ORIGINAL RESEARCH ARTICLE

Pediatric Drug Safety Surveillance: A 10-Year Analysis of Adverse Drug Reaction Reporting Data in Calabria, Southern Italy

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Abstract

Introduction The paucity of pediatric clinical trials has led to many medicines frequently prescribed to children without a license for use in pediatrics, resulting in an increased risk of adverse drug reactions. Pharmacovigilance databases remain, among others, a valuable tool for evaluating pediatric drug safety in the real-life setting.

Objective We aimed to characterize pediatric adverse drug reactions reported in the Italian Pharmacovigilance database coming from the Calabria region (Southern Italy) over 10 years.

Methods All Individual Case Safety Reports (ICSRs) concerning individuals aged under 18 years were extracted from 2010 to 2019. Duplicate and vaccine ICSRs were excluded. The remaining ICSRs were analyzed with respect to patients' demographic data, suspected drugs, and category of adverse drug reactions across different age groups.

Results Among 6529 selected ICSRs, 395 pediatric ICSRs corresponding to 556 adverse drug reactions were analyzed. From 2010 to 2015, an increasing number of ICSRs were observed, but the reporting rate decreased after 2015. The highest proportion of ICSRs concerned children and adolescents. Around 52% of ICSRs involved boys: a trend observed in all age groups excluding newborns. Sixty ICSRs were serious and among them, 75% required hospitalization mainly in children and adolescents. Most of the ICSRs were issued by physicians (64.1%), followed by other healthcare professionals (22.5%) and pharmacists (9.9%). Anti-infective agents for systemic use and skin disorders were, respectively, the most frequently reported drug group and adverse drug reaction category.

Conclusions This study provides an overview of adverse drug reactions reported in the pediatric population of the Calabria region and emphasizes the need for strengthening the surveillance in specific age subgroups and on given drugs in relation to their pattern of use.

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Key Points

This study presents for the first time a descriptive overview of pediatric Individual Case Safety Reports registered in the Italian Pharmacovigilance Database coming from the Calabria region (Southern Italy) across one decade.

Some differences have been observed across child age groups, between boys and girls, and both in the frequency and the type of Individual Case Safety Reports between children and adults.

A drug-specific, sex-specific, or age-specific approach is needed when investigating pharmacovigilance databases to evaluate the safety of drugs in pediatric patients, in order to target specific drugs or patient age groups that may have an increased risk for particular adverse drug reactions.

1 Introduction

One of the main issues about drug safety in pediatric age concerns the paucity of clinical studies in this setting. Recently, the pediatric population has been largely under-represented in pre-marketing clinical trials owing to the lower prevalence of many diseases in children compared with adults and elderly individuals as well as the practical and ethical challenges of carrying out clinical studies in children. Moreover, the development of pediatric medicines is typically associated with a small market size and unprofitability, dissuading pharmaceutical companies from addressing needs related to the pediatric population [1]. Furthermore, fewer pediatric compared with adult randomized trials have been reported to investigate safety outcomes [2, 3], supporting previous concerns about the quality of drug trials conducted in children [4]. Thus, many medicines frequently prescribed to children are not specifically approved for use in pediatric patients, and insufficient evidence exists about their safety and efficacy in this population [2]. As a result, when prescribing medications to children, physicians frequently tend or have to draw their conclusions from adult drug trials, without age-specific information on correct dosing and/or on drug efficacy and safety [5, 6]. Consistently, accruing evidence has shown a widespread use of unlicensed or 'off-label' drugs to treat children [7–10]. Off-label use reflects the prescription of drugs outside the terms of their marketing authorization with respect to dosage or frequency, age

groups, clinical indication, or route; unlicensed use refers to: (1) licensed drugs whose formulation is modified; (2) drugs manufactured as extemporaneous preparations; (3) drugs imported or used before license granting; or (4) chemicals used as drugs for lack of pharmaceutical preparation [8]. The main problem related to off-label/unlicensed drug prescribing in children is setting up the proper and safer dose of medications tested only in adult patients showing substantial age-related differences in terms of drug absorption, action, metabolism, and toxicity. The benefit-risk drug profile may be thus considerably variable between pediatric and adult patients. In addition, children are particularly susceptible to unwanted and toxic drug effects because of significant pathophysiological developmental changes resulting in dramatic effects on pharmacokinetics and pharmacodynamics [6, 11]. Consequently, this type of prescribing in children is potentially associated with a greater risk of adverse drug reactions (ADRs) and/or a lack of therapeutic effectiveness, as suggested by many studies both in hospital and outpatient care [12–17].

Over the years, the need for improving the evidence driving the use of medicines in pediatrics has fostered several initiatives worldwide to increase pediatric drug research [18]. In 2007, the "Regulation n. 1901/2006 on Medicinal Products for Paediatric use" came into effect in the European Union (EU), compelling pharmaceutical companies to agree and submit a pediatric investigation plan to the European Medicines Agency's Paediatric Committee for every new medicine, indication, and pharmaceutical form. After more than 10 years of implementation, the main objective of the "EU Paediatric Regulation" has been fully fulfilled, resulting in more pediatric clinical trials and more information on the pediatric use of medicinal products in the EU and beyond [1].

Despite this "cultural shift," the investigation of pediatric drug safety remains still unsatisfactory because pre-marketing clinical drug research is unable to detect serious, rare, and unexpected ADRs in daily medical practice [19]. Therefore, post-marketing surveillance through spontaneous reporting system (SRS) databases continues to play a crucial role in monitoring drug safety in children in the 'real-life' setting. Actually, SRS databases are an essential source of valuable information to identify, and possibly prevent, drug-related pediatric safety issues [20]. Generally, spontaneous ADR reports are regularly collected in national databases and then sent as Individual Case Safety Reports (ICSRs) to supranational repositories such as EudraVigilance in the EU (which includes also ICSRs coming from non-European countries) and VigiBase, the unique World Health Organization global database managed by the Uppsala Monitoring Center [21]. In Italy, spontaneous ADR reports are first sent to the local contact person for pharmacovigilance (responsible for pharmacovigilance)

who may work in a local hospital or health service unit. This person has to entry reports (within 7 days of their receipt) as valid ICSRs into the Italian Pharmacovigilance Database, also known as the National Pharmacovigilance Network (Rete Nazionale di Farmacovigilanza, RNF), which is strictly linked to EudraVigilance [22]. Following the launch of the new EudraVigilance system on 22 November, 2017 [23], new simplified electronic reporting rules have been implemented. Accordingly, the RNF (as well as other national pharmacovigilance databases in European countries) no longer has to send its own ICSRs to the World Health Organization-Uppsala Monitoring Center database, which receives this information directly from EudraVigilance. Moreover, marketing authorization holders no longer have to electronically transmit ICSRs (received from patients) to the national database, but must submit them directly to EudraVigilance, which in turn is able to forward these data to the RNF database by a specific functionality called "re-routing". As a result, all ICSRs collected in the RNF are regularly (every day) submitted to EudraVigilance and vice versa, i.e., from EudraVigilance to RNF (only in relation to Italian ICSRs that do not fall within the framework of clinical trials), in order to ensure the comprehensiveness of both national and European databases [22, 24].

The Italian SRS database has been recently investigated, highlighting characteristics of pediatric ICSRs consistent with those from other national and worldwide SRSs [25]. Over the last decade, the Calabria region has carried out several active pharmacovigilance projects (including studies specifically targeted to pediatric ADRs and safety data) at the "Mater Domini" University Hospital of Catanzaro, where a "Pharmacovigilance and Drug Information Center" was created by the end of 2010, with the ultimate goal of spreading the culture of pharmacovigilance among regional healthcare professionals and citizens/patients and thus improving the regional reporting system [26].

The aim of the current study is to, for the first time, provide a descriptive overview of the characteristics of pediatric ICSRs registered in the Italian SRS database coming from the Calabria region (Southern Italy) over a 10-year period and to compare pediatric with adult ICSRs. The results will serve as a baseline to explore whether lessons can be learned for the Calabrian Pharmacovigilance System with special reference to pediatric pharmacovigilance, passing 10 years since the establishment of the Regional Reference Center of Pharmacovigilance and Drug Information.

2 Methods

2.1 Data Source

Data were retrieved from the RNF, a nationwide spontaneous reporting database that allows the collection, management, and analysis of suspected ICSRs. The RNF has been active since 2001 and managed by the national regulatory agency, the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA), in compliance with EU regulations. This system networks regions, regional centers for pharmacovigilance, more than 350 peripheral structures (hospitals and local health service units), and marketing authorization holders to the Pharmacovigilance Office of the AIFA [21].

Each ICSR includes information on patient demographics (e.g., initials, age, sex, and region), description of ADRs (unstructured narrative of each adverse event), date of onset and outcome of the suspected ADR, ADR seriousness, information for as many drugs (both suspected and concomitant) as reported for each event (active ingredient name, trade name, dosage, frequency, and route of administration, therapy start and end dates, and therapeutic indications), clinical history with relevant laboratory tests and comorbidities, and report source. Adverse reactions due to unauthorized uses of medicines, medication errors, and occupational exposure are also considered as ADRs and are included in the RNF database. Duplicate ICSRs are automatically detected from the system [21, 27]. Drugs reported as suspected or interacting are classified by using the Anatomical Therapeutic Chemical (ATC) classification [28]. Suspected ADRs are codified according to the hierarchical structure of the *Medical Dictionary for Regulatory Activities* (MedDRA®) [29].

2.2 Data Setting and Extraction

Calabria is a small geographical region in Southern Italy with almost two million inhabitants across a total area of approximately 15,222 square kilometers [30]. No specialized children's hospitals are located in this region. However, 21 Pediatric Hospital Units and two Pediatric Emergency Departments are currently active [31].

For this retrospective observational study, the RNF was screened for all suspected ICSRs concerning individuals aged under 18 years (including ICSRs related to pregnancy exposure), as registered in the database coming from the Calabria region of Italy during the period 1 January, 2010 until 31 December, 2019. Adult ICSRs (aged ≥ 18 years) were also extracted for comparison. The search included both unsolicited (e.g., spontaneous reports, literature reports, reports from non-medical sources, internet or digital media) and solicited reports (derived from organized data collection

systems, such as non-interventional studies, registries, and others) [26]. Any suspected duplicate was excluded. All ICSRs in which age, suspected drug, or event was missing were excluded. We also excluded vaccine-related ICSRs (defined as ICSRs with at least one drug from the ATC classification group J07) because their proportion in the Calabrian RNF database over the study period was over 50% of the ICSRs regarding the 0–17 years of age group.

2.3 Data Analysis and Statistics

A descriptive analysis of regional pediatric ICSRs was conducted to evaluate their frequency, basal demographic, and drug-related characteristics. Specifically, we performed the following analyses for the "child ICSRs" (i.e., including all ICSRs in the 0–17 years of age group):

1. over time;
2. by sex;
3. by ADR seriousness;
4. by ADR outcome;
5. by reporting source (type of reporter);
6. by healthcare facility of origin;
7. by drug and ADR groups: (a) ATC classification system was used to characterize drugs reported as suspected or interacting, specified for the anatomical main group (first-level ATC classification) and (b) System Organ Class (SOC) terms according to MedDRA® (version 24.0) were used to classify ADRs. (Note that the same ICSR can be counted in more than one ATC or SOC group because a single ICSR may have more than one suspected drug or ADR, and single suspected drugs can belong to different ATC groups.) When the same ICSR listed more than one suspected drug or ADR belonging, respectively, to the same ATC first-level or SOC, that ATC group or SOC was counted only once.

Seriousness was categorized as death, life threatening, hospitalization or extended hospital stay, persistent or significant disability/incapacity, congenital anomaly/birth defect or other medically relevant conditions, according to the definition of Good Pharmacovigilance Practices (GVP), Module VI [32].

Main analyses were stratified by the patient's age at onset as follows [33]: newborns (≤ 27 days), infants (28 days to 23 months), children (2–11 years), and adolescents (12–17 years). Only suspected or interacting drugs were considered and analyzed. Within each pediatric age category, the three most frequently involved therapeutic subgroups (second-level ATC classification) were described in relation to the three most commonly reported ADRs (by using MedDRA® SOC terms). We also focused on the single suspected drugs (by active substances: fifth-level ATC classification)

involved in ten or more ICSRs and the proportion of serious ADRs related to these medicines by dividing the number of serious ADRs for the specific active substance by the total number of ADRs for each active substance. Furthermore, we compared the proportion of ICSRs stratified by drug group (first-level ATC classification) and by ADR group (MedDRA® SOC) in children versus adults. A case-by-case clinical evaluation of pediatric ICSRs was performed with the aim of identifying possible ADRs resulting from off-label or unlicensed drug use in pediatric patients. Finally, we focused on possible pediatric ICSRs due to other drug uses outside the marketing authorization such as misuse, abuse, and medication errors. Conditions of use outside the marketing authorization were investigated and assessed both by using the advanced function of the RNF database for the analysis of ICSRs and by referring to the approved product information document for each suspected drug involved in ADRs.

Regarding off-label use, misuse, abuse, and medication error, pediatric ICSRs were characterized according to the definitions of GVP, Module VI [32].

Characteristics of pediatric ICSRs were analyzed using descriptive statistics. Quantitative variables were expressed as mean ± standard deviation, but also as median and interquartile range, assuming that the distribution of the population was not normal. Qualitative (categorical) variables were expressed as relative and absolute frequencies. Proportions were compared by using the chi-square test in order to check the hypotheses of uniform data distribution. Means were compared by applying the Student's t test, which was used to compare the mean age among the pediatric age categories (see Table 1), or Mann–Whitney U test, as appropriate. The statistical significance level was set at a p-value of < 0.05. The statistical method adopted to analyze pediatric ICSRs consisted of two steps: (1) investigation of age dependence (i.e., testing the hypothesis of uniform distribution from a statistical point of view by only analyzing the first row of Table 1) and (2) study of a more suitable statistical distribution for all analyzed quantities: sex, seriousness, type of seriousness, and outcome (i.e., the information categorized into the other rows of Table 1). The Statistics Package for Social Sciences (SPSS for Windows, version 21.0; SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

3 Results

3.1 Number and Types of ICSRs by Age Group

During the study period, the RNF database collected 7131 suspected ICSRs in the population of the Calabria region. After the exclusion of ICSRs including vaccines ($n = 458$;

Table 1 Characteristics of pediatric ICSRs registered in the Rete Nazionale di Farmacovigilanza coming from the Calabria region, distributed by age groups, during the period 2010–9

Age group	Total	≤ 27 days (newborns)	28 days to 23 months (infants)	2–11 years (children)	12–17 years (adolescents)	p value[a] (stratified analysis)	p value[a] (overall analysis)
N (%)	395	12 (3.0)	62 (15.7)	207 (52.4)	114 (28.9)		
Mean age (± SD)	7.5 (5.6)	11.9 days (10.1)	9.8 months (3.7)	5.9 (2.9)	14.9 (1.7)		
Median age (IQR)	7 (10.5)	13.5 days (18.5 days)	12 months (3 months)	5 (5)	15 (3)		
Sex, n (%)							
Male	206 (52.1)	6 (50.0)	36 (58.1)	106 (51.2)	58 (50.9)	< 0.05	> 0.05
Female	184 (46.6)	6 (50.0)	26 (41.9)	101 (48.8)	51 (44.7)	< 0.05	> 0.05
Missing	5 (1.3)	–	–	–	5 (4.4)	NA	NA
Seriousness, n (%)							
Serious	60 (15.2)	3 (25.0)	9 (14.5)	25 (12.1)	23 (20.2)	< 0.05	> 0.05
Type of seriousness, n (% within seriousness)							
Hospitalization	45 (75.0)	–	8 (88.9)	21 (84.0)	16 (69.6)	< 0.05	> 0.05
Other medically significant conditions	10 (16.7)	3 (100)	1 (11.1)	1 (4.0)	5 (21.7)	NA[b]	NA[b]
Life threatening	5 (8.3)	–	–	3 (12.0)	2 (8.7)	NA[b]	NA[b]
Outcome, n (%)							
Fully recovered	83 (21.0)	–	11 (17.7)	42 (20.3)	30 (26.3)	< 0.05	> 0.05
Improved	228 (57.7)	10 (83.3)	48 (77.5)	124 (59.9)	46 (40.3)	< 0.05	< 0.05
Unknown	79 (20.0)	2 (16.7)	3 (4.8)	37 (17.9)	37 (32.5)	< 0.05	< 0.05
Not yet recovered	5 (1.3)	–	–	4 (1.9)	1 (0.9)	NA[b]	NA[b]

ICSRs Individual Case Safety Reports, *IQR* Interquartile Range, *NA* not applicable, *SD* standard deviation

Vaccines were excluded from this analysis

[a]Chi-square test was used to compare the proportions and the means related to ICSRs across age groups. Means were compared by using either the Student's *t* test or Mann–Whitney *U* test, as appropriate. A *p*-value < 0.05 was considered to be statistically significant

[b]Analysis was not performed because of the small sample size

6.4%) and ICSRs in which age was missing (*n* = 144; ~ 2%), a total of 6529 ICSRs remained and were analyzed, of which 395 (~ 6%) concerned the pediatric population corresponding to a total of 556 pediatric ADRs (on average, about 40 pediatric ICSRs were annually submitted, corresponding to approximately 1.4 ADR per ICSR). Parent-child/fetus cases were identified in seven pediatric ICSRs: pregnancy exposure-related ADRs were reported in three ICSRs while two ICSRs exemplified cases of drug exposure via breastfeeding. Regarding the remaining two parent-child/fetus cases, it was unclear whether ADRs in the newborns were related to pregnancy exposure or breastfeeding. Among pediatric ICSRs, 394 originated from spontaneous reporting whereas the remaining was attributable to other unspecified sources. A very slightly heterogeneous origin was observed for adult ICSRs: spontaneous ICSRs (*n* = 6097; 99.4%), ICSRs derived from other unspecified sources (*n* = 27; 0.4%), and ICSRs originating from non-interventional studies (*n* = 9;

~ 0.2%). Source information was not available for only one adult ICSR.

3.2 Regional Pediatric Reporting Over Time

The number of analyzed pediatric ICSRs showed an approximately exponential increase in the 6-year period 2010–15 (2010: 1 ICSR; 2011: 6 ICSRs; 2012: 29 ICSRs; 2013: 63 ICSRs; 2014: 75 ICSRs; 2015: 101 ICSRs), but the reporting rate decreased after 2015 (2016: 70 ICSRs; 2017: 14 ICSRs; 2018: 28 ICSRs; 2019: 8 ICSRs).

3.3 Overall Characterization of Regional Pediatric ICSRs by Age Categories

Characteristics of regional pediatric ICSRs distributed by age categories over the study period are summarized in Table 1. The highest proportion of ICSRs concerned

children (aged 2–11 years) and adolescents (aged 12–17 years). The mean age at the time of ADR occurrence was 7.5 years (standard deviation ± 5.6). The majority of ICSRs concerned male patients ($n = 206$; 52.1%) and this trend was observed in all age groups except for newborns. About 15% ($n = 60$) of the total ICSRs described serious ADRs: among these, 45 (75%) cases required patient hospitalization while the remaining ICSRs referred to other medically significant conditions (16.7%) or life-threatening episodes (8.3%): a case-by-case clinical description of life-threatening ICSRs is provided in Table 1 of the Electronic Supplementary Material (ESM). A greater rate of serious ADRs was observed for children (41.7% of total serious ICSRs) and adolescents (38.3% of total serious ICSRs) compared with the other age categories. Consistently, hospitalization-related ADRs were predominantly reported in both children and adolescents. The large majority of ADRs resulted in improvement ($n = 228$; 57.7%) and full recovery ($n = 83$; 21%); however, an unknown outcome was reported in 79 cases. Actually, the distribution of pediatric ICSRs was significantly different among age categories by separately analyzing data stratified for sex, seriousness, type of seriousness, and outcome. In particular, several differences were observed in terms of ADR seriousness and outcome. Concerning the second step of analysis (see Sect. 2.3), it is possible to assume the frequency distribution of the whole dataset as valid (with a significance level of 0.05) for the subsets of sex, seriousness, type of seriousness, and outcome. Significant differences were observed only as a function of the ADR outcome, with special reference to ICSRs reporting "improvement" or "unknown outcome" of the noxious events (these two subsets seem to follow different distributions from the overall subset).

3.4 Pediatric ICSRs by Type of Reporter, Age Category, and Seriousness

Most of the ICSRs were issued by physicians ($n = 253$; 64.1%), followed by other healthcare professionals ($n = 89$; 22.5%) and pharmacists ($n = 39$; 9.9%). The different types of reporters were heterogeneously distributed across age groups. Interestingly, the proportion of ICSRs notified by physicians linearly decreased from the newborn to adolescent age group (from 91.7 to 52.6%), while an opposite trend could be observed for the other healthcare professionals (from 11.3 to 33.3%). Over 80% of serious ICSRs ($n = 49$) were from physicians.

3.5 Pediatric ICSRs by Healthcare Facility of Origin

Stratification by healthcare facility of origin also indicated that the "Mater Domini" University Hospital of Catanzaro ($n = 179$) and the Provincial Health Unit of Catanzaro ($n = 81$)

had submitted to the RNF the most child ICSRs in the study period (over 65% of total pediatric ICSRs). The number and proportion of pediatric ICSRs by healthcare facility of origin are detailed in Table S2 of the ESM.
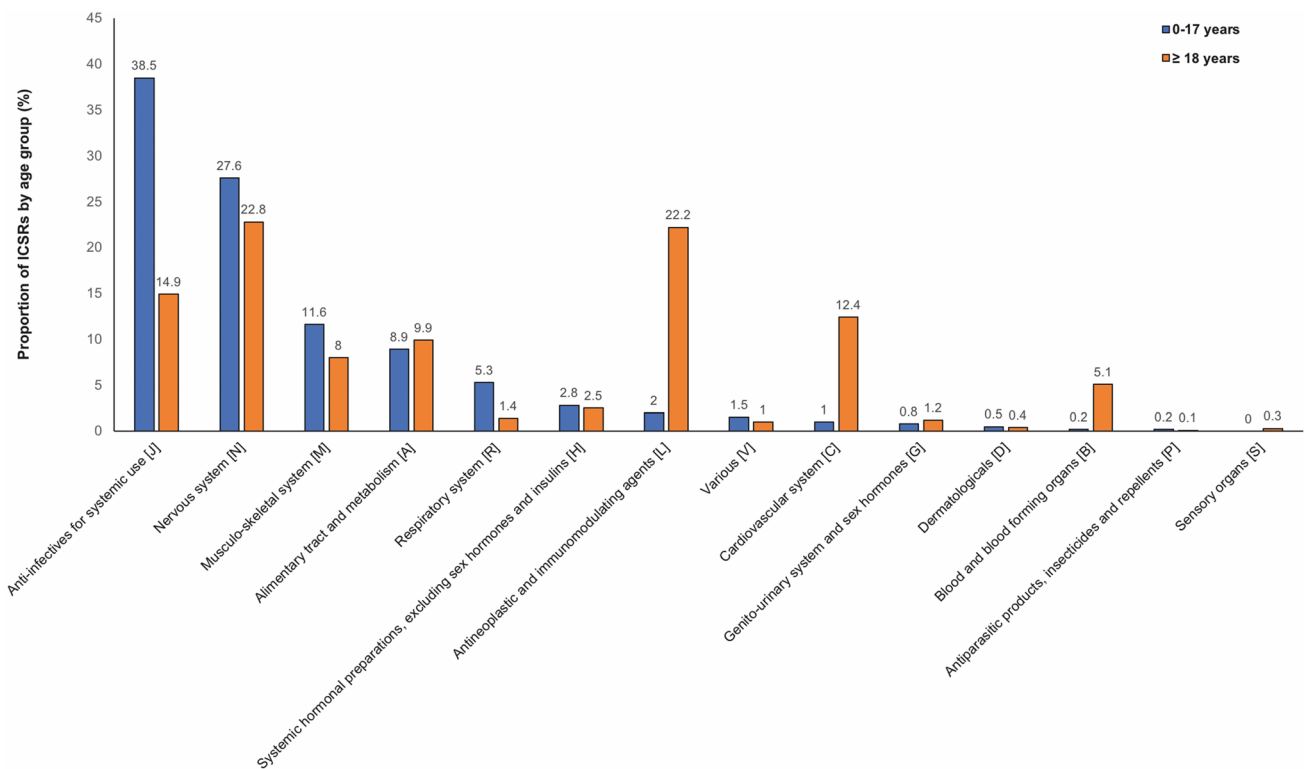
3.6 ICSRs by First-Level ATC Classification in the Child and Adult Groups

Looking at the suspected drugs, the proportions of ICSRs by first-level ATC classification (anatomical main group) in the child and adult groups are displayed in Fig. 1. Regarding children, *Anti-infectives for systemic use* was the most frequently reported drug group ($n = 152$ ICSRs; 38.5%), followed by the *Nervous system* ($n = 109$ ICSRs; 27.6%) and *Musculo-skeletal system* ($n = 46$ ICSRs; 11.6%) ATC groups. Amoxicillin/clavulanic acid, paracetamol, and ibuprofen were, respectively, the most reported active substances in the above ATC groups.

In the adult group, the most frequently reported drugs belonged to the *Nervous system*, *Antineoplastic and immunomodulating agents*, and *Anti-infectives for systemic use* ATC groups. In comparison to adults, the child group showed a higher proportion of ICSRs for drugs belonging to eight ATC groups: the highest difference in percentage units was observed in the anti-infective (38.5 vs 14.9%), nervous (27.6 vs 22.8%), respiratory (5.3 vs 1.4%), and musculo-skeletal system (11.6 vs 8%) ATC groups. No ICSRs for drugs belonging to the sensory organs were found in children.

3.7 ICSRs by SOC in the Child and Adult Groups

Looking at the reported events, the proportions of ICSRs by MedDRA SOCs in the child and adult groups are displayed in Fig. 2. Skin and subcutaneous tissue disorders were the most frequently reported ADRs for children ($n = 231$ ICSRs; 58.5%), followed by psychiatric disorders ($n = 40$ ICSRs; 10.1%), general disorders ($n = 35$ ICSRs; 8.9%), gastrointestinal disorders ($n = 34$ ICSRs; 8.6%), and nervous system disorders ($n = 28$ ICSRs; 7.1%). *Urticaria* ($n = 99$ ICSRs), *erythema* ($n = 56$ ICSRs), *rash* ($n = 42$ ICSRs), *irritability* ($n = 10$ ICSRs), *vomiting* ($n = 10$ ICSRs), *nausea* ($n = 8$ ICSRs), *lips edema* ($n = 7$ ICSRs), *drug ineffective* ($n = 5$ ICSRs), *edema* ($n = 5$ ICSRs), *hallucination* ($n = 4$ ICSRs), *confusional state* ($n = 4$ ICSRs), *asthenia* ($n = 4$ ICSRs), *pyrexia* ($n = 4$ ICSRs), *drowsiness* ($n = 4$ ICSRs), *tremor* ($n = 4$ ICSRs), *loss of consciousness* ($n = 3$ ICSRs), and *seizure* ($n = 3$ ICSRs) were the most reported MedDRA® Preferred Terms (PTs) associated with the above SOCs. The highest proportion of ICSRs was observed for the *Skin and subcutaneous tissue disorders* SOC in both children (n

Fig. 1 Proportion of Individual Case Safety Reports (ICSRs) by drug group (first-level Anatomical Therapeutic Chemical [ATC] classification, anatomical main group) within each age group (child and adult). Proportion is based on the number of ICSRs with the specific ATC group/total number of ICSRs for the specific age group (child = 395, adult = 6134). Note: one ICSR can be counted in more than one ATC group (one ICSR can list more than one suspected drug and each suspected drug can belong to more than one ATC group). The figure is sorted in descending order of the proportion for the child group

= 231; 58.5%) and adults (*n* = 1425; 23.2%). However, the top five SOCs were not consistently reported in both age groups (0–17 years and ≥18 years). The child group showed a higher proportion (more than one percentage unit) of ICSRs than adults for skin disorders, psychiatric disorders, and immune system disorders, despite the absolute number of ICSRs (related to these SOCs) was higher in the adult group rather than in the child group.

In the child group, most of the reported skin disorders were immune-mediated skin ADRs: out of total 264 PTs associated with the *Skin and subcutaneous tissue disorders* SOC, 260 PTs were reported (by both notifiers and senders of ICSRs) to be related to an allergic mechanism.

3.8 Distribution of the Most Frequently Reported Therapeutic Subgroups (ATC Second Level) by SOC and Pediatric Age Category

The three most frequently involved therapeutic subgroups (by second-level ATC) with respect to the three most commonly reported ADRs (in terms of MedDRA SOCs) were stratified by all child age categories (Table 2).

Overall, therapeutic subgroups were heterogeneously distributed with respect to the different SOCs among the age categories. However, when analyzing skin disorders, the distribution of therapeutic subgroups was comparable in all age groups excluding newborns: antibacterials for systemic use (J01), anti-inflammatory and antirheumatic drugs for systemic use (M01), and analgesics (N02) were consistently the most frequently reported therapeutic classes (amoxicillin/clavulanic acid, ibuprofen, and paracetamol were, respectively, the most commonly implicated active substances). When investigating ADRs associated with gastrointestinal disorders, we observed an essential change in the first most frequently reported therapeutic subgroup across the age categories: psycholeptics (N05) and psychoanaleptics (N06) were replaced by antibacterials for systemic use (J01) moving from newborns to children and adolescents. Similarly, a shift from miscellaneous drug classes reported in infants to antiepileptic drugs (N03) reported in children and adolescents was documented for psychiatric disorders.
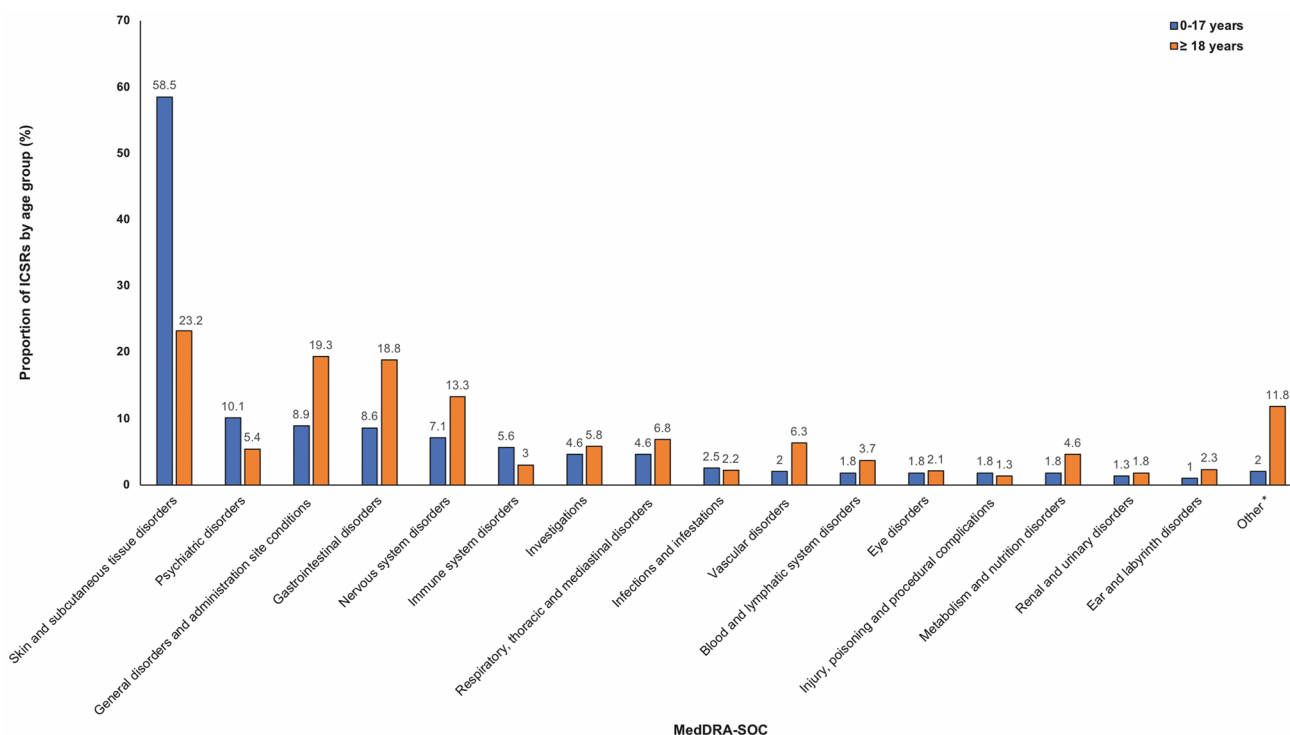
Fig. 2 Proportion of Individual Case Safety Reports (ICSRs) by *Medical Dictionary for Regulatory Activities* (MedDRA®) System Organ Class (SOC) within each age group (child and adult). Proportion is based on the number of ICSRs with the specific SOC/total number of ICSRs for the specific age group (child = 395, adult = 6134). Note: one ICSR can be counted in more than one SOC (one ICSR can list more than one adverse drug reaction). The figure is sorted in descending order of the proportion for the child group. (Asterisk)

Other includes the MedDRA® SOCs reported in < 1% of pediatric ICSRs [Musculoskeletal and connective tissue disorders; Reproductive system and breast disorders; Cardiac disorders; Endocrine disorders; Hepatobiliary disorders; Product issues; Congenital, familial and genetic disorders; Neoplasms benign, malignant and unspecified (including cysts and polyps); Pregnancy, puerperium and perinatal conditions; Social circumstances; Surgical and medical procedures]

Regarding skin disorders, antibacterials for systemic use (J01) were implicated in over 51% (*n* = 117) of pediatric ICSRs related to allergic skin reactions.

Generally, antibiotics (J01) were the therapeutic subgroup associated with the highest number of ICSRs and serious ADRs across all pediatric age categories (see Table 3).

3.9 Drugs (Active Substances, ATC Fifth Level) Reported as Suspected Cause of Pediatric ADRs

Table 3 underlines the single active substances (fifth-level ATC) identified as suspected causes of pediatric ADRs in ten ICSRs and beyond. All the other drugs reported as suspected causes of pediatric ADRs are displayed in Table S3 of the ESM. Amoxicillin/clavulanic acid, paracetamol, and ibuprofen were the top three most frequently reported suspected drugs,

being involved in about 27% (*n* = 106) of total ICSRs and about 25% of the total number of ADRs in the pediatric population. Antibiotics such as amoxicillin/clavulanic acid, ceftriaxone, and cefaclor represented the top three drugs associated with the greatest number of serious ADRs.

A possible drug–drug interaction was suspected in one ICSR reporting the combination of valproic acid (involved in 19 ICSRs) with lamotrigine.

3.10 Most Frequent Pediatric Drug-ADR Pairs

At the drug-ADR pair level, antibiotics, paracetamol, and anti-inflammatory drugs were the mostly involved agents in skin ADRs. Amoxicillin/clavulanic acid-skin disorders were the most frequently reported pediatric drug-ADR pair (44 pairs). Furthermore, amoxicillin/clavulanic acid was involved

Table 2 Distribution of the most frequently reported therapeutic subgroups (ATC second level) stratified by SOC and age category

SOC (top 3 in each age category)	Number of ICSRs (% on total number of ICSRs in each age category)[a]	Top 3 most frequently reported therapeutic subgroups, ATC second level[b], by SOC (% within SOC in each age category)
≤ 27 days (n = 12)		
Skin and subcutaneous tissue disorders	4 (33.3)	A03 (75); N02 (25)
Gastrointestinal disorders	2 (16.7)	N05 (50)/N06 (50)
General disorders and administration-site conditions	2 (16.7)	A03 (50)/N06 (50)
Nervous system disorders	2 (16.7)	N05 (50)/N06 (50)
28 days to 23 months (n = 62)		
Skin and subcutaneous tissue disorders	47 (75.8)	J01 (55); M01 (17); N02 (9)
General disorders and administration site conditions	6 (9.7)	J01 (50); C08 (17)/H01 (17)/N02 (17)
Immune system disorders	5 (8.1)	J01 (40); A03 (20)/M01 (20)/R05 (20)
Psychiatric disorders	5 (8.1)	C08 (20)/H02 (20)/J01 (20)/N02 (20)/N06 (20)
2–11 years (n = 207)		
Skin and subcutaneous tissue disorders	134 (64.7)	J01 (53); M01 (15); N02 (14)
Gastrointestinal disorders	16 (7.7)	J01 (38); M01 (19); N03 (13)
Psychiatric disorders	16 (7.7)	N03 (50); R03 (19); N05 (13)
12–17 years (n = 114)		
Skin and subcutaneous tissue disorders	46 (40.3)	J01 (46); M01 (13); N02 (11)/N03 (11)
Psychiatric disorders	18 (15.8)	N03 (56); N05 (17); H02 (11)
Gastrointestinal disorders	14 (12.3)	J01 (57); B03 (7)/L04 (7)/N02 (7)/N03 (7)/R03 (7)/V01 (7)/V03 (7)

ATC Anatomical Therapeutic Chemical, *ICSRs* Individual Case Safety Reports, *SOC* System Organ Class

[a]Within each age category, the SOCs are ranked according to the number of ICSRs for the specific SOC (the SOCs with the same ranking are all listed). For each SOC, the three most frequently involved therapeutic subgroups (ATC second level) are described (when the same ICSR lists more than one suspected drug or adverse drug reaction belonging respectively to the same ATC second level or SOC, that ATC group or SOC is counted only once). A "/" between therapeutic subgroups indicates that each therapeutic subgroup is involved in the same number of ICSRs

[b]Abbreviations list used for the most frequently reported therapeutic subgroups (ATC second level): *A03* drugs for functional gastrointestinal disorders, *B03* antianemic preparations, *C08* calcium channel blockers, *H01* pituitary and hypothalamic hormones and analogues, *H02* corticosteroids for systemic use, *J01* antibacterials for systemic use, *L04* immunosuppressants, *M01* anti-inflammatory and antirheumatic drugs for systemic use, *N02* analgesics, *N03* antiepileptics, *N05* psycholeptics, *N06* psychoanaleptics, *R03* drugs for obstructive airway diseases, *R05* cough and cold preparations, *V01* allergens, *V03* all other therapeutic products

in one-third of pediatric ICSRs about allergic skin reactions from antibiotic use.

3.11 Pediatric ICSRs Resulting from Off-Label/Unlicensed Drug Use

Table 4 provides a case-by-case clinical description of pediatric ICSRs following off-label/unlicensed drug prescribing. These ICSRs were equally distributed between male and female patients, with a mean age of 8.2 years (standard deviation ± 6.5). Out of a total 14 ICSRs, 71.4% (*n* = 10) were assessed as non-serious and only four cases were serious requiring patient hospitalization. Most ICSRs (*n* = 9; 64.3%) showed "improvement" as the outcome at the time of reporting. In step with the trend observed for all analyzed pediatric ICSRs, physicians notified the majority of the above ICSRs (*n* = 8; 57.1%), followed by other healthcare professionals (*n* = 4; 28.6%) and pharmacists (*n* = 2; 14.3%). Anti-infective (*n* = 5; 35.7%) and nervous system (*n* = 5; 35.7%) drugs

were the most commonly reported drug groups (first-level ATC). Overall, 14 ICSRs referred to a total of 19 ADRs. According to MedDRA® hierarchy, *Skin and subcutaneous tissue disorders* was the top frequently reported SOC (*n* = 6 out of 14 ICSRs; *n* = 6 out of 19 ADRs) and *urticaria* was the most reported PT (*n* = 3 out of six PTs) within this SOC. Off-label drug prescribing associated with ICSRs was mainly due to a non-approved age (ten cases were off-label by patient age).

3.12 Pediatric ICSRs Due to Drug Misuse, Abuse, and Medication Errors

Among pediatric ICSRs associated with other drug uses outside the terms of the marketing authorization, two cases of misuse were recognized (Table 5). Both of them involved over-the-counter drugs (nonprescription drugs), suggesting situations where the medicinal product was intentionally and inappropriately used by patients (or most likely by their

Table 3 Drugs[a] (active substances, ATC fifth level) reported as suspected causes of pediatric ADRs

Drug (active substance)	Number of ICSRs	Number of ADRs	Number of serious ADRs (%)
Amoxicillin/clavulanic acid	50	64	12 (19)
Paracetamol	31	41	7 (17)
Ibuprofen	25	32	4 (13)
Cefaclor	20	29	11 (38)
Valproic acid	19	25	0 (0)
Azithromycin	17	19	2 (11)
Amoxicillin	15	20	8 (40)
Clarithromycin	15	23	3 (13)
Levetiracetam	15	21	1 (5)
Ceftriaxone	14	25	12 (48)
Ketoprofen	12	17	2 (12)

ADRs adverse drug reactions, *ATC* Anatomical Therapeutic Chemical, *ICSRs* Individual Case Safety Reports

[a]Only drugs involved in ≥ 10 ICSRs have been included. For each drug, the total number of ADRs is greater than the total number of ICSRs because each ICSR may list more than one ADR (a single ICSR may describe more than one drug/ADR pair). The proportion of serious ADRs is calculated by dividing the number of serious ADRs for the specific active substance with the total number of ADRs for each active substance

relatives in this setting) not in compliance with the authorized product information (no medical purpose). Only one case involving ibuprofen was judged as serious and required hospitalization because of lower limb vasculitis. Its outcome was unknown.

Cases of drug abuse were described in seven ICSRs, corresponding to a total of 12 PTs (Table 6). Five cases were registered as serious and involved haloperidol (two cases), quetiapine, paliperidone, topiramate (two cases), and trimethoprim-sulfamethoxazole (life-threatening case). All of these cases had an unknown outcome. Intentional self-injury (*Psychiatric disorders*) was reported in three serious ICSRs whereas skin disorders were associated with the life-threatening case involving trimethoprim-sulfamethoxazole. Other SOCs related to serious cases of drug abuse were *Ear and labyrinth disorders* and *Injury, Poisoning and Procedural Complications*.

Medication errors were observed in about 2% (*n* = 8 cases) of pediatric ICSRs, which reported a total of 19 PTs (Table 7). Accidental exposure occurred in five cases and inappropriate dose administration (administration error) was the type of error reported in two patients. Possible failure of child-resistant product closure (packaging issues) was responsible for accidental exposure in another patient. A seriousness criterion was assigned to 50% of medication error cases, involving oral suspension of paracetamol and

mebendazole, olmesartan tablets, and an unspecified oral formulation of amitriptyline.

4 Discussion

4.1 Proportion of Pediatric ICSRs in the Calabrian Pharmacovigilance Database

During the 10-year period covered by our analysis, after exclusion of duplicates, vaccines, and ICSRs containing missing age data, reporting of suspected ADRs in the pediatric population of the Calabria region represented about 6% of all ICSRs collected in the Calabrian Pharmacovigilance database. This proportion was lower than that reported in the EudraVigilance database (11.2%) [34] and the Portuguese pharmacovigilance database (9.7%) [35], but it was similar to the percentage of pediatric ICSRs reported in the whole RNF database (6.8%) [25], in the Spanish pharmacovigilance database (7%) [36], and in VigiBase (7.7%) [37]: similar to our study, the RNF database and VigiBase analyses excluded vaccine-related reports.

The low proportion of ICSRs on suspected pediatric ADRs in the Calabria region may be partially explained considering that the regional pediatric population significantly decreased in the same period [38], as well as the Italian pediatric population [39]: these demographic data are consistent with the similar percentages of pediatric ICSRs reported in the Calabrian and the Italian pharmacovigilance databases. However, the well-known under-reporting of pediatric ADRs in SRSs [40] could also have contributed to the low proportion of ICSRs concerning the pediatric population of the Calabria region. Indeed, pediatric ADRs can be difficult to characterize as many of the tools available are unsuitable for use in pediatrics [40]. Furthermore, reporting of ADRs in children is more challenging than in adults as it generally involves the parent as an essential intermediary and because children may not be as able as adults to describe their symptoms [34]. Therefore, a greater engagement of parents in their child's treatment and a better communication between clinicians and parents about any potential risks associated with medicines may help with early detection and reporting of pediatric ADRs.

4.2 Brief Overview of the Regional Pediatric ICSRs

This descriptive analysis identified the characteristics of suspected ICSRs concerning the pediatric population from the Calabrian RNF database across a 10-year period. First, we observed a decline in the number of pediatric ICSRs after 2015. A greater number of ICSRs was found in male subjects aged 28 days up to 17 years. Only 15.2% of the total

Table 4 Case-by-case clinical description of pediatric ICSRs resulting from off-label/unlicensed drug use

Sex (M/F)	Age	Adverse reaction (PT)	Seriousness	Outcome	Off-label/unlicensed drug (active substance)[a]	Therapeutic indication	Dosage/frequency (exposure length)	Route	Considerations
F	3 years	Irritability	Non-serious	Full recovery	Amoxicillin[b]	Gastrointestinal fungal infection	18 mL/daily (7 days)	Oral	Off-label use: the drug is not licensed for this therapeutic indication
M	4 years	Urticaria	Non-serious	Improvement	Diflucan® 10 mg/mL powder for oral suspension, flacon 60 mL (fluconazole)	Ichthyosis vulgaris	100 mg/daily (2 days)	Oral	Off-label use: the drug is not licensed for this therapeutic indication
M	3 years	Abnormal ECG, prolonged QT	Serious (hospitalization)	Improvement	Almarytm® 20 tablets 100 mg (flecainide)	Paroxysmal supraventricular tachycardia	125 mg/total (1 day)	Oral	Off-label use: this drug is not licensed for use in children aged < 12 years Unlicensed use: the dosage suggests probable crushing of tablets to obtain a liquid preparation
F	12 years	Increased appetite, weight gain	Non-serious	Unknown	Zyprexa® 28 tablets 5 mg (olanzapine)	Psychomotor retardation	10 mg/daily (384 days)	Oral	Off-label use: this drug is not indicated for children and adolescents aged younger than 18 years
F	14 years	Mental confusion, motor hyperactivity	Serious (hospitalization)	Improvement	Thiocolchicoside[b]	Lower back pain	8 mg/daily (2 days)	Intramuscular	Off-label use: this drug must not be used in children and adolescents aged younger than 16 years old because of safety concerns
M	13 years	Laryngeal edema, skin rash	Non-serious	Unknown	Trobalt®c 21 tablets 100 mg (retigabine)	Partial seizures	450 mg/daily (13 days)	Oral	Off-label use: this drug is indicated for patients aged ≥ 18 years

Table 4 (continued)

Sex (M/F)	Age	Adverse reaction (PT)	Seriousness	Outcome	Off-label/unlicensed drug (active substance)[a]	Therapeutic indication	Dosage/frequency (exposure length)	Route	Considerations
M	3 years	Sleep apnea syndrome	Non-serious	Not yet recovered	Fluimucil Antibiotico® 500 mg/4 mL powder and solvent for injectable solution, vaporizer and endotracheobronchial instillation, vials (thiamphenicol)	Adenoid hypertrophy	500 mg/daily (7 days)	Inhaled	Off-label use: this formulation is not licensed for children
M	11 years	Hypertonia, seizures	Serious (hospitalization)	Improvement	Plasil® 10 mg/10 mL syrup, flacon 120 mL (metoclopramide)	Meteorism	10 mL/daily (2 days)	Oral	Off-label use: the drug is not licensed for this therapeutic indication (see Sect. 4.8)
M	2 months	Urticaria	Serious (hospitalization)	Improvement	Klacid® 125 mg/5 mL granule for oral suspension, flacon 100 mL (clarithromycin)	Bronchial pneumonia	30 mg/daily (2 days)	Oral	Off-label use: this pediatric suspension is indicated in children aged from 6 months to 12 years
F	15 years	Urticaria	Non-serious	Improvement	Unidrox® 5 tablets 600 mg (prulifloxacin)	Urinary infection	600 mg/daily (2 days)	Oral	Off-label use: this drug must not be used in children and adolescents aged younger than 18 years old because of safety concerns
F	1 year	Erythema	Non-serious	Improvement	Dibase® 10.000 IU/mL oral drops, solution, flacon 10 mL (cholecalciferol)	Vitamin D deficiency	10 drops/daily (32 days)	Oral	Off-label use: dose greater than the maximum recommended daily dose for treatment (i.e., 4 drops/daily)
F	1 year	Skin rash	Non-serious	Improvement	Baby Rinolo C.M.® 2.4 g/100 mL + 0.015 g/100 mL Syrup, flacon 120 mL (paracetamol/chlorphenamine)	Cough	15 mL/daily (2 days)	Oral	Off-label use: the drug is contraindicated for use in patients aged < 3 years

Table 4 (continued)

Sex (M/F)	Age	Adverse reaction (PT)	Seriousness	Outcome	Off-label/unlicensed drug (active substance)[a]	Therapeutic indication	Dosage/frequency (exposure length)	Route	Considerations
M	17 years	Transaminases increased	Non-serious	Unknown	Zyprexa® 28 tablets 10 mg (olanzapine)	Infantile psychosis	5 mg/daily (146 days)	Oral	Off-label use: this drug is not indicated for children and adolescents aged younger than 18 years
F	17 years	Sedation complication	Non-serious	Improvement	Seroquel® 10 tablets 50 mg (quetiapine)	Bipolar disorder	50 mg/daily (114 days)	Oral	Off-label use: this drug must not be used in children and adolescents aged younger than 18 years

ECG electrocardiogram, *F* female, *ICSRs* Individual Case Safety Reports, *M* male, *PT* Preferred Term

[a] Brand name is indicated with the symbol ®

[b] Brand name not reported

[c] Active substance voluntarily withdrawn from the market in 2017 because of its limited usage

ICSRs were classified as serious and most of them required hospitalization, with over two thirds of serious cases involving children (aged 2–11 years) and adolescents (aged 12–17 years). However, around 80% of the ADRs completely recovered or improved. The majority of pediatric ICSRs were issued by physicians.

Interestingly, the ADR outcome was reported to be unknown in 20% of ICSRs. This is in line with the 22% of pediatric ICSRs without a known outcome previously reported in the whole RNF database [25]. Such a proportion of ICSRs indicates a need to improve the reporting of patients' outcomes and, more generally, the follow-up of the cases (by the local individuals responsible for pharmacovigilance) to obtain supplementary detailed information significant for their scientific evaluation. For this reason, since 22 June 2022, the new RNF has been operational, including a new international standard format (ISO ICSR format) for reporting suspected ADRs, which, as from 30 June, 2022, must be used in all EU countries to send and receive ICSRs to and from EudraVigilance [41]. The updated data structure of the new reporting form aims at improving the quality of ICSR content by adding specific data fields for each single suspected ADR: onset and end dates, seriousness, seriousness criteria, and outcome are provided at the ADR level and no longer at the case level [41, 42].

4.3 Pediatric ICSRs by Age Category and Sex

Our findings are largely consistent with several previous studies investigating pediatric reporting patterns in other national and international SRSs [25, 35–37, 43, 44]. In accordance with findings from VigiBase [37] and the Italian SRS database [25], most child ICSRs corresponded to children aged 2 up to 17 years and about 52% of all ICSRs concerned boys, mainly from 28 days to 17 years of age. The higher proportion of ICSRs that we found in the 2–11 and 12–17 years of age groups could be owing to the greater prevalence of drug use among older children [45], but it might be also related to the increasing demographic drop of the Calabria region [46]. However, the sex pattern might in part reflect the greater prevalence and incidence of some childhood diseases (e.g., asthma, certain infections, and epileptic syndromes) in the male sex [47, 48]. However, it is unclear whether boys are more likely to require medication or to be involved in an ICSR. Our data regarding sex differences across the age groups are inconsistent with previous findings showing prevalence rates for drug use as higher in adolescent girls than in adolescent boys, whereas an opposite trend had been reported for younger age categories [45]. Accordingly, male prevalence reversed in adolescents when examining the Italian SRS database [25] and other nationwide and supranational pharmacovigilance networks [35–37,

Table 5 Case-by-case clinical description of pediatric ICSRs resulting from drug misuse (no medical purpose)

Sex (M/F)	Age (years)	Adverse reaction (PT)	Seriousness	Outcome	Drug inappropriately used (active substance)[a]	Therapeutic indication	Dosage/ frequency (exposure length)	Route	Considerations
M	5	Vasculitis	Serious (hospitalization)	Unknown	Nurofen® 12 tablets 200 mg (ibuprofen)	Pyrexia	200 mg/total (1 day)	Oral	Misuse: the drug is contraindicated for use in children aged younger than 12 years
F	8	Urticaria	Non-serious	Improvement	Vivin C® 10 effervescent tablets 330 mg + 200 mg (acetylsalicylic acid/ ascorbic acid)	Pyrexia	530 mg/as required (2 days)	Oral	Misuse: the drug is contraindicated for use in children aged younger than 16 years

F female, *ICSRs* Individual Case Safety Reports, *M* male, *PT* Preferred Term

[a]Brand name is indicated with the symbol ®

43]. The changeability of reporting habits (including under-reporting) between different drugs and patient age categories may partially justify the different sex pattern reported in our analysis [44, 49].

4.4 Who Did Report Pediatric ADRs? What About the Seriousness of Reported Pediatric ADRs?

In line with national [25] and VigiBase data [37], physicians were the main reporters among healthcare workers, being actively involved in over 64% of pediatric ICSRs and over 80% of serious ICSRs. In fact, it has been reported that seriousness is a pivotal factor driving physicians' reporting [50]: this attitude may probably justify the small number of pediatric cases retrieved and analyzed in the study period. With rising age groups, the proportion of ICSRs decreased for physicians while increased for the other healthcare workers. Such an outcome does not offer an easy explanation. Moreover, our dataset did not include any information about the type of reporting physicians that it would have been diriment in this setting. However, we might speculate a gradual decreased involvement of pediatricians and a greater engagement of nurses and other healthcare workers in drug safety monitoring from infant to adolescence age. Indeed, Italian pediatricians are entrusted with children's medical care up to the age of 14 years, thus all pediatric clinical information (including specialist and hospital care) is stored in their medical records [45]. Similar to the Spanish pharmacovigilance system [36], physicians were more likely to report serious ADRs than other notifiers in our study, disagreeing with findings from the Danish ADR database [43].

4.5 Regional Healthcare Facilities Submitting Pediatric ICSRs to the RNF

During the study period, most child ICSRs submitted to the RNF database were issued from the "Mater Domini" University Hospital (Catanzaro), where a Regional Center of Drug Information was institutionalized by the end of 2010 thanks to the pharmacovigilance funding program during 2008–9. This center is carrying out active pharmacovigilance projects with the aim of improving regional spontaneous reporting and promoting a more rational use of medicines in clinical practice [21, 26]. Such an activity of disseminating pharmacovigilance knowledge and training for healthcare professionals could explain the increasing pediatric reporting rate observed in the early study period. Conversely, the recent declining reporting rate is worrying from a public health viewpoint because it might reflect a decreasing awareness of iatrogenic disease among reporters. It is also important to note that the large majority of child ICSRs (~67%) came from the area of Catanzaro where one Pediatric University Unit, four Pediatric Hospital Units, and one Neonatal Intensive Care Unit have been operational for many years.

4.6 Anatomical Main Groups (ATC First Level) and SOCs Involved in ADRs

Following stratification by drug group and SOC, ICSRs involving anti-infective, nervous system, and respiratory system drugs as suspected medicines and skin disorders as ADRs were proportionally higher in the child group compared with the adult group. Of note, the distribution of the

Table 6 Clinical description of pediatric ICSRs due to drug abuse

Sex (M/F)	Age (years)	Adverse reaction (PT)	Seriousness	Outcome	Drug/s (active substance/s)[a]	Dosage/frequency (exposure length)	Route	Considerations
F	15	Intentional self-injury, dizziness	Serious (other medically significant condition)	Unknown	Haldol® 10 mg oral drops, solution, flacon 30 mL (haloperidol)	Unknown (1 day)	Oral	
F	4	Drowsiness	Serious (hospitalization)	Unknown	Seroquel®[b] (quetiapine) Topamax®[b] (topiramate) Haldol®[b] (haloperidol)	Unknown (1 day)	Oral	
F	15	Intentional self-injury	Serious (other medically significant condition)	Unknown	Invega® 28 tablets 9 mg (paliperidone)	63 mg/total (1 day)	Oral	Report with no associated suspected adverse reaction/ symptoms: case not reportable as a valid ICSR and submission not requested (see Sect. 4.9)
M	7	Bullous dermatitis, macular rash	Serious (life-threatening)	Unknown	Bactrim® 80 mg/5 mL + 400 mg/5 mL Oral suspension, flacon 100 mL (trimethoprim/ sulfamethoxazole)	2 dosage units/ total (1 day)	Oral	
F	15	Intentional self-injury, dyspepsia	Non-serious	Improvement	Tardyfer® tablets 80 mg (ferrous sulfate)	800 mg/total (1 day)	Oral	
F	17	Intentional self-injury, hypotension	Non-serious	Improvement	Dulcolax® 24 tablets 5 mg (bisacodyl)	240 mg/total (1 day)	Oral	
F	17	Intentional self-injury, intentional overdose	Serious (other medically significant condition)	Unknown	Topamax® tablets 100 mg (topiramate)	1500 mg/total (1 day)	Oral	Report with no associated suspected adverse reaction/ symptoms: case not reportable as valid ICSR and submission not requested (see Sect. 4.9)

F female, *ICSRs* Individual Case Safety Reports, *M* male, *PT* Preferred Term

[a]Brand name is indicated with the symbol ®

[b]The exact dosage form is not reported

Table 7 Clinical description of pediatric ICSRs due to medication errors

Sex (M/F)	Age (years)	Adverse reaction (PT)	Seriousness	Drug/s (active substance/s)[a]	Route	Type of error	Considerations
F	8	Altered mood, lethargy, irritability, incorrect dose administered, wrong technique in product usage process	Non-serious	Keppra® 60 tablets 500 mg (levetiracetam)	Oral	Administration error	
M	2	Tachycardia, device use error	Non-serious	Fluspiral®b (fluticasone) Ventolin®b (salbutamol)	Inhaled	Administration error, overdose (accidental)	
M	2	Accidental overdose	Serious (hospitalization)	Tachipirina® 120 mg/5 mL Syrup, 120 mL flacon (paracetamol)	Oral	Accidental exposure	Medication error without clinical consequences: case not reportable as valid ICSR and submission not requested (see Sect. 4.9)
M	3	Accidental exposure	Non-serious	Bentelan® 10 tablets 1 mg (betamethasone)	Oral	Accidental exposure	Medication error without clinical consequences: case not reportable as valid ICSR and submission not requested (see Sect. 4.9)
F	4	Accidental exposure, ataxia, hallucination, failure of child resistant product closure	Serious (other medically significant condition)	Vermox® 20 mg/mL Oral suspension, 30 mL flacon (mebendazole)	Oral	Accidental exposure, packaging issues	
M	1	Nausea, accidental exposure	Serious (hospitalization)	Olmetec® 28 tablets 20 mg (olmesartan medoxomil)	Oral	Accidental exposure	
M	2	Nausea, accidental exposure	Non-serious	Replens®c 1970.5 mg/2.5 g Vaginal gel (purified water/policarbofil)	Oral	Accidental exposure	
F	12	Drowsiness, accidental exposure	Serious (hospitalization)	Amitriptilind	Oral	Accidental exposure	

F female, ICSRs Individual Case Safety Reports, M male, PT Preferred Term

[a]Brand name is indicated with the symbol ®

[b]The exact dosage form is not reported

[c]Medicinal product no longer authorized

[d]Brand name not reported

ICSRs in terms of suspected drugs and ADRs is in accordance with several other SRSs. The greater proportion of ICSRs relating to anti-infectives (excluding vaccines) and respiratory tract medicines for children than for adults supports the fact that asthma and infections are common childhood diseases [47]. In fact, these drug classes have been reported as the most commonly prescribed medicines in all pediatric age categories in Italy and other European countries [45]. Similarly, the higher proportion of ICSRs involving nervous system drugs in children as compared with adults is likely to reflect that some neurologic disorders (e.g., epilepsy) are common in childhood [51]. Moreover, children show an increased susceptibility to convulsions because their brain is still immature and continues to develop [52]. In addition, drug utilization research in children has proven a moderate prevalence of prescriptions for nervous system agents in European countries [45].

Congruent with previous studies excluding vaccine-related ICSRs [25, 37], skin adverse reactions were the most commonly notified ADRs for both children and adults, but they were reported more frequently in the child group than in the adult group. This could be owing to a greater susceptibility of children to cutaneous ADRs, based on their different skin physiology compared with adults [53]. Additionally, as previously confirmed [25], our findings corroborate that antibiotic use is well known to induce allergic reactions, especially in children [54]: antibiotics were the most frequently used drugs in relation to pediatric skin disorders in our study. Moreover, antibiotics were involved in over half of pediatric ICSRs reporting allergic skin reactions (see also Sect. 4.7). With regard to these findings, it should be considered that changeable patterns of disease, pharmacokinetics, and pharmacodynamics associated with pathophysiological changes could justify the differences in relation to drugs and ADRs observed across age. Consistent with results from the Spanish ADR database [36], *urticaria* was the most common PT described in pediatric ICSRs.

4.7 Single Suspected Drugs (Active Substances) Involved in Pediatric ADRs and Most Recurrent Pediatric Drug-ADR Pairs

At the level of a single suspected drug, amoxicillin/clavulanic acid was primarily involved in terms of the absolute number of pediatric ICSRs, ADRs, and serious ADRs. At the drug-ADR pair level, amoxicillin/clavulanic acid was the mostly implicated drug in skin disorders in the pediatric population. In particular, amoxicillin/clavulanic acid was involved in one-third of pediatric ICSRs related to allergic skin reactions from antibiotic use. Overall, antibiotics were associated with the highest number of ICSRs and serious ADRs in the pediatric population.

The involvement of antibiotics in the highest number of pediatric ICSRs reflects previous national and European results showing that this therapeutic group was the most commonly prescribed in children [45]. Among the most reported antibiotics, amoxicillin/clavulanic acid, ceftriaxone, and cefaclor were primarily associated with serious ADR occurrences. Moreover, in step with the RNF database [25], amoxicillin/clavulanic acid-skin reactions were the most recurrent pediatric drug-ADR pair. This trend is relatively predictable if considering that broad-spectrum penicillins and third-generation cephalosporins represent, respectively, the largest subgroup of systemic antibiotics and the most common cephalosporins prescribed to children in Italy [55]. Furthermore, a pediatric cohort study in five European countries has recently reported the highest prescription rate for amoxicillin plus an enzyme inhibitor in Italy [55]. Unsurprisingly, the outpatient pediatric prescription patterns seem to also support our ranking of amoxicillin/clavulanic acid, paracetamol, and ibuprofen as the top three most frequently reported active substances [45, 55].

Noteworthy, a possible pharmacokinetic drug–drug interaction was suspected in one pediatric case of hyperammonemia involving the combination of lamotrigine and valproic acid. Consistently, it has been previously reported that the combined use of lamotrigine with valproic acid might potentiate the risk of an elevated blood ammonia level and/or valproic acid-induced hyperammonemic encephalopathy [56]. This may be justified by the competition between lamotrigine and valproic acid for the UDP-glucuronosyltransferase metabolic pathway [57]. However, other studies showed opposite findings in relation to the aforementioned drug interaction [58, 59].

4.8 Off-Label/Unlicensed Drug Prescribing and ADR Occurrence in Pediatric Patients: Which Evidence?

Off-label/unlicensed drug use was recognized in 3.5% of pediatric ICSRs included in our analysis, suggesting that ADR occurrence was not significantly related to off-label prescribing. This evidence is in line with previous results of a French survey on pediatric drug prescribing [60]. However, off-label prescription in pediatric practice has been shown to be common among drugs reported as possible cause of ADRs in different pediatric patient settings [15, 61]. Such data inconsistency could be explained considering that pediatric ADRs are notably under-reported in SRSs [40], especially after off-label use [61]. Our ICSRs mostly concerned children and adolescents, although newborns had been identified as the most exposed group to off-label use in a previous literature review [7]. In contrast to the findings from a Swedish observational analysis of spontaneous ADR reports [15], in our study, off-label drug prescribing was

more frequently associated with non-serious ICSRs, but it mainly involved an age not labeled in both investigations. Consistent with our findings, drugs for the treatment of nervous system disorders ranked first among off-label ICSRs in a recent descriptive analysis of ADR notifications in the pediatric population from Germany [62]. Further, a previous prospective study in a pediatric hospital population in Germany had reported anti-infectives to be suspected more frequently in ADRs, especially those related to off-label drug use [63]. In addition, results from a very recent multicenter trial showed that off-label use of antidepressants and antipsychotics in children and adolescents was not a risk factor for the occurrence of serious ADRs [64]. However, off-label prescribing mainly involved an unapproved indication in previous French surveys investigating the relationship between off-label drug use and an increased risk of ADRs in pediatric patients [14, 60]. We also found skin disorders to be the most frequently reported pediatric ADRs associated with prescriptions outside the specifications of product license, while psychiatric disorders and mucocutaneous inflammatory reactions were the most common clinical conditions identified in the Swedish study [15]. With reference to serious ADRs linked to off-label drug use, the metoclopramide-hypertonia and seizures pair deserves a special consideration, based on previous regulatory actions in children. Noteworthy, in 2004, AIFA contraindicated the prescription of metoclopramide in patients aged younger than 16 years, according to the increasing number of neurological adverse events (including extrapyramidal disorders) reported in the RNF for this age group population [25]. After a formal re-assessment of safety and efficacy data, in October 2013, the European Medicines Agency restricted the use of metoclopramide in pediatric patients > 1 year of age as a second choice to prevent delayed nausea and vomiting after chemotherapy and to treat postoperative nausea and vomiting [65].

Among non-serious ICSRs, one case (submitted to the RNF in 2013) involved retigabine, which was voluntarily withdrawn from the market in 2017 because of its limited usage [66].

4.9 Drug Use Outside the Marketing Authorization and ADR Occurrence in Pediatric Patients. What About Misuse, Abuse, and Medication Error Cases?

Only two inappropriate self-medication cases were identified in the children category (aged 2–11 years), involving over-the-counter medicines. This confirms that self-medication bears the risk of misuse, further supporting the well-known link between over-the-counter use and ADRs. The risks of inappropriate self-medication also include incorrect self-diagnosis, delay in consulting a physician, use of excessive dosages, prolonged drug-use duration, drug interactions, polypharmacy, and drug abuse [67, 68]. In our study, a serious case of vasculitis involved ibuprofen, which represents one of the most common self-medication drugs [69]. Based on patients' ages in Table 5, their parents (or relatives) were probably responsible for the inappropriate use of nonprescription drugs, potentially owing to a lack of knowledge of anti-inflammatory and analgesic drug use. Indeed, inappropriate nonprescription use is often associated with limited information and low medication literacy in adults, resulting in a higher risk of hospitalization and serious adverse drug events [67].

Regarding drug abuse, five out of seven cases concerned intentional self-injury in adolescent girls and mainly involved nervous system drugs. Sixty percent ($n = 3$) of intentional self-injury episodes were classified as serious. An opposite sex pattern has been reported in a previous 10-year analysis of psychiatric ADRs in a Swedish pediatric population where boys were over-represented, particularly among serious cases [70]. Remarkably, we noted that two serious cases of intentional self-injury were not associated with any symptoms/suspected adverse events (e.g., asymptomatic abuse): these cases were improperly submitted to the RNF database because they were not reportable as valid ICSRs in accordance with GVP, Module VI [32].

Almost 2% of pediatric ICSRs were related to medication errors, half of which were serious and occurred mainly in children (aged 2–11 years). Medication errors represent an important concern both in hospital and outpatient settings. However, ADRs associated with medication errors are highly under-reported because of several barriers, including fear of potential disciplinary actions, fear of a lack of confidentiality, lack of time, and a lack of awareness that an error has occurred [71]. Therefore, it is essential to improve pediatric patient safety by fostering pharmacovigilance knowledge, by strengthening the continuous training of healthcare professionals, and by educating families in the prevention of medication error problems in the pediatric population. This last goal seems to be particularly important in our study context, considering that most medication error cases (accidental exposure) occurred in very young children probably because of their parents' carelessness. Moreover, a young boy experienced tachycardia related to an accidental overdose with respiratory drugs because of improper use of an inhalation device by his father. In EudraVigilance, pediatric ADR errors were mainly associated with inappropriate dose and indication [34] whereas errors related to accidental overdoses were prevalent in VigiBase [37].

A careful analysis of regional pediatric ADR errors showed that two cases were not associated with suspected clinical consequences/ADRs (e.g., asymptomatic medication errors) and, thus, they were not required to be submitted as ICSRs: medication errors without suspected ADRs do not

fall in the definition of a valid reportable ICSR in line with GVP, Module VI [32].

4.10 Comparing Calabrian Spontaneous Reporting Database with the RNF and Other Nationwide and Worldwide Pharmacovigilance Networks

Taken together, the characteristics of pediatric ICSRs stored in the Calabrian ADR database agree with those from the RNF and the other European and worldwide spontaneous reporting databases. This could reflect a relatively harmonized implementation of the new European pharmacovigilance legislation across countries [26]. Nevertheless, we observed small discrepancies with the RNF database, probably reflecting regional differences in drug exposure, reporting habits and/or region-specific active pharmacovigilance projects. We also reported small variations compared with other nationwide SRSs, which could be interpreted in a similar way.

4.11 Implications for Pharmacovigilance Activities

Of note, our analysis highlights some differences within child age groups and between children and adults, emphasizing the need for an age-specific approach when investigating epidemiological data on ADRs. This could help to target specific patient age groups that are more likely to have an increased risk for particular ADRs. Notably, in further supporting previous national and supranational findings [25, 34, 37] showing differences between pediatric and adult ICSRs in terms of drugs involved and ADRs, our descriptive analysis may help to identify pharmacovigilance activities that should be strengthened to reduce the burden of ADRs in children.

4.12 Strengths and Limitations

To the best of our knowledge, this study presents for the first time a descriptive overview of the characteristics of pediatric ICSRs reported to the Calabrian SRS database across one decade, also comparing pediatric with adult ICSRs. Our descriptive overview of all regional pediatric ICSRs suggests that the Calabrian SRS has enriched the RNF database by submitting particular information reflecting local drug prescribing patterns and specific drug surveillance projects coordinated by the Regional Center of Drug Information at "Mater Domini" University Hospital. However, caution must be used when interpreting the findings of the present study because of several limitations, mainly related to the small number of pediatric ICSRs. In particular, the ICSRs analyzed do not necessarily indicate variations in the risk of ADRs in different age groups, which can be confirmed only by pharmacoepidemiology research. Indeed, because of the

lack of drug-exposure data and the need for data about the background incidence of diseases in interpreting the study findings, estimation of the exact incidence of pediatric ADRs cannot be obtained through the analysis of the number of ADRs spontaneously reported in the Calabrian ADR database [34, 71]. Furthermore, the descriptive nature of our analysis does not allow a causality assessment between drugs and suspected ADRs.

In general, this study, as all analyses of SRS databases, suffers from other specific biases and confounding issues inherent to spontaneous reporting, such as the size and type of spontaneous reporting databases [72], the detail and quality of the reported data, and the length of time that a product has been on the market [73]. Noteworthy, different attitudes to the reporting activities and local pediatric pharmacovigilance projects [74] might have affected both the quantity and quality of pediatric ICSRs analyzed in our study. Similarly, the frequency of ICSRs for each single drug might have been influenced by the length of time on the market. Other biases possibly affecting the information reported in spontaneous ICSRs on ADRs are represented by the public attention to specific safety issues (i.e., notoriety bias) [75] and the absence of information on the severity of underlying illnesses. The presence or the lack of hospitals/hospital units for children in the different areas of the Calabria region represents another important limitation of our study findings. Last but not least, our results could be influenced by under-reporting that commonly hinders SRSs [49], resulting in a small number of reported cases compared with those that have actually occurred. This is true especially for ADRs resulting from off-label uses because of the worry of potential legal consequences [61]. Other factors associated with the under-reporting problem are the lack of motivation and time of reporting [76].

Nevertheless, SRS databases at both the local and national level remain a valuable tool to quickly detect drug safety signals, especially in vulnerable populations that are rarely represented in clinical trials, such as pediatric patients.

Apart from biases of spontaneous reporting, another possible study limitation deserves to be mentioned. Our search on pediatric ICSRs was stopped in 2019 because the "Pharmacovigilance and Drug Information Center" of the Calabria region no longer had the credentials to access the datasets on regional ADR reports stored in the RNF database. This regulation was adopted following the outbreak of the coronavirus disease 2019 pandemic. Therefore, we were not able to include and analyze regional ICSRs registered in the RNF database from January 2020 until December 2021. Accordingly, we are not aware of whether an updated search could provide different findings.

5 Conclusions

This study presents an overview of ADRs reported in the pediatric population of the Calabria region as well as offering a reference point for additional research on specific child age categories and on given drugs with respect to their pattern of use. The pediatric ADR reporting rate peaked in 2015 but has declined in more recent years. This trend reflects an initial positive impact of the educational and training activities carried out through the AIFA-funded projects coordinated by the "Mater Domini" University Hospital of Catanzaro. However, the recent declining reporting rate suggests that specific initiatives to stimulate pediatric ADR surveillance need to be steadily supported in order to engage all stakeholders and to obtain steadier results in the long term.

Prevalence of off-label prescribing is low among drugs reported to have caused pediatric ADRs; however, the latter remain an important problem in children after off-label drug use. In this context, pediatric pharmacovigilance plays an essential role for a proper benefit-risk assessment of off-label drug use.

Our descriptive overview of ICSRs underscores some differences across child age groups, between boys and girls, and both in the frequency and the type of ICSRs between children and adults. These results emphasize the need for using a drug-specific, sex-specific, or age-specific approach when analyzing pharmacovigilance databases to evaluate the safety of drugs in pediatric patients. More importantly, in further defining how pediatric ADRs show different patterns from those of adults, our findings could be used to inform regional pharmacovigilance activities in order to improve drug use and monitoring in children.

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Declarations

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Conflict of interest The authors declare that they have no potential conflicts of interest that might be relevant to the content of this article.

Ethical approval Ethics approval was not considered necessary for this study because of the nature of the study, which is a retrospective analysis of reports registered in the Italian pharmacovigilance database coming from the Calabria region over 10-year period. Minimal personal data were collected and were codified in order to guarantee confidentiality.

Consent to participate Not applicable. Patient consent was waived because of the type of study, being a retrospective analysis, and no patient interviews were required.

Consent for publication All the authors give the publisher license of the copyright which provides the publisher with the exclusive right to publish and sell the research findings.

Availability of data and material The datasets for this manuscript are not publicly available because pharmacovigilance data in a single non-aggregated form are available only under a specific authorization released by the Italian Medicines Agency, which is the custodian of data stored in the RNF database. Requests to access the datasets should be directed to the Italian Medicines Agency.

Code availability The RNF codes were used in order to guarantee confidentiality.

Authors' contributions CL and GDS contributed to the development and formulation of the research question. BP performed the data extraction. CL, CDS, CP, and IC performed the data analysis, with assistance from the other authors. All authors contributed to the interpretation of the results. The manuscript was primarily written by CL, and it was revised and edited by RC and GDS. All authors have read and approved the final version of the manuscript.

References

1. Tomasi PA, Egger GF, Pallidis C, Saint-Raymond A. Enabling development of paediatric medicines in Europe: 10 years of the EU paediatric regulation. Pediatr Drugs. 2017;19:505–13.
2. Bourgeois FT, Murthy S, Pinto C, Olson KL, Ioannidis JPA, Mandl KD. Pediatric versus adult drug trials for conditions with high pediatric disease burden. Pediatrics. 2012;130:285–92.
3. Leitzen S, Dubrall D, Toni I, Stingl J, Schulz M, Schmid M, et al. Analysis of the reporting of adverse drug reactions in children and adolescents in Germany in the time period from 2000 to 2019. PLoS ONE. 2021;16: e0247446.
4. Martinez-Castaldi C, Silverstein M, Bauchner H. Child versus adult research: the gap in high-quality study design. Pediatrics. 2008;122:52–7.
5. Lindkvist J, Airaksinen M, Kaukonen AM, Klaukka T, Hoppu K. Evolution of paediatric off-label use after new significant medicines become available for adults: a study on triptans in Finnish children 1994–2007. Br J Clin Pharmacol. 2011;71:929–35.
6. Elzagallaai AA, Greff MJE, Rieder MJ. Adverse drug reactions in children: the double-edged sword of therapeutics. Clin Pharmacol Ther. 2017;101:725–35.
7. Cuzzolin L, Atzei A, Fanos V. Off-label and unlicensed prescribing for newborns and children in different settings: a review of the literature and a consideration about drug safety. Expert Opin Drug Saf. 2006;5:703–18.
8. Conroy S, Raffaelli MP, Rocchi F, Bonati M, Jong G, De Hoog M, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. BMJ. 2000;320:79–82.
9. Carnovale C, Conti V, Perrone V, Antoniazzi S, Pozzi M, Merlino L, et al. Paediatric drug use with focus on off-label prescriptions in Lombardy and implications for therapeutic approaches. Eur J Pediatr. 2013;172:1679–85.
10. Bernardini R, Vespasiani GT, Giannetti A. An overview of off-label use of humanized monoclonal antibodies in paediatrics. Medicina. 2022;58:625.
11. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology: drug disposition, action, and therapy in infants and children. N Engl J Med. 2003;349:1157–67.

12. Saiyed MM, Lalwani T, Rana D. Is off-label use a risk factor for adverse drug reactions in pediatric patients? A prospective study in an Indian tertiary care hospital. Int J Risk Saf Med. 2015;27:45–53.

13. Turner S, Nunn AJ, Fielding K, Choonara I. Adverse drug reactions to unlicensed and off-label drugs on paediatric wards: a prospective study. Acta Paediatr Int J Paediatr. 1999;88:965–8.

14. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol. 2002;54:665–70.

15. Ufer M, Kimland E, Bergman U. Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf. 2004;13:147–52.

16. Gore R, Chugh PK, Tripathi CD, Lhamo Y, Gautam S. Pediatric off-label and unlicensed drug use and its implications. Curr Clin Pharmacol. 2017;12:18–25.

17. Bouquet É, Star K, Jonville-Béra AP, Durrieu G. Pharmacovigilance in pediatrics. Therapie. 2018;73:171–80.

18. Choonara I. Regulation of drugs for children in Europe. BMJ. 2007;335:1221–2.

19. Loke YK, Golder su P, Vandenbroucke JP. Comprehensive evaluations of the adverse effects of drugs: importance of appropriate study selection and data sources. Ther Adv Drug Saf. 2011;2:59–68.

20. Star K. Detecting unexpected adverse drug reactions in children. Pediatr Drugs. 2011;13:71–3.

21. Mazzitello C, Esposito S, De Francesco A, Capuano A, Russo E, De Sarro G. Pharmacovigilance in Italy: an overview. J Pharmacol Pharmacother. 2013;4:S20–8.

22. Baldo P, Francescon S, Fornasier G. Pharmacovigilance workflow in Europe and Italy and pharmacovigilance terminology. Int J Clin Pharm. 2018;40:748–53.

23. European Medicines Agency. New EudraVigilance system is live. https://www.ema.europa.eu/en/news/new-eudravigilance-system-live. Accessed 4 Aug 2022.

24. Italian Medicines Agency. European eudravigilance system. https://www.aifa.gov.it/en/web/guest/sistema-europeo-eudravigilance. Accessed 4 Aug 2022.

25. Ferrajolo C, Capuano A, Trifirò G, Moretti U, Rossi F, Santuccio C. Pediatric drug safety surveillance in Italian pharmacovigilance network: an overview of adverse drug reactions in the years 2001–2012. Expert Opin Drug Saf. 2014;13:S9-20.

26. Leporini C, Marrazzo G, Mumoli L, Esposito S, Gallelli L, Mangano G, et al. Adverse drug reactions reporting in Calabria (Southern Italy) in the four-year period 2011–2014: impact of a regional pharmacovigilance project in light of the new European Legislation. Expert Opin Drug Saf. 2017;16:515–22.

27. Rafaniello C, Ferrajolo C, Sullo MG, Sessa M, Sportiello L, Balzano A, et al. Risk of gastrointestinal complications associated to NSAIDs, low-dose aspirin and their combinations: results of a pharmacovigilance reporting system. Pharmacol Res. 2016;104:108–14.

28. WHO Collaborating Centre for Drug Statistics Methodology, Norwegian Institute of Public Health. ATC index with DDDs. https://www.whocc.no/atc_ddd_index/. Accessed 16 Nov 2021.

29. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). Drug Saf. 1999;20:109–17.

30. Regione Calabria. Portale Istituzionale. https://www.regione.calabria.it/website/. Accessed 2 Aug 2022.

31. Corsello G, Ferrara P, Chiamenti G, Nigri L, Campanozzi A, Pettoello-Mantovani M. The child health care system in Italy. J Pediatr. 2016;177:S116–26.

32. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VI: collection, management and submission of reports of suspected reactions to medicinal products (Rev 2). https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-submission-reports_en.pdf. Accessed 17 Nov 2021.

33. European Medicines Agency. ICH Topic E 11. Clinical investigation of medicinal products in the paediatric population: note for guidance on clinical investigation of medicinal products in the paediatric population. https://www.ema.europa.eu/en/documents/scientific-guideline/international-conference-harmonisation-technical-requirements-registration-pharmaceuticals-human-use-en-1.pdf. Accessed 7 Apr 2022.

34. Blake KV, Zaccaria C, Domergue F, La Mache E, Saint-Raymond A, Hidalgo-Simon A. Comparison between paediatric and adult suspected adverse drug reactions reported to the European medicines agency: implications for pharmacovigilance. Paediatr Drugs. 2014;16:309–19.

35. Nogueira Guerra L, Herdeiro MT, Ribeiro-Vaz I, Clérigo MIP, Rocha C, Araújo A, et al. Adverse drug reactions in children: a ten-year review of reporting to the Portuguese pharmacovigilance system. Expert Opin Drug Saf. 2015;14:1805–13.

36. Aldea A, García Sánchez-Colomer M, Fernández Quintana E, García SM. Paediatric adverse drug reactions reported to the Spanish pharmacovigilance system from 2004 to 2009. Eur J Clin Pharmacol. 2012;68:1329–38.

37. Star K, Norén GN, Nordin K, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. Drug Saf. 2011;34:415–28.

38. ISTAT. Struttura della popolazione e indicatori demografici della regione Calabria negli ultimi anni. Elaborazioni su dati ISTAT. https://www.tuttitalia.it/calabria/statistiche/indici-demografici-struttura-popolazione/. Accessed 30 July 2022.

39. ISTAT. Struttura della popolazione e indicatori demografici dell'Italia negli ultimi anni. Elaborazioni su dati ISTAT. https://www.tuttitalia.it/statistiche/indici-demografici-struttura-popolazione/. Accessed 30 July 2022.

40. Bracken L, Nunn A, Peak M, Turner M. Challenges in the assessment of adverse drug reactions in children and neonates. Adverse Drug React Bull. 2018;308:1191–4.

41. Italian Medicines Agency. New National Pharmacovigilance Network (RNF) lauched. https://www.aifa.gov.it/en/-/al-via-la-nuova-rnf. Accessed 1 Aug 2022.

42. European Medicines Agency. Mandatory use of international standard for the reporting of side effects to improve safety of medicines. https://www.ema.europa.eu/en/news/mandatory-use-international-standard-reporting-side-effects-improve-safety-medicines. Accessed 1 Aug 2022.

43. Aagaard L, Weber CB, Hansen EH. Adverse drug reactions in the paediatric population in Denmark: a retrospective analysis of reports made to the Danish Medicines Agency from 1998 to 2007. Drug Saf. 2010;33:327–39.

44. Wallerstedt SM, Brunlöf G, Sundström A. Rates of spontaneous reports of adverse drug reactions for drugs reported in children: a cross-sectional study with data from the Swedish Adverse Drug Reaction Database and the Swedish Prescribed Drug Register. Drug Saf. 2011;34:669–82.

45. Sturkenboom MCJM, Verhamme KMC, Nicolosi A, Murray ML, Neubert A, Caudri D, et al. Drug use in children: cohort study in three European countries. BMJ. 2008;337: a2245.

46. ISTAT. Popolazione Calabria 2001–2020. Grafici e statistiche su dati ISTAT al 31 dicembre di ogni anno. https://www.tuttitalia.it/calabria/statistiche/popolazione-andamento-demografico/. Accessed 24 Nov 2021.

47. Dey AN, Schiller JS, Tai DA. Summary health statistics for U.S. children: National Health Interview Survey, 2002. Vital Health Stat. 2004;10:1–78.

48. Fiest KM, Sauro KM, Wiebe S, Patten SB, Kwon CS, Dykeman J, et al. Prevalence and incidence of epilepsy. Neurology. 2017;88:296–303.

49. Hazell L, Shakir SAW. Under-reporting of adverse drug reactions: a systematic review. Drug Saf. 2006;29:385–96.

50. Belton KJ, Gram LF, Royer RJ, Feely J, McGettigan P, Velo GP, et al. Attitude survey of adverse drug-reaction reporting by health care professionals across the European Union. Eur J Clin Pharmacol. 1997;52:423–7.

51. Hsia Y, Neubert A, Sturkenboom MCJM, Murray ML, Verhamme KMC, Sen F, et al. Comparison of antiepileptic drug prescribing in children in three European countries. Epilepsia. 2010;51:789–96.

52. Benes FM. The development of the prefrontal cortex: the maturation of neurotransmitter systems and their interactions. In: Cicchetti D, Cohen DJ (eds) Developmental psychopathology. 2nd ed. Hoboken, NJ: Wiley; 2015. pp. 216–58.

53. Fluhr JW, Pfisterer S, Gloor M. Direct comparison of skin physiology in children and adults with bioengineering methods. Pediatr Dermatol. 2000;17:436–9.

54. Gruchalla RS, Pirmohamed M. Antibiotic allergy. N Engl J Med. 2006;354:601–9.

55. Holstiege J, Schink T, Molokhia M, Mazzaglia G, Innocenti F, Oteri A, et al. Systemic antibiotic prescribing to paediatric outpatients in 5 European countries: a population-based cohort study. BMC Pediatr. 2014;14:1–10.

56. Fan CC, Huang MC, Liu HC. Lamotrigine might potentiate valproic acid-induced hyperammonemic encephalopathy. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1747–8.

57. Koristkova B, Grundmann M, Brozmanova H, Kacirova I. Lamotrigine drug interactions in combination therapy and the influence of therapeutic drug monitoring on clinical outcomes in paediatric patients. Basic Clin Pharmacol Toxicol. 2019;125:26–33.

58. Tseng YL, Huang CR, Lin CH, Lu YT, Lu CH, Chen NC, et al. Risk factors of hyperammonemia in patients with epilepsy under valproic acid therapy. Medicine (Baltimore). 2014;93: e66.

59. Yamamoto Y, Takahashi Y, Imai K, Mishima N, Kagawa Y, Inoue Y. Changing incidence of hyperammonemia in Japan from 2006 to 2013: expansion of new antiepileptic drugs reduces the risk of hyperammonemia. Eur J Clin Pharmacol. 2015;71:1517–24.

60. Palmaro A, Bissuel R, Renaud N, Durrieu G, Escourrou B, Oustric S, et al. Off-label prescribing in pediatric outpatients. Pediatrics. 2015;135:49–58.

61. Wimmer S, Neubert A, Rascher W. The safety of drug therapy in children. Dtsch Arztebl Int. 2015;112:781–7.

62. Dubrall D, Leitzen S, Toni I, Stingl J, Schulz M, Schmid M, et al. Descriptive analysis of adverse drug reaction reports in children and adolescents from Germany: frequently reported reactions and suspected drugs. BMC Pharmacol Toxicol. 2021;22:56.

63. Haffner S, Von Laue N, Wirth S, Thürmann PA. Detecting adverse drug reactions on paediatric wards: intensified surveillance versus computerised screening of laboratory values. Drug Saf. 2005;28:453–64.

64. Egberts KM, Gerlach M, Correll CU, Plener PL, Malzahn U, Heuschmann P, et al. Serious adverse drug reactions in children and adolescents treated on- and off-label with antidepressants and antipsychotics in clinical practice. Pharmacopsychiatry. 2022.

65. European Medicines Agency. European Medicines Agency recommends changes to the use of metoclopramide. https://www.ema.europa.eu/en/news/european-medicines-agency-recommends-changes-use-metoclopramide. Accessed 22 Mar 2022.

66. Brickel N, Hewett K, Rayner K, Mcdonald S, De'ath J, Daniluk J, et al. Safety of retigabine in adults with partial-onset seizures after long-term exposure: focus on unexpected ophthalmological and dermatological events. 2020;102:106580.

67. Lee CH, Chang FC, Der HS, Chi HY, Huang LJ, Yeh MK. Inappropriate self-medication among adolescents and its association with lower medication literacy and substance use. PLoS ONE. 2017;12: e0189199.

68. Ruiz M. Risks of self-medication practices. Curr Drug Saf. 2010;5:315–23.

69. Kusturica MP, Tomic Z, Bukumiric Z, Ninkovic L, Tomas A, Stilinovic N, et al. Home pharmacies in Serbia: an insight into self-medication practice. Int J Clin Pharm. 2015;37:373–8.

70. Bygdell M, Brunlöf G, Wallerstedt SM, Kindblom JM. Psychiatric adverse drug reactions reported during a 10-year period in the Swedish pediatric population. Pharmacoepidemiol Drug Saf. 2012;21:79–86.

71. López-Valverde L, Domènech È, Roguera M, Gich I, Farré M, Rodrigo C, et al. Spontaneous reporting of adverse drug reactions in a pediatric population in a tertiary hospital. J Clin Med. 2021;10:5531.

72. Caster O, Aoki Y, Gattepaille LM, Grundmark B. Disproportionality analysis for pharmacovigilance signal detection in small databases or subsets: recommendations for limiting false-positive associations. Drug Saf. 2020;43:479–87.

73. Begaud B, Moride Y, Tubert-Bitter P, Chaslerie A, Haramburu F. False-positives in spontaneous reporting: should we worry about them? Br J Clin Pharmacol. 1994;38:401–4.

74. Saullo F, Saullo E, Caloiero M, Menniti M, Carbone C, Chimirri S, et al. A questionnaire-based study in Calabria on the knowledge of off-label drugs in pediatrics. J Pharmacol Pharmacother. 2013;4:S51–4.

75. Pariente A, Gregoire F, Fourrier-Reglat A, Haramburu F, Moore N. Impact of safety alerts on measures of disproportionality in spontaneous reporting databases: the notoriety bias. Drug Saf. 2007;30:891–8.

76. Goldman SA. Limitations and strengths of spontaneous reports data. Clin Ther. 1998;20:C40–4.