

## Electronic supplementary material [ESM])

**Title: Adverse drug reactions in children: comparison of reports collected in a pharmacovigilance project versus spontaneously collected ADR reports**

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The analyzed ADRs cover also medication error related ADRs [7, 17]. Due to the extension of the ADR definition in 2012, conditions like overdose, misuse, abuse, medication errors and occupational exposure are now included in the ADR definition. Although, theoretically all such reports retrieved in our analyses should be associated with a suspected ADR, we cannot exclude the presence of reports not being associated with a co-suspected ADR among them (see section 2.5).

**Table 1.** Evaluation of documentation quality.

	<b>KiDSafe reports (systematically collected reports) n = 845</b>	<b>EudraVigilance reports (spontaneous reports)  n = 697</b>
Mean	0.64	0.63
SD	0.25	0.25
IQR	0.45	0.48
Q0	0.22	0.17
Q25	0.45	0.42
Q50	0.61	0.61
Q75	0.90	0.9
Q100	1	1
Range	0.22-1	0.17-1

SD = standard deviation. IQR= interquartile range. Q0= lowest value. Q25=lowest quartile.

Q50=medium quartile. Q75= upper quartile. Q100= highest value. Range = from lowest to highest value

**Table 2.** Primary reporting source.

	<b>KiDSafe reports (systematically collected reports) n = 845</b>	<b>EudraVigilance reports (spontaneous reports) n = 697</b>
HCP	845 (100.0 %)	609 (87.4 %)
non-HCP	0 (0.0 %)	88 (12.6 %)

HCP = Healthcare Professionals; non-HCP = non- Healthcare Professionals

**Table 3.** Seriousness criteria. Multiple assignments were possible.

<b>Seriousness Criterion</b>	<b>KiDSafe reports (systematically collected reports) n = 845</b>	<b>EudraVigilance reports (spontaneous reports) n = 692<sup>a</sup></b>
Death	1 0.1 %	16 2.3 %
Life-threatening	70 8.3 %	95 13.7 %
Hospitalisation	845 100.0 %	692 100.0 %
Disabling	1 0.1 %	9 1.3 %
Congenital Anomaly	0 0.0 %	11 1.6 %
Other	149 17.6 %	211 30.5 %

<sup>a</sup>This in depth analysis was performed on a later date than the analyses depicted in the main manuscript. The main manuscript refers to 697 reports. However, 5 cases were subsequently deleted from EudraVigilance by the EMA and thus the analyses depicted above refers to n=692 reports.

**Table 4.** Age and sex distribution.

Age group	KiDSafe reports (systematically collected reports) n = 843 <sup>a</sup>				EudraVigilance reports (spontaneous reports) n = 696 <sup>a</sup>			
	SUM	Female (n= 479, 56.8%)	Male (n= 361, 42.8%)	Not specified (n= 4, 0.5%)	SUM	Female (n= 358, 51.4%)	Male (n= 325, 46.7%)	Not specified (n= 13, 1.9%)
0-1M	6 100.0%	3 50.0%	3 50.0%	0 0.0%	48 100%	12 25.0%	32 66.7%	4 8.3%
2M-1Y	100 100.0%	42 42.0%	58 58.0%	0 0.0%	81 99.9%	41 50.6%	36 44.4%	4 4.9%
2-3Y	95 100%	37 38.9%	57 60.0%	1 1.1%	57 100%	24 42.1%	33 57.9%	0 0.0%
4-6Y	83 100%	36 43.4%	47 56.6%	0 0.0%	56 100%	26 46.4%	29 51.8%	1 1.8%
7-12Y	157 99.9%	77 49.0%	79 50.3%	1 0.6%	175 100.1%	82 46.9%	92 52.6%	1 0.6%
13-17Y	402 100%	283 70.4%	117 29.1%	2 0.5%	279 100%	173 62.0%	103 36.9%	3 1.1%

<sup>a</sup>Two reports from the KiDSafe group and one report from the EudraVigilance group were without age information.

**Table 5.** Top 10 drugs most frequently reported as suspected.

Top 10 suspected drugs KiDSafe reports (systematically collected reports) n = 845			Top 10 suspected drugs EudraVigilance reports (spontaneous reports) n = 697		
IBUPROFEN	7.5%	63	INSULIN ASPART	6.0%	42
LEVETIRACETAM	6.6%	56	MITE ALLERGEN EXTRACT	4.4%	31
INSULIN ASPART	5.7%	48	ALLERGENS	3.6%	25
VALPROIC ACID	5.6%	47	PALIVIZUMAB	3.6%	25
METHYLPHENIDATE	4.1%	35	METHYLPHENIDATE	3.0%	21
OXCARBAZEPINE	3.6%	30	IBUPROFEN	2.6%	18
LAMOTRIGINE	3.4%	29	VALPROIC ACID	2.4%	17
PARACETAMOL	3.3%	28	ADALIMUMAB	2.2%	15
AMOXICILLIN	2.7%	23	CORYLUS AVELLANA	2.2%	15
INSULIN GLARGINE	2.7%	23	PLANTAGO LANCEOLATA	2.2%	15

**Table 6.** Drugs most frequently reported as suspected per age group within the KiDSafe reports (systematically collected reports; n = 845).

0-1M			2M-1Y			2-3Y			4-6Y			7-12Y			13-17Y		
Active Substance (High Level)	in %	(n = 6)	Active Substance (High Level)	in %	(n = 100)	Active Substance (High Level)	in %	(n = 95)	Active Substance (High Level)	in %	(n = 83)	Active Substance (High Level)	in %	(n = 157)	Active Substance (High Level)	in %	(n = 402)
CAFFEINE. ERYTHRO- MYCIN. OPIPR- MOL. PERME- THRIN. THEO- PHYLLIN. ZIDO- VUDINE	16.7	1	LEVETIRACETAM	13	13	VALPROIC ACID	8.4	8	OXCARBA- ZEPINE	13.3	11	INSULIN ASPART	8.9	14	IBUPROFEN	11.4	46
			AMOXICILLIN	8	8	LEVETIRA- CETAM	6.3	6	LEVETIR- ACETAM/ VALPROIC ACID	10.8	9	VALPROIC ACID	8.3	13	INSULIN ASPART	8.2	33
			VALPROIC ACID/ CEFACTOR	6	6	CICLO- SPORIN	5.3	5	SALBU- TAMOL/ SULTIAME	4.8	4	OXCARBAZEPIN E	7.6	12	PARACETAMOL	6.5	26
			CO-TRIMOXAZOLE	4	4	DIMEN- HYDRINATE/ IBUPROFEN	4.2	4	AMOXI- CILLIN/CLOB AZAM	3.6	3	METHYLPHENID ATE	7.0	11	METHYLPHENIDATE	5.7	23
			CEFIXIME.IBUPROFEN. LAMOTRIGINE. PHENO- BARBITAL. PREDNISOLONE. SALBUTAMOL. SULTAMI- CILLIN. TACROLIMUS. TOPIRAMATE	3	3	CEFACTOR. DIMETINDEN. LORAZEPAM. AMOXI-CILLIN	3.2	3	CEFACTOR. CEFUROX- IME.DIAZEP AM.FLUTICA SONE.IBUPR OFEN.INSULI N			LEVETIRACETA M	6.4	10	FLUOXETINE	4.7	19
			CEFPODOXIME. CEFU- ROXIME CIPROFLOXACIN. CLOBAZAM. DIMEN- HYDRINATE. FLUTICA- SONE. LITHIUM. METHO- TREXATE. TRAMADOL. VIGABATRIN.	2	2	FERROUS GLYCINE. CEFUROXIME. ERYTHROMYC IN.ETHOSUXI MIDE.HALOPE RAIDOL.LAMO TRIGINE.MYC OPHENOLATE. PREDNISOLON E.TACROLIMU S.VIGABATRIN	2.1	2	HUMAN.LEV OTHYROXIN E.MIDAZOLA M.MYCOPHE NOLATE.PAR ACETAMOL. SULFAMETH OXAZOLE.VI GABATRIN.V ITAMIN D	2.4	2	IBUPROFEN	5.1	8	LAMOTRIGINE	4.2	17
			XYLOMETAZOLINE	2	2												

**Table 7.** Drugs most frequently reported as suspected per age group within the EudraVigilance reports (spontaneous reports; n = 697).

0-1M			2M-1Y			2-3Y			4-6Y			7-12Y			13-17Y		
Active Substance (High Level)	in %	n = 48	Active Substance (High Level)	in %	n = 81	Active Substance (High Level)	in %	n = 57	Active Substance (High Level)	in %	n = 56	Active Substance (High Level)	in %	n = 175	Active Substance (High Level)	in %	n = 279
MISOPROSTOL	12.5	6	PALIVIZUMAB	29.6	24	NUSINERSEN	12.3	7	VALPROIC ACID	8.9	5	MITE ALLERGEN EXTRACT	13.7	24	INSULIN ASPART	7.5	21
PAROXETINE	4.2	2	DIMENHYDRINATE	4.9	4	AMOXICILLIN	5.3	3	INSULIN ASPART	7.1	4	ALLERGENS	10.3	18	METHYLPHENIDATE	5.4	15
PIVMECILLINAM	4.2	2	CYTARABINE	3.7	3	ASFOTASE ALFA. CANDESARTAN. CEFACTOR. CEFUROXIME. ECULIZUMAB. IBUPROFEN. INFLIXIMAB. VALPROIC ACID	3.5	2	IBUPROFEN	5.4	3	INSULIN ASPART	8.0	14	METAMIZOLE	3.9	11
55 further drugs and combinations <sup>a</sup>	2.1	1	PREDNISON	3.7	3				MIDAZOLAM	5.4	3	CORYLUS AVELLANA	5.7	10	ADALIMUMAB	3.6	10
			VINCRIStINE	3.7	3				OXCARBAZEPI NE	5.4	3	PLANTAGO LANCEOLATA	5.7	10	DIENOGEST. ETHINYLESTRADIOL	3.2	9
			ADALIMUMAB. ALEMTUZUMAB. ALPROSTADIL. AMOXICILLIN. BLINATUMOMAB. CEFACTOR. CEFIXIME. CEFUROXIME. CYCLOPHOSPHAMI DE. FLUDARABINE. INSULIN ASPART. PEGINTERFERON BETA-1A. PHENPROCOUMON. SULTAMICILLIN	2.5	2				SALBUTAMOL	5.4	3	SECALE CEREALE	5.7	10	IBUPROFEN	2.9	8
			AZACITIDINE. EVEROLIMUS. FLUTICASONE. HUMAN NORMAL IMMUNO- GLOBULI. LAMOTRIGIN. SULTIAME	3.6	2				ALNUS. ALUMINIUM HYDROXIDE. ARTEMISIA VULGARIS. BETULA. CORYLUS AVELLANA. PHLEUM PRATENSE. PLANTAGO LANCEOLATA. TRITICUM AESTIVUM and Combinations	5.1	9	MYCOPHENOLIC ACID	2.9	8			
															ISOTRETINOIN. METOCLOPRAMIDE	2.5	7

<sup>a</sup>ALEMTUZUMAB, AMISULPRIDE, AMITRIPTYLINE, AMPICILLIN, SULBACTAM, ARIPIRAZOLE, CAFFEINE, CANDESARTAN, CERTOLIZUMAB,

CLOZAPINE, COLECALCIFEROL, CYTARABINE, DAUNORUBICIN, DOXEPIN, DRONABINOL, ESKETAMINE, ETOPOSIDE, GLATIRAMER, INFLIXIMAB,



INSULIN ASPART, INSULIN HUMAN, INTERFERON BETA-1A, KETAMINE, KLEBSIELLA PNEUMONIAE (INACTIVATED), LAMOTRIGINE, LANOLIN, LIDOCAINE, PRILOCAINE, LISINAPRIL, METFORMIN HYDROCHLORIDE (& Combinations), METHYLDOPA, METYRAPONE, NATALIZUMAB, NIFEDIPINE, NITRIC OXIDE, NITROUS OXIDE & OXYGEN, OCTENIDINE DIHYDROCHLORIDE, OPIPRAMOL, OXYCODONE, OXYMETAZOLINE, PALIVIZUMAB, PARACETAMOL, PENTOXYVERINE, PHENOBARBITAL, PHENYLEPHRINE, POTASSIUM (& Combinations), PREGABALIN, PRILOCAINE, PROPOFOL, RIVAROXABAN, SERTRALINE, SILDENAFIL, TRAMADOL, TROPICAMIDE

**Table 8.** Reported medical history.

Patient Medical History PT KiDSafe reports (systematically collected reports)  n = 729 with medical history			Patient Medical History PT EudraVigilance reports (spontaneous reports)  n = 519 with medical history		
Epilepsy <sup>a</sup>	18.4 %	n = 134	Type 1 diabetes mellitus	7.1 %	n = 37
Type 1 diabetes mellitus	10.3 %	n = 75	Epilepsy <sup>a</sup>	6.9 %	n = 36
Depression	7.8 %	n = 57	Asthma	6.2 %	n = 32
Attention deficit hyperactivity disorder	6.3 %	n = 46	Premature baby	6.2 %	n = 32
Pyrexia	5.8 %	n = 42	Non-tobacco user	5.4 %	n = 28
Partial seizures	4.9 %	n = 36	Depression	4.4 %	n = 23
Developmental delay	4.9 %	n = 36	Attention deficit hyperactivity disorder	4.2 %	n = 22
Upper respiratory tract infection	3.4 %	n = 25	Abstains from alcohol	4.0 %	n = 21
Asthma	3.3 %	n = 24	Seasonal allergy	4.0 %	n = 21
Obesity	3.2 %	n = 23	Hypersensitivity	3.5 %	n = 18

<sup>a</sup> In addition, the number of reports related to epilepsy was analyzed on HLT-level in both datasets in order to prevent inconsistent epilepsy coding in the spontaneous reports which could have resulted in a lower number of these reports. At the HLT-level, the terms *absence seizures*, *generalized tonic-clonic seizures*, *partial complex seizures*, *partial simple seizures NEC*, and *seizures and seizure disorders NEC* were included. For the systematically collected reports, the share was 25.4% (185/729), and for the spontaneous reports 6.9% (59/519).