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SHORT COMMUNICATION

Comparison Between Paediatric and Adult Suspected Adverse Drug Reactions Reported to the European Medicines Agency: Implications for Pharmacovigilance

Kevin V. Blake · Cosimo Zaccaria · Francois Domergue · Edith La Mache · Agnes Saint-Raymond · Ana Hidalgo-Simon

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Abstract

Background Databases systematically collecting reports of suspected adverse drug reactions (ADRs) are a cornerstone of pharmacovigilance in that they provide on-going large-scale surveillance in the 'real-world' setting. Several studies have provided data on ADRs in children reported to national databases. EudraVigilance (EV) is the European Medicines Agency's (EMA) web-based system for reporting and evaluating suspected ADRs. Due to requirements on pharmaceutical companies to report ADRs that originate both inside and outside Europe, the data in EudraVigilance are global in nature. As such, it is potentially a rich source of information for paediatric pharmacovigilance.

Aim The present study sought to provide a descriptive overview comparing ADRs involving children and adolescents aged less than 18 years with those involving adults reported to EudraVigilance across national boundaries. The results will serve as a baseline to explore whether lessons can be learned for paediatric pharmacovigilance.

Methods All ADR reports received in EudraVigilance up to 13 June 2013 were analysed for overall numbers, age, gender, and geographic origin. Accurate age was determined when reported in valid format or calculated from the interval between date of birth and the reaction start date. The nature of the ADRs and the most frequently reported drug substances and drug event combinations were evaluated using Medical Dictionary for Regulatory Activities (MedDRA) 'preferred terms' (PTs) and 'system organ classes' (SOCs). The distribution over time of reported paediatric ADRs was also analysed.

Results As of 13 June 2013, EudraVigilance contained 3,291,593 spontaneous reports, for 75.9 % of which accurate age was determined; 11.2 % of these were paediatric reports. Paediatric ADRs were more common than those in adults under the MedDRA SOCs 'general and administration site', 'nervous system', 'skin and subcutaneous' and 'infections and infestations'. For children, the three most frequently reported MedDRA PTs, i.e. pyrexia, vomiting and convulsion (13, 6 and 4 % of reports, respectively), accounted for a greater proportion of reports than the corresponding top three in adults, i.e. nausea, dyspnoea and pyrexia (4, 4 and 3 % of reports, respectively). The 20 most reported active substances (12 of which are vaccines) together accounted for 52 % of paediatric reports as compared with 28 % of adult reports.

Conclusions The present study applied a first-time approach to one of the largest databases worldwide of reported ADRs. It confirmed that reports of reactions in children were different to those in adults, not only in terms of reactions and drugs involved but also more concentrated around limited sets of reaction types and drugs. The possible causal association between a medicine or vaccine and the suspected ADR was not formally assessed in this study since the study analysed the characteristics of reported ADRs that were suspected and therefore not proven. However, the findings may help to identify pharmacovigilance activities that should be strengthened to reduce the burden of ADRs in children.

K. V. Blake (✉) · C. Zaccaria · F. Domergue · E. La Mache · A. Saint-Raymond · A. Hidalgo-Simon
European Medicines Agency, 7 Westferry Circus, Canary Wharf, London E14 4HB, UK
e-mail: kevin.blake@ema.europa.eu

Key Points

While descriptions of paediatric adverse drug reactions (ADRs) reported to national databases are published, this study presents for the first time a descriptive overview of the reports in one of the largest databases of spontaneous reports worldwide

The majority of paediatric ADRs relate to vaccines, which may be anticipated given their widespread use in this population

Fewer drugs and reaction types account for a greater proportion of paediatric than of adult reactions reported to the European Medicines Agency

1 Introduction

Regulatory authorities, including the European Medicines Agency (EMA), approve marketing authorisations for medicinal products on the basis that, in the specified clinical indication(s), at the time of authorisation, the benefit–risk profile is judged to be positive for the target population. This is based on the populations studied in clinical trials. In the past, children have been under-represented in such clinical trials [1], resulting in medicines not being adequately studied in the paediatric population. Consequently, these medicines have not been authorised for use in children and their use has been 'off-label' [2].

An adverse drug reaction (ADR) is a response that is noxious and unintended to a medicinal product. This includes ADRs that arise from the use of a medicinal product outside the terms of the marketing authorisation. The new pharmacovigilance legislation since July 2012 has strengthened the legal basis for the reporting of ADRs arising in such use [3]. Data have suggested an increased risk of ADRs related to off-label drug use in children [4]. Other potential consequences of inadequate paediatric drug development programmes include lack of information on effective dosing and non-availability of therapeutic advances, suitable forms, formulations and routes of administration. These concerns, and an over-arching desire to ensure provision of safe, effective and good-quality medicines to children, have resulted in the EU Paediatric Regulation, which came into force on 26 January 2007 [5]. This legislation includes obligations on pharmaceutical companies to agree a paediatric investigation plan (PIP) for all new compounds, indications and pharmaceutical forms, and to submit the results of paediatric clinical trials to National Competent Authorities (NCAs) and the EMA. However, elucidation of safety in the clinical trial setting may not reflect the risks of a medicinal product in the 'real-life' setting. The risk management plan (RMP) for a medicine, therefore, needs to address the availability of paediatric data from clinical trials in addition to any known risks concerning children [6]. Along with these pre- and post-authorisation initiatives, databases systematically collecting reports of ADRs are a cornerstone of pharmacovigilance in providing new information about safety through on-going large-scale surveillance in the 'real-world' setting. Several studies have provided data on ADRs in children reported to national databases, including from a number of EU Member States, Canada and the USA [7–12].

EudraVigilance is the EMA's central database of reports of suspected ADRs [13]. For all medicinal products authorised in the EU, all suspected ADRs, including those from national spontaneous reporting systems, are reportable to EudraVigilance as detailed in the good pharmacovigilance practices (GVP) Module VI [14]. To inform on the safety profile of all medicinal products authorised in the EU (through central and national procedures), Marketing Authorisation Holders (MAHs) are required to report all serious ADRs occurring outside the EEA (the economic entity comprising all EU member states plus Iceland, Liechtenstein and Norway) in addition to all serious and non-serious ADRs occurring within the EEA. The EMA also shares with the World Health Organization (WHO) all ADRs reported to EudraVigilance. These arrangements result in the data in EudraVigilance being global in nature.

As such, EudraVigilance supports the electronic exchange of suspected ADR reports between the EMA, NCAs, MAHs, and sponsors of clinical trials in the EEA. The database, therefore, presents the opportunity to analyse very large numbers of ADRs across national boundaries. In light of this, the objective of the present study is to, for the first time, provide a descriptive overview comparing paediatric versus adult ADRs reported to EudraVigilance as a baseline to explore whether lessons can be learned for paediatric pharmacovigilance for public health benefit.

2 Methods

EudraVigilance includes two modules. One is the Clinical Trial Module (EVCTM) for reporting of Suspected Unexpected Serious Adverse Reactions (SUSARs) (an adverse reaction related to a product studied in a clinical trial that is both unexpected [not consistent with the applicable product information] and also meets the definition of a serious adverse reaction, i.e. one that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant

disability or incapacity, or consists of a congenital anomaly or birth defect). The other is the Post-Authorisation Module (EVPM) for spontaneous reporting of post-authorisation suspected ADRs in format and content termed Individual Case Safety Reports (ICSRs).

Reports are transmitted to EudraVigilance by EU regulatory agencies, pharmaceutical companies, healthcare professionals and consumers. The first electronic transmissions began in December 2001 but became a legal requirement only in November 2005. All ADRs reported in the interval between the creation of the EU pharmacovigilance system [15] on 1 January 1995 and the start of electronic reporting by each sender, termed 'backlog' reports, have been retrospectively included in the database.

Spontaneous reports in EudraVigilance from 1 January 1995 to the final date of data extraction 13 June 2013 were analysed for overall numbers, age, gender, and primary source (EEA/non-EEA) in the paediatric population, defined as from birth up to the last day of the 17th year inclusive, and in adults (18 years and upwards). Reports were categorised as age 'unknown' if the patient's age was not provided and age could not be calculated from the date of birth to the date of the start of the ADR (e.g. if the reaction start date was not in a valid format, day and month missing). However, if date of birth was provided and the month and year of the reaction start date was provided, age was estimated to the first day of the month. All reports classified as age 'unknown' were excluded from subsequent analyses. Paediatric and adult data were further evaluated for the nature of the adverse reactions by Medical Dictionary for Regulatory Activities (MedDRA) 'preferred term' (PT) and 'system organ class' (SOC) [16]. An ADR report may contain one or more ADRs; however, the unit of analysis was one report. Frequency statistics were calculated for reported suspect/interacting drug substances and drug–event combinations (DECs). The possible causal association between medicine/vaccine and the suspected ADR was not formally assessed in this study. Ethics approval was not required.

In addition, the distribution over time of the 'receive dates' (the date of initial receipt of a report by a pharmaceutical company or national regulatory authority), as reported in EudraVigilance, by 'report type' was also described for all reports, including those reported cumulatively to regulatory authorities in periodic safety update reports (PSURs).

To detect duplicates, the EMA applies an algorithm based on both rule-based methods and probabilistic record matching. The latter is an adaptation of the hit-miss model for statistical record-linkage [17, 18]. This screens the data in EudraVigilance for duplicate reports, but not all will be captured. The results of the present study, therefore, might contain a small proportion (in the order of 10 %) of duplicates.

The extent to which a given reaction associated with a drug was a known reaction was assessed against its inclusion among the reactions listed in the available product information, i.e. the EU Summary of Product Characteristics (SPC) for centrally authorised products and a UK SPC (chosen for English language) for nationally authorised products.

3 Results

At the time of the current review, EudraVigilance contained 3,291,593 spontaneous reports. Accurate age was provided in 1,879,307 reports (57.1 %), and age could be calculated using the date of birth and the reaction start date in 618,467 of the remaining 1,412,286 reports. A total of 2,497,774 reports (75.9 %) could therefore be used in the analysis. Of these, 279,359 (11.2 %) were from children and adolescents aged less than 18 years.

Figure 1 illustrates the distribution of the paediatric reports in EudraVigilance grouped by the International Conference on Harmonisation (ICH) E11 guideline classification [19] and gender. While reporting by gender is similar overall (females 48 % and males 47 %), there is a difference in the age distribution of reports.

There is a trend for gender to be better reported in older children, with data on gender missing in 12 % of reports involving children aged 0–27 days compared with 2 % in those aged 12–18 years.

Regarding the source of reports, 36 % of all reports are from the EEA, with 63 % non-EEA (1 % not specified), while 49 % of the paediatric ADRs reported are from the EEA, with 50 % non-EEA (1 % not specified).

The relative proportions of paediatric and adult reports for each MedDRA SOC were compared (Fig. 2). Paediatric

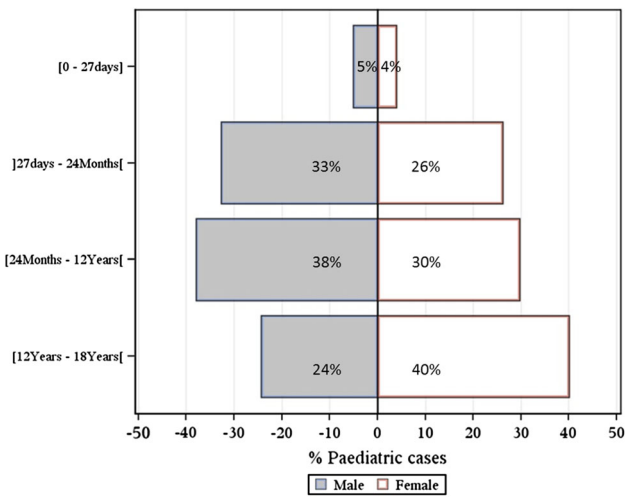

Fig. 1 Age distribution of paediatric reports by gender

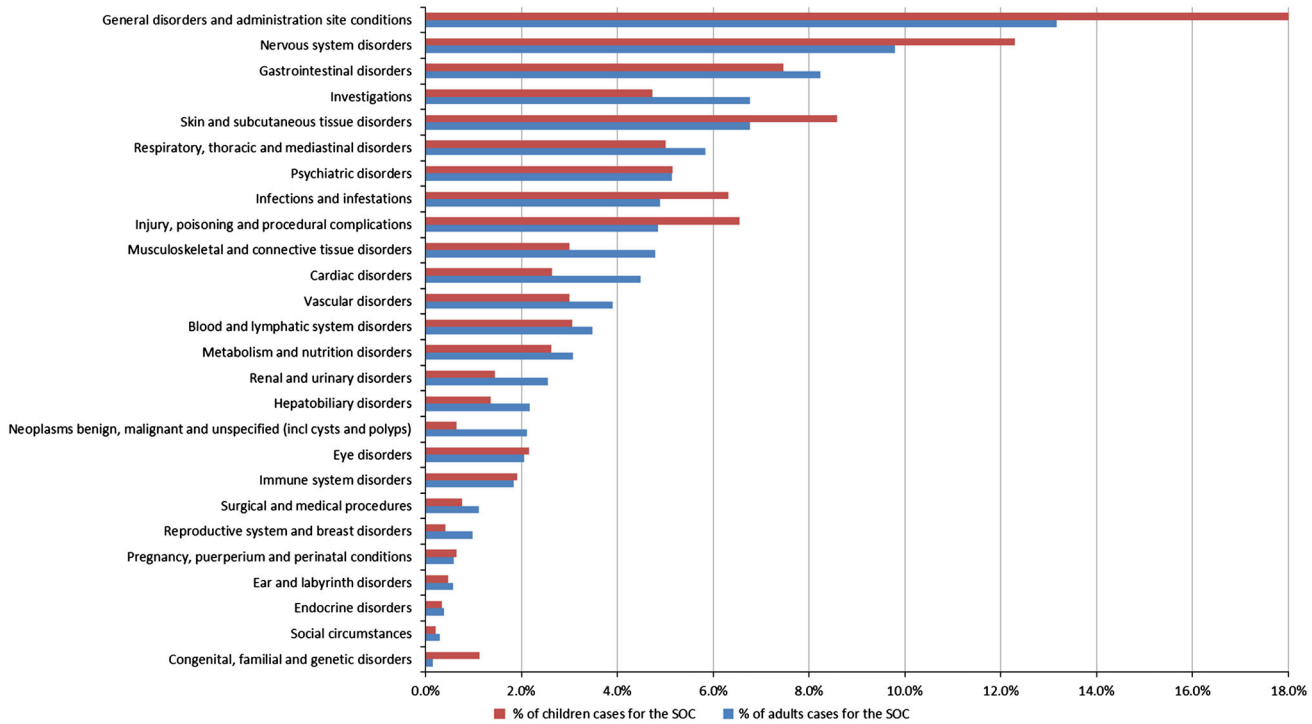

Fig. 2 Proportion of paediatric cases compared with adult cases by organ system/MedDRA SOC. Note paediatric reports only represent 11.2 % of the total but proportions are presented for comparative purposes. *MedDRA* Medical Dictionary for Regulatory Activities, *SOC* system organ class

ADRs are more common than adult reports under the 'general and administration site', 'nervous system', 'skin and subcutaneous' and 'infections and infestations' SOCs.

Table 1 shows the frequency distribution for the ten most reported MedDRA PTs separately for children and adults. Although six of the terms are common to both children and adults, the proportion of reports for which individual terms account varies. For children, the three most frequently reported MedDRA PTs, i.e. pyrexia, vomiting and convulsion (13, 6 and 4 % of reports, respectively), accounted for a greater proportion of reports than the corresponding top three in adults, i.e. nausea, dyspnoea and pyrexia (4, 4 and 3 % of reports, respectively). The top ten terms account for 44 % of the total number of reports for children as compared with 29 % of the total for adults.

Table 2 ranks the 20 most frequently reported active substances in paediatric compared with adult case reports in EudraVigilance.

The 20 most frequently reported substances in paediatric ADRs together account for approximately 52 % of all paediatric reports; 12 of these are vaccines. The most frequently occurring DEC in paediatric reports were, therefore, separated into those associated with vaccines and those associated with non-vaccines. These are listed in Tables 3 and 4. In comparison, there are no vaccines among the 20 most frequently reported substances in adults, which together account for only 28 % of the total of adult reports. The most frequent DEC in adult reports are presented in Table 5.

The distribution over time of reporting to EudraVigilance of all paediatric ADRs was determined (Fig. 3). Data are presented from 2001 when electronic real-time reporting to EudraVigilance started for reports from post-marketing (EVPM ICSRs) and clinical trials (EVCTM ICSRs). The figure also presents the receipt of backlog reports, which were retrospectively transmitted to EudraVigilance from 1995 and, as such, are counted separately. Reports that could be submitted cumulatively in PSUR ICSRs instead of being submitted individually by direct reporting are also counted separately, so any interpretation of the rates of direct reporting over time is clearer.

4 Discussion

4.1 Implications for Pharmacovigilance

Paediatric pharmacovigilance has had to deal with the fact that historically many medicines were used, but not officially indicated, in children. The present evaluation of

Table 1 Most frequent adverse events (reported as MedDRA preferred terms) in paediatric and adult case reports

Rank	Paediatric		Adult	
	PT	Number (%) of reports	PT	Number (%) of reports
1	**Pyrexia**	37,548 (13)	**Nausea**	92,985 (4)
2	**Vomiting**	15,652 (6)	Dyspnoea	83,411 (4)
3	Convulsion	12,009 (4)	**Pyrexia**	72,736 (3)
4	**Rash**	10,432 (4)	**Vomiting**	65,325 (3)
5	**Headache**	9,512 (3)	**Headache**	64,341 (3)
6	Crying	8,601 (3)	Dizziness	61,635 (3)
7	Urticaria	8,567 (3)	**Diarrhoea**	57,071 (3)
8	**Diarrhoea**	7,467 (3)	**Rash**	53,847 (2)
9	**Nausea**	7,464 (3)	Death	53,748 (2)
10	Drug ineffective	6,024 (2)	Fatigue	52,309 (2)
Total		**123,276 (44)**		**657,408 (29)**

Bold formatting indicates terms common to both adult and paediatric case reports

MedDRA Medical Dictionary for Regulatory Activities, *PT* MedDRA preferred terms

EudraVigilance data confirms that paediatric ADRs are very different from adult data in terms of the adverse reactions reported. This may be expected given different use of medicines between these populations, particularly the widespread use of vaccines in children. However, the diagnosis and reporting of ADRs in children is more complex than in adults as it generally involves the parent as a necessary intermediary and because children may not be able to describe their symptoms using the range of terms available to adults. While paediatric ADRs are more common than adult reports, e.g. under the 'general and administration site' and 'nervous system' SOCs, analysis of reported PTs suggests this may be attributable to a small number of terms e.g. 'pyrexia' and 'crying' under the general and administrative site SOC and 'convulsion' and again 'crying' under the nervous system disorder SOC. A relative excess in the 'Injury, poisoning and procedural complications' suggests a proportionally higher rate of events including medication errors in children and 'drug ineffective' is the tenth most frequently reported PT in children. Reports of unexpected lack of effect were a significant finding in a WHO Vigibase study [20] and can signify a range of underlying problems such as inappropriate dose or indication, or ineffectiveness in the paediatric subpopulations.

We have also confirmed that reported ADRs differ between children and adults in relation to the substances reported, particularly vaccines versus non-vaccines. The apparently high absolute number of ADRs for vaccines is expected, especially for those vaccines that belong to routine immunisation schedules for which exposure will be widespread. It is generally understood that minor local and systemic reactions, such as fever, may occur following immunisation. More serious reactions are expected to occur less frequently and adverse events involving the central nervous system such as convulsions may be the result of stimulated reporting [21]. Differences in safety profiles between children and adults may also be due to increased susceptibility to some ADRs (e.g. convulsion) because organs are still immature and continue to develop, e.g. the brain [22, 23]. As convulsion is more common in children than in adults, it may be mistaken as an ADR. It is, therefore, important to interpret the information with the knowledge of background incidence of the disease.

Of interest is the difference in cumulative frequency distributions of substances reported, i.e. top 20 accounts for 52 % of paediatric reports, compared with 28 % of adult reports. In addition, the relative frequency of common ADRs shows a similar trend: while the top ten most frequent ADRs (as MedDRA PTs) for adults accounts for 29 % of the total, in paediatric reports it accounts for 44 %. This relative concentration of paediatric ADRs around limited sets of drugs and reactions has the potential to inform pharmacovigilance activities and could be the focus of specific efforts to prevent ADRs. This will be the subject of further research at the EMA. Although new paediatric medicines will certainly benefit from risk management activities, well established therapies should also benefit from this increased safety profile knowledge.

4.2 Implications for Practice

The steady increase in the number of adverse reactions reported from 2003 (Fig. 3) may reflect an increased awareness of healthcare professionals, MAHs and regulatory authorities in the surveillance of the safety of drugs

Table 2 The 20 most frequent active substances in paediatric and adult reports in EudraVigilance (1 January 1995–13 June 2013)

Rank in Eudra Vigilance	Active substance	Number (%) of paediatric reports	Active Substance	Number (%) of adult reports
1	Pneumococcal polysaccharide conjugate vaccine (adsorbed)	24,493 (9)	**Etanercept**	146,600 (7)
2	Human papillomavirus vaccine	22,487 (8)	Varenicline	40,873 (2)
3	Measles, mumps and rubella vaccine (live)	13,435 (5)	Infliximab	40,809 (2)
4	Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated.) And haemophilus type b conjugate vaccine (adsorbed)	12,328 (4)	Acetylsalicylic acid	31,371 (1)
5	Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed)	8,954 (3)	Pregabalin	30,830 (1)
6	Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed)	8,691 (3)	Clozapine	30,486 (1)
7	A/California/7/2009 (H1N1)v-like virus	7,041 (3)	Calcium chloride, sodium chloride, glucose, sodium lactate, magnesium chloride	25,591 (1)
8	Mycobacterium bovis, Danish strain 1331	5,887 (2)	Dabigatran	24,057 (1)
9	Rotavirus vaccine, live, oral, pentavalent	5,389 (2)	Drospirenone, ethinylestradiol	21,463 (1)
10	Isotretinoin	5,156 (2)	Quetiapine	21,338 (1)
11	Methylphenidate	4,370 (2)	Calcium chloride, glucose, anhydrous, sodium chloride, sodium lactate, magnesium chloride	21,330 (1)
12	**Etanercept**	4,116 (1)	Atorvastatin	20,475 (1)
13	**Paracetamol**	3,933 (1)	**Paracetamol**	20,155 (1)
14	Hepatitis B vaccine	3,905 (1)	Methotrexate	20,011 (1)
15	Haemophilus type b conjugate vaccines	3,850 (1)	Zoledronic acid	19,655 (1)
16	Varicella virus	3,375 (1)	Diclofenac	19,540 (1)
17	Ibuprofen	3,217 (1)	Risperidone	19,328 (1)
18	Carbamazepine	3,078 (1)	Rofecoxib	19,316 (1)
19	Ciclosporin	3,045 (1)	Levonorgestrel	19,121 (1)
20	Valproic acid	3,032 (1)	Olanzapine	18,852 (1)
Total		**149,782 (52)**		**611,201 (28)**

Bold formatting indicates terms common to both adult and paediatric case reports

MedDRA Medical Dictionary for Regulatory Activities, *PT* MedDRA preferred terms

used by children. The temporary peak in reporting to 2009 and subsequent fall to 2010 is not considered an artefact of electronic or PSUR reporting of cases to EudraVigilance but may reflect external factors, e.g. the 2009 influenza pandemic and the associated extensive vaccination campaigns. After this apparent gap in 2010, the number of reports is again increasing every year. ADRs in children reported to EudraVigilance by consumers in Europe from 2007 to 2011 have been characterised [24] and, while few were found, the results of the study indicated that consumer reports can provide information about serious and unknown ADRs from medicine use in children. Since July 2012, the EU pharmacovigilance legislation allows consumers to report ADRs in all EU countries [3] and the relative contribution of consumer reporting since then is an area for future research by the EMA.

The present study, which is an overview of the reactions cumulatively reported to EudraVigilance, confirmed that the most frequent reactions and substances reported are already known associations as indicated by being either directly listed or considered covered by a similar term in the official product information. This finding supports the assertion that paediatric pharmacovigilance should not be limited to capturing associations between drugs and events for clues on how to prevent harm in children [25]. To this end, ADR reporting to EudraVigilance on a continuous basis allows routine analysis of the safety of drugs in children, including an in-depth analysis of new reports

Table 3 The 20 most frequent paediatric vaccine drug–event combinations reported in EudraVigilance (1 January 1995–13 June 2013) (20 most frequent reaction MedDRA preferred terms grouped by active substance)

Active substance	Reaction PT	Number of cases	% of all reports	Overall rank in EudraVigilance
Pneumococcal polysaccharide conjugate vaccine (adsorbed)	Pyrexia[a]	9,580	3	1
	Crying[a]	3,442	1	4
	Vomiting[a]	1,380	<1	20
	Rash[a]	1,376	<1	21
Diphtheria, tetanus, pertussis (acellular, component), hepatitis b (rDNA), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed)	Pyrexia[a]	4,133	1	2
	Crying[a]	1,623	1	17
Measles, mumps and rubella vaccine (live)	Pyrexia[a]	3,878	1	3
Diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed)	Pyrexia[a]	3,196	1	5
	Crying[a]	2,020	1	14
Human papillomavirus vaccine	Headache[a]	3,175	1	6
	Dizziness[a]	3,085	1	7
	Syncope[a]	2,714	1	8
	Nausea[a]	2,412	1	10
	Pyrexia[a]	2,028	1	13
	No adverse event[b]	1,704	1	15
Mycobacterium bovis, Danish strain 1331	Injection site abscess[a]	2,434	1	9
A/California/7/2009 (H1N1)v-like virus	Pyrexia[a]	2,120	1	11
	Hyperpyrexia	1,644	1	16
Diphtheria, tetanus and pertussis (acellular, component) vaccine (adsorbed)	Pyrexia[a]	2,104	1	12
Varicella vaccine (live)	Varicella[a]	1,622	1	18

ADR adverse drug reaction, *MedDRA* Medical Dictionary for Regulatory Activities, *PT* preferred term

[a] ADR already listed in product information

[b] 'No adverse event' is the reported MedDRA PT and relates to cases of maternal exposure where no adverse event per se has occurred in the offspring

received on a monthly basis in signal detection activities at the EMA and the EU Regulatory Network. In its signal detection activities, the EMA routinely screens all paediatric cases by automatically flagging them as high priority during the 'signal identification' phase. In addition, as part of its data mining activities, the EMA has developed a standard query in EudraVigilance to explore rates of occurrence in children as compared with adults of suspected safety issues that may require further investigation. The query specifically allows determination of whether or not a safety issue is significantly more reported in children than in adults and whether or not specific drugs are reported more than others (e.g. within a class) within the paediatric population. The query does not evaluate the causality or the exact incidence of the reaction in the paediatric population.

It is important to note that 14 of the 20 most frequently reported non-vaccine DECs relate to medicines that carry restrictions on their use in children (Table 4). For example, paroxetine carries statements that it should not be used for the treatment of children and adolescents to age 17 years; isotretinoin is not indicated for the treatment of prepubertal acne and is not recommended for use in patients less than 12 years of age; the indications for use of etanercept vary with age but it is indicated for certain forms of arthritis in children from the age of 2 years; and, paracetamol is indicated for infants from 2 months. At a high level, this suggests an over-representation of drugs used 'off-label' among paediatric ADRs, but further drilling down to the level of these examples highlights the complexities around what constitutes 'on-label'. Of note, 1 % of the ADRs reported in association with isotretinoin were in children under 12 years of age.

The complexities of paediatric prescribing reflect evidence from clinical trials being only available for subgroups of the paediatric population in terms of ages and indications studied. The EMA Paediatric Committee is seeking to address this by systematically encouraging paediatric studies for off-patent medicines authorised in adults for which a paediatric indication may be sought.

Table 4 The 20 most frequent paediatric non-vaccine drug–event combinations reported in EudraVigilance (1 January 1995–13 June 2013) (20 most frequent reaction MedDRA preferred terms grouped by active substance)

Active Substance	Reaction PT	Number of cases	% of all reports	Overall rank in EudraVigilance
Paroxetine	Foetal exposure during pregnancy[a]	1,417	1	19
	Atrial septal defect[a]	522	<1	123
Isotretinoin	Depression[a]	1,301	<1	25
	Inflammatory bowel disease[a]	1,006	<1	41
	Colitis ulcerative[b]	752	<1	69
	Crohn's disease[b]	613	<1	97
	Dry skin[a]	496	<1	132
	Lip dry[a]	450	<1	148
	Suicidal ideation[a]	392	<1	187
	Blood triglycerides increased[a]	381	<1	191
Etanercept	Injection site pain[a]	943	<1	47
	Injection site erythema[a]	473	<1	141
Carbamazepine	Pyrexia[a]	559	<1	114
	Rash[a]	383	<1	190
Palivizumab	RSV infection[c]	558	<1	115
	Respiratory syncytial virus bronchiolitis[c]	445	<1	151
Drospirenone, ethinylestradiol	Pain[a]	469	<1	145
Paracetamol	Overdose[a]	434	<1	158
	Vomiting[a]	394	<1	185
Octocog alfa	Factor VIII inhibition[a]	385	<1	188

MedDRA Medical Dictionary for Regulatory Activities, *PT* preferred term, *RSV* respiratory syncytial virus

[a] Already listed or included in a warning in the Product Information

[b] For isotretinoin, colitis is listed and Crohn's disease is considered covered by the term Inflammatory Bowel Disease

[c] Palivizumab is indicated for the prevention of serious lower respiratory tract disease requiring hospitalisation caused by RSV in children at high risk for RSV disease

This is being done through the incentives of the Paediatric Use Marketing Authorisation (PUMA) introduced by the Paediatric Regulation [26]. These incentives include automatic access to the centralised procedure for marketing authorisations and benefits regarding regulatory data protection and the name of the product. Of note, the time distribution of reporting of paediatric ADRs from clinical trials to EudraVigilance (Fig. 3), although the numbers are small relative to those reported spontaneously, may be considered as supportive of the findings of an EMA report showing no increase in clinical trial discontinuation for reasons of safety [27].

4.3 Implications for Research

The 24.1 % of reports for which age could not be accurately determined is similar to the 22 % of reports in the WHO Vigibase without age specified [18]. This proportion of reports indicates a need to improve the reporting of age. This is all the more important as some ADRs are not expected in children (e.g. myocardial infarct) and the interpretation and potential impact on benefit–risk profile of such reports would be very different than for reports in adults. While the general quality of the reports submitted to EudraVigilance is outside the scope of the present paper, there are processes in place to constantly improve the content of reports, e.g. business rules applicable to all stakeholders transmitting ADR reports to EudraVigilance [28] and manual quality checks on a sample of reports.

A total of 49 % of paediatric reports for which accurate age was available originated in the EEA (approximately 138,000 reports); however, the data in EudraVigilance do not allow for direct analysis of reporting rates from inside or outside the EEA in the absence of denominators, i.e. exposure data. While the relative contribution of reports in EudraVigilance from countries in terms of geographic origin including from within or outside the EEA or from individual member states within the EEA is also outside the present scope, this is an area for further research by the EMA.

Table 5 The 20 most frequent adult drug–event combinations reported in EudraVigilance (1 January 1995–13 June 2013) (20 most frequent reaction MedDRA preferred terms grouped by active substance)

Active substance	Reaction PT	Number of cases	%	Overall rank in EudraVigilance
Etanercept	Injection site pain[a]	25,207	1	1
	Injection site erythema[a]	17,591	1	2
	Injection site swelling[a]	9,429	<1	4
	Injection site pruritus[b]	9,124	<1	5
	Injection site bruising[a]	8,993	<1	6
	Rheumatoid arthritis[c]	8,730	<1	7
	Arthralgia[c]	7,647	<1	9
	Psoriasis[c]	7,645	<1	10
	Injection site reaction[a]	7,380	<1	11
	Drug ineffective	7,214	<1	12
	Headache[a]	6,249	<1	14
	Fatigue[a]	5,552	<1	20
Varenicline	Nausea[a]	9,681	<1	3
	Depression[a]	5,908	<1	16
Drospirenone, ethinylestradiol	Pain[a]	7,794	<1	8
	Pulmonary embolism[a]	6,901	<1	13
	Injury[d]	5,867	<1	17
	Deep vein thrombosis[a]	5,828	<1	18
Rofecoxib	Myocardial infarction[e]	5,980	<1	15
Calcium chloride, sodium chloride, glucose, sodium lactate, magnesium chloride	Peritonitis[f]	5,735	<1	17

MedDRA Medical Dictionary for Regulatory Activities, *PT* preferred term

[a] Listed in Product Information

[b] Considered listed by other various injection site reaction terms

[c] Indication for use

[d] Reported in context of pulmonary embolism, thrombosis and gallbladder injury, cholelithiasis or cholecystectomy

[e] Substance withdrawn due to concerns over cardiovascular safety

[f] Considered to reflect use in peritoneal dialysis solutions

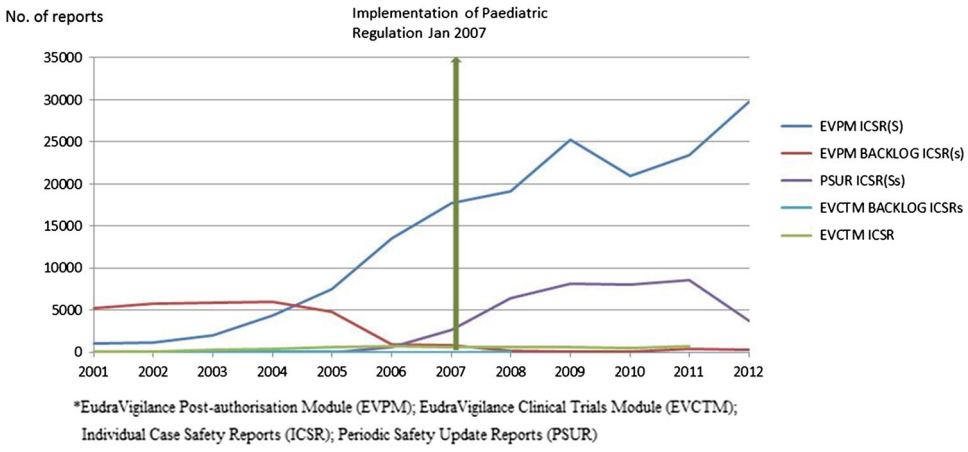

Fig. 3 Distribution over time of paediatric reports by type of EudraVigilance report by calendar year (2001–2012)

The different age distribution of reports by gender may be taken as reflecting differences in drug use, e.g. use of human papillomavirus vaccine in female adolescents, but further research is needed to confirm this.

4.4 Limitations

It is also important to note that the limitations of spontaneous reporting should be taken in account in the interpretation of the results of the present study. Underreporting is a known feature of spontaneous reports [29]. In addition, due to lack of exposure data and the need for data on background incidence of disease in interpreting the results, analysis of the number of ADRs spontaneously reported in EudraVigilance cannot inform on the exact incidence of the reaction in the paediatric population nor, in itself, evaluate the causality.

5 Conclusions

The present descriptive analysis of ADRs reported to EudraVigilance has raised issues for further research on the available data. It also further demonstrates that the number and the quality of information in paediatric ADRs, particularly relating to provision of age details, can be substantially improved, to raise the level of key safety information they provide. While the most frequently reported reactions and drugs relate to known associations, in further defining how paediatric adverse reactions follow different patterns from those of adults, the results can be used by the EMA and other stakeholders to inform activities, e.g. risk management planning and signal detection activities, in EudraVigilance directed at improving drug use and monitoring in children.

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Data sharing EudraVigilance data is available subject to the 'EudraVigilance access policy for medicines for human use' available at http://eudravigilance.ema.europa.eu/human/EudraVigilanceAccessPolicy.asp.

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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