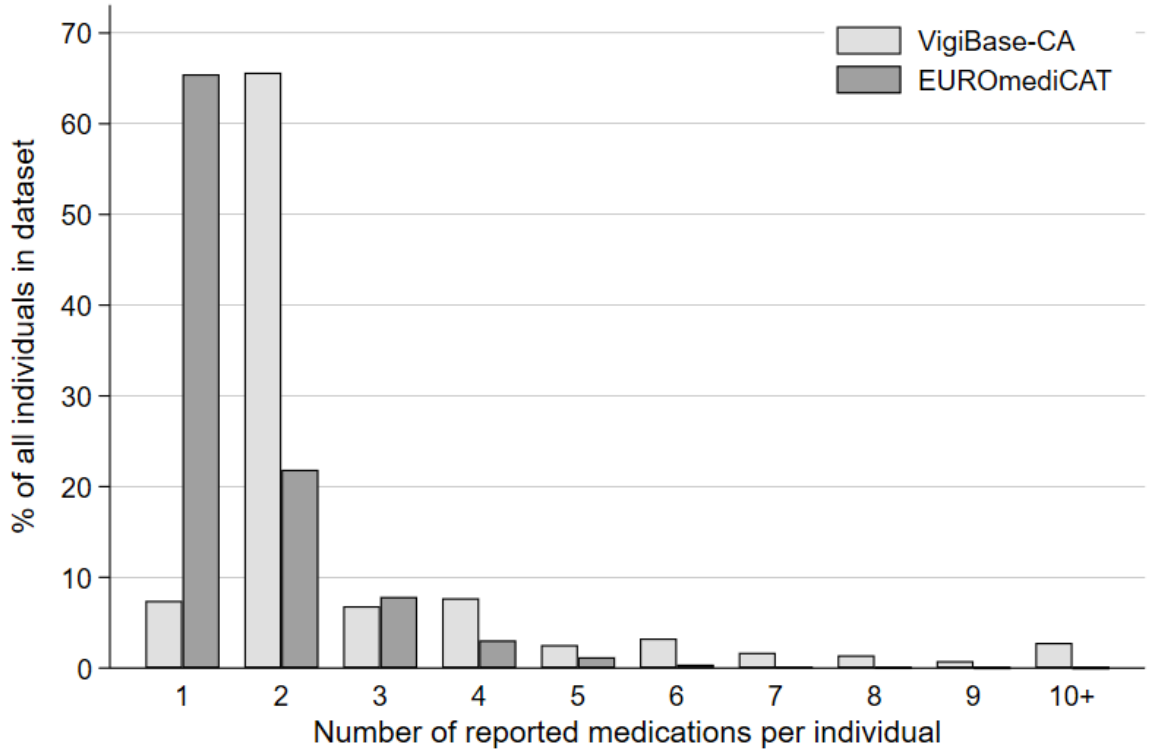
***ATC**, Anatomical Therapeutic Chemical classification.*

[a] For ATC-4-drugs this refers to labels for the ATC-5 substances for which there were reports in VigiBase

[b] Rating of evidence from literature/ regulatory labelling*: *** Well established human teratogenicity; ** Some evidence of human teratogenicity in the literature/regulatory labelling; * Limited or no evidence of human teratogenicity in the literature/regulatory labelling*

[c] *Overall evaluation, combining existing evidence ratings and EUROmediCAT and VigiBase data: **Established teratogen**, teratogenicity already well established; **Maternal disease**, association likely to be due to maternal disease rather than medication.*

Supplementary Figure 1. Number of drug exposures per malformed case in EUROmediCAT and VigiBase-congenital anomaly [a] datasets



[a] *VigiBase data accounts only for drugs characterized as suspected or interacting in the individual case safety reports*

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