

# EXPERT OPINION

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## The importance of monitoring adverse drug reactions in pediatric patients: the results of a national surveillance program in Italy

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**Objective:** To gain information on safety of drugs used in pediatrics through a 4-year post-marketing active pharmacovigilance program. The program sampled the Italian population and was termed 'Monitoring of the Adverse Effects in Pediatric population' (MEAP).

**Research design and methods:** Adverse drug reactions (ADRs) were collected for individuals aged 0 – 17 years treated in hospitals and territorial health services in Lombardy, Tuscany, Apulia and Campania; located to gain an appropriate sampling of the population. ADRs were evaluated using the Adverse Drug Reaction Probability Scale (Naranjo) and analyzed with respect to time, age, sex, category of ADR, seriousness, suspected medicines, type of reporter and off-label use.

**Results:** We collected and analyzed reports from 3539 ADRs. Vaccines, anti-neoplastic and psychotropic drugs were the most frequently pharmacotherapeutic subgroups involved. Seventeen percent of reported ADRs were serious; of them fever, vomiting and angioedema were the most frequently reported. Eight percent of ADRs were associated with off-label use, and 10% were unknown ADRs. Analysis of these revealed possible strategies of therapy optimization.

**Conclusions:** The MEAP project demonstrated that active post-marketing pharmacovigilance programs are a valid strategy to increase awareness on pediatric pharmacology, reduce underreporting and provide information on drug actions in pediatrics. This information enhances drug therapy optimization in the pediatric patients.

**Keywords:** adverse drug reaction, off-label drug use, pediatric, pharmacovigilance, post-marketing surveillance

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### 1. Introduction

The relative absence of pharmacological and toxicological information on drugs intended for pediatric use is a significant, yet unresolved issue. Children are in general excluded from premarketing clinical trials unless the medicine is specifically developed for them, limiting access to age-specific information on dose recommendations, efficacy and risks. Physiological parameters in neonates, infants, children and adults differ significantly from each other. This leads to significant differences in absorption, distribution, metabolism and excretion of drugs rendering impossible

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to transfer reliably information obtained in adults to children, infants and neonates [1,2].

The off-label use of drugs in the pediatric setting currently ranges between 18 and 65% of prescriptions in hospitals and between 11 and 31% in primary care settings [3], with high rates of prescription of drugs contraindicated in children, such as fluoroquinolones [4]. The off-label/unlicensed use in pediatric patients is associated with an increased risk of developing adverse drug reactions (ADRs) [5].

The pediatric regulation implemented by the regulatory agencies has significantly increased the number of clinical trials in children [6]. Yet, post-marketing studies will always be an important tool to establish the safety of drugs in both adult and pediatric populations. Spontaneous reporting is more important in children because of the large extent of off-label use and thus missing knowledge on correct doses and ADRs [7].

To enhance high-quality spontaneous reporting of ADRs in children from hospital and family pediatricians, the Clinical Pharmacology and Pediatric Units of the L. Sacco University Hospital in collaboration with the Italian Medicines Agency (AIFA) and the Pharmacovigilance Regional Centres of Lombardy, Campania, Tuscany and Apulia developed a nationwide pharmacovigilance project, named 'Monitoring of the Adverse Effects in Pediatric population' (MEAP). Herein, we illustrate the results obtained within this program.

## 2. Methods

The MEAP project was a prospective active pharmacovigilance project, to assess ADRs in the pediatric population, coordinated by the Unit of Clinical Pharmacology of the L. Sacco University Hospital. It started in 2009 in Lombardy, was extended in 2012 to Campania Tuscany and Apulia and ended in 2013. The project involved 18 hospitals and 20 local territorial health districts (Azienda Sanitaria Locale-ASL). It also included a scientific institute specialized in oncology and one in neurological rehabilitation. The involved institutions serve different catchment areas and altogether account for a significant fraction of the overall hospitals and ASL located in the regions involved in our study. Further, they are distributed to represent the whole regional territory and provide a comprehensive overview of pediatric ADRs.

Because of the dimension and distribution of the involved regions, the results may be considered representative of the Italian situation as a whole.

In each center, a physician was selected and was informed about the aims of the MEAP study; for each structure, a monitor selected by the Pharmacovigilance Center of the involved regions with a degree in pharmacy, medicine or biology was assigned who were appropriately trained with an intensive course on theoretical and practical aspects of pharmacovigilance in pediatric setting.

We followed the definition of ADR as stated by the European Directive DIR 2001/83/EC Art 1(11), that is, a response

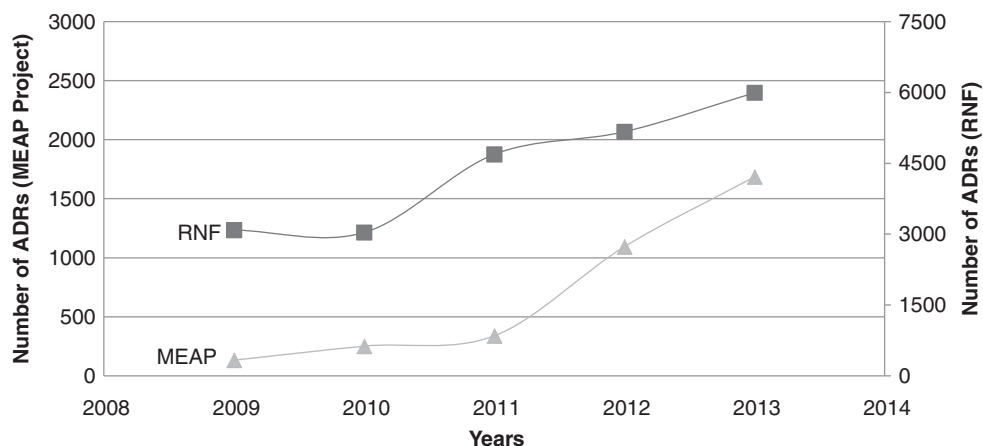
to a medicinal product that is noxious and unintended [8]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Art 101 (1) in the same directive clarifies that an adverse reaction may arise from the use of a product within or outside the terms of its marketing authorization (off-label use, overdose, misuse, abuse and medication errors) or from occupational exposure [8].

All physicians were provided with the official Italian ADRs reporting form in an online version, in order to simplify the compilation. ADR diagnoses were confirmed by the physician in charge in each institution and final causality assessed by the coordinating center using the Adverse Drug Reaction Probability Scale (Naranjo) [9]. Causality assessment for vaccines was done with the WHO causality assessment scale [10]. As we did not find significant differences with previous studies [11,12], we choose to report here only the causality assessment for drugs.

The following information on each patient experiencing an ADR was collected: date of birth and gender; clinical status; ongoing therapy (suspected and concomitant drugs, route, duration and dosage); therapeutic indication of suspected drug and concomitant diagnosis. ADRs were codified as detailed by the Medical Dictionary for Regulatory activities (MedDRA) [13] and organized according to the System Organ Class (SOC) classification and preferred terms; history or familiarity for previous ADRs; management and outcome of the ADR. Collected ADRs were subdivided into age groups based on the International Conference on Harmonisation guideline on Clinical Investigation of Medicinal Products in the Pediatric Population [14]. The notoriety of the event for each drug involved was assessed by the terms provided in the Summary of Product Characteristics (SmPC). ADRs were classified as serious or non-serious according to the WHO Critical Term List [15]. The off-label definition used to describe ADRs consequent to an off-label use of the drugs is the following 'all uses of a marketed drug not detailed in the SPC including therapeutic indication, use in age-subset, appropriate dosage, pharmaceutical form and route of administration' [16]. We considered a use to be off-label if the drug was used in age-subsets that were not detailed in the SPC [16]. Bimonthly reports containing an overview of the ADRs, patients' features and drugs were made available to all participating centers. For each unknown and serious ADRs, an additional specific report was prepared and made available.

### 2.1 Limits and strengths

We cannot exclude, despite the active nature of the project, the problem of underreporting, a known issue in this type of studies [17]. In addition, the study was initiated at different times in the four regions involved. Some ADR reports might have been counted in more than one Anatomical Therapeutic System (ATC) or SOC group when more than one suspected substance was involved or when substances belonged to more



**Figure 1. Trend in the reporting rate of ADR in the MEAP project.** Shown is the yearly reporting rate for ADRs observed in the MEAP project (triangles) versus those registered in the same period in the Italian network of pharmacovigilance (RNF) (squares).

ADRs: Adverse drug reactions; MEAP: Monitoring of the Adverse Effects in Pediatric population.

than one ATC group. The lack of denominator data such as the user population or drug exposure patterns is another limitation. The strength of this study is that it was designed to sample pediatric use of drugs nationwide; in addition it relied on spontaneous reports, recognized to be one of the system providing essential information of clinical importance in the absence of personal clinical records.

### 3. Results

We detected 3539 cases of pediatric ADRs stemming from 18 hospital (66%), 20 ASL (26%) and 2 two scientific institutes (8%), distributed in the four regions involved in the project. The total number of annual reports increased from 2011 to 2013. In the same period, an increase in the reporting of pediatric ADRs was observed also in the National Pharmacovigilance Network most likely because of an improvement of pharmacovigilance activities by AIFA and Regional Pharmacovigilance Centres; however, this was smaller in size, indicating the efficacy of specific active pharmacovigilance programs (Figure 1).

Indeed the project led to an increase in spontaneous reporting to the coordinating center by pediatricians from centers not involved in the project, which reached 6% in the years 2012 – 2013. The number of ADRs reported in hospitals and by the family pediatricians of the local territorial health districts was 70 and 30%, respectively. The greatest numbers of ADR cases were observed in the age groups 2 – 11 years (48.4%) and 1 month to 2 years (26%) with a peak in 1-year-old patients (17%). No gender predominance was observed.

The drugs most frequently reported to be associated with ADRs belonged to the anti-infectives for systemic use (60%), nervous system (14%) and antineoplastic and

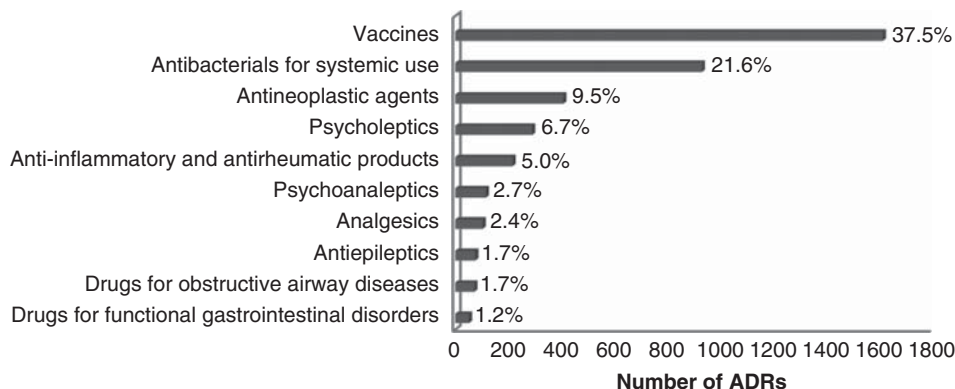
immune-modulating agents (10%) ATC groups. In terms of therapeutic main groups involved (ATC level 2) vaccines and antibacterials for systemic use, antineoplastic agents and psychoactive drugs were those most frequently involved (Figure 2). The high number of vaccine-related ADRs confirms previous findings in the literature [18-21]. The total number of molecules involved in ADRs was 395, with the most reported substances being amoxicillin, risperidone, paracetamol and vincristine.

Skin and subcutaneous tissue disease was the MedDRA SOCs most frequently involved followed by the general disorders and administration site conditions, gastrointestinal disorders and nervous system disorders SOCs (Figure 3).

Among the 3539 cases, 17% were classified as serious. The top reported serious reactions were fever, vomiting, urticaria, angioedema and drowsiness. Vaccines (hexavalent, antipneumococcal, anti-meningococcus, trivalent measles/mumps/rubella), nonsteroidal anti-inflammatory drugs (paracetamol, ibuprofen), antineoplastic agents (vincristine, methotrexate), anti-infectives agents (amoxicillin, ceftriaxone, clarithromycin), antihistamines drugs (oxatomide) were those mostly involved in serious ADRs development (Table 1).

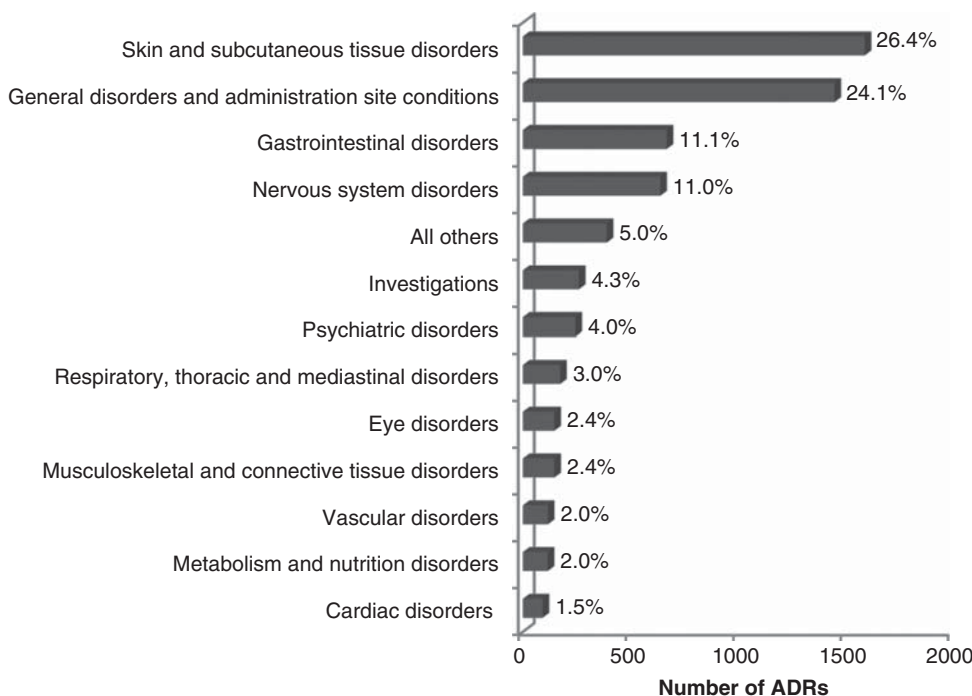
We found that 10% of ADRs was previously unknown, that is, not specifically reported in the SmPC. Domperidone inducing severe vomiting in dysphagic children and the human papilloma virus (HPV) vaccines inducing acute disseminated encephalomyelitis and paresthesia were the unknown reaction most frequently reported. Chlorpromazine inducing tinnitus and oxatomide inducing dysarthria, sleep disruption and proprioceptive delirium due to paracetamol were also relatively frequent as previously unknown ADRs.

We also found that > 8% of pediatric ADRs was related to an off-label use, that is, to a use in age-subsets not detailed in the SPC, mostly following etoposide (14%)



**Figure 2. Therapeutic groups mostly involved in ADRs.** Shown on the x axis is the number of ADRs registered in the MEAP project subdivided according to the ATC classification. The percentage relative to the total for each ATC group is reported alongside the relevant bar. Shown are the 10 most relevant ATC groups.

ADRs: Adverse drug reactions; ATC: Anatomical therapeutic system; MEAP: Monitoring of the Adverse Effects in Pediatric population.



**Figure 3. ADR distribution in the various systems and organs according to the MedDRA SOC classification.** Shown on the x-axis is the number of ADRs registered in the MEAP project subdivided according to the MedDRA SOC classification. The percentage relative to the total for each MedDRA SOC group is reported alongside the relevant bar.

ADRs: Adverse drug reactions; MEAP: Monitoring of the Adverse Effects in Pediatric population; MedDRA: Medical dictionary for regulatory activities; SOC: System organ class.

and aripiprazole (12%) use, followed by alogliquin, olanzapine and levofloxacin. Clinical events reported were extrapyramidal syndrome, irritability, weight gain, seizures and aggression (Table 1).

Most of the ADRs related to drugs were classified as possible (94%), followed by probable (6%) and definite (< 1%). No uncertain ADRs were detected in our study.

#### 4. Discussion

The morbidity and mortality in pediatric population due to drug-induced reactions is still unacceptably high [22], with incidence rates ranging from 0.4 to 10.3% for ADRs causing hospital admission and from 0.6 to 16.8% for ADRs occurring during hospital stay [23].

**Table 1. Most commonly reported serious ADRs and ADRs related to the off-label drug use.**

Active substance	% reporting rate	ADRs mostly reported
<i>Serious ADRs</i>		
Hexavalent vaccine	7.1	Hypotonia, loss of consciousness, pyrexia
Pneumococcal vaccine	6.6	Fever, hypotonia, loss of consciousness
Amoxicillin + clavulanic acid	5.1	Angioedema, urticaria, vomiting
Measles, mumps and rubella vaccine	3.6	Crisis seizure, fever, urticaria
Paracetamol	3.4	ALT increased, giant rash, urticaria
Human papilloma virus vaccines	3.4	Headache, pain on others, PAP smear positive
Ibuprofen	2.7	Ecchymosis, edema, thrombocytopenia
Ceftriaxone	2.6	Anaphylaxis, angioedema, urticaria
Vincristine	2.4	Febrile aplasia, hypertension, polyneuropathy
Domperidone	1.7	Aggravated vomiting, gastric stasis, increased peristalsis
Oxatomide	1.7	Drowsiness, overdose, somnolence
Clarithromycin	1.6	Angioedema, cough, urticaria
Methotrexate	1.6	Acute renal failure, headache, mucositis
Risperidone	1.5	Amenorrhoea, angioedema, psychomotor agitation
<i>Off-label-related ADRs</i>		
Etoposide	14.0	Diarrhea, gingivostomatitis, vomiting
Aripiprazole	12.0	Alkaline phosphatase increased, irritability, weight gain
Aloperidol	11.0	Extrapyramidal syndrome, sedation, shortness of breath
Olanzapine	4.4	Aggression, seizures, weight gain
Levofloxacin	4.0	Hyperemia, palpitation, seizure
Fentanyl	3.0	Bronchospasm, hives, rash
Fluconazole	3.0	Hyperpigmentation of the skin, rash
Quetiapine	3.0	Acute psychosis, behavior disorder, irritability, motor tic
Efavirenz + emtricitabina + tenofovir disoproxil	2.2	Trigeminal neuralgia, urticaria
Lamotrigine	2.2	Fever, hives, urticaria
Alprazolam	2.0	Regurgitation infant, speech disorder
Metoclopramide	2.0	Extrapyramidal syndrome, diplopia
Rituximab	2.0	Burning the esophagus, thrombocytosis

Shown in the Table 1 are the drugs involved, alongside the type of ADR. The first section refers to the serious ADRs, the second one to those related to an off-label use.

ADRs: Adverse drug reactions.

Although the missing of denominator data, such as the user population or drug exposure patterns, does not permit a direct comparison with other studies, the number of ADRs reported in this first Italian pediatric pharmacovigilance project is considerably high and supports data from previous surveys showing a high number of pediatric ADRs [18,24-26].

We also observed an increase in reporting frequency over the 4 years of the project. This observation suggests that underreporting is still a significant issue. In our case underreporting lessened over time, most likely because of the close two-way collaboration with pediatricians established in the project in the form of bimonthly reports and constant feedback to increase awareness to the ADR issue.

The high reporting rate for children aged 2 – 11 years we observed is in line with that of other studies [26-28] and can be explained by the high number of drug prescriptions in children of this age range and the closer monitoring by physicians and parents [4]. At variance with other study [18,26], but similarly to studies in Spain and Denmark [24,25], we did not find gender predominance in the reported ADRs. Different patterns of drug utilization may explain discrepancies among countries.

The most frequently observed patterns of ADRs were the skin and subcutaneous tissue disorders, followed by the general disorders and administration site conditions, and the gastrointestinal and nervous system disorders confirming observations in other countries [18,24-26]. Also in line with previous studies are the top reported reactions in our analysis, that is, fever, vomiting, urticaria, angioedema, drowsiness, loss of consciousness and polyneuropathy, as well as the percentage of serious ADRs (17%) [18,24,25].

The unknown ADRs were ~ 10%; of these notable are domperidone inducing severe vomiting in dysphagic patients, oxatomide inducing dysarthria, HPV vaccines inducing acute disseminated encephalomyelitis, paracetamol inducing sleep disruption and proprioceptive delirium and chlorpromazine inducing tinnitus [7,29-33]. For each of these cases, we investigated in the literature the pharmacological and pharmacoepidemiological aspects leading to suggestions on how to improve their use [7,32,33]. In the case of domperidone, a follow-up study showed that its use in dysphagic pediatric patients affected by brain injury could be optimized, and the risk of vomiting minimized by assessing the presence/absence of pyloric obstructions via a gastric

transit examination early after initiating domperidone administration [33].

The most frequently reported therapeutic main group of drugs in previous European studies were antibiotics [18,34,35]. We instead found that vaccines (hexavalent, anti-pneumococcal, anti-meningococcus, trivalent measles/mumps/rubella) were those most commonly reported, in line with another observational survey [18,36-38]. This finding may be explained by different prescription patterns in the various countries, the recent Italian governmental programs aimed at fostering the immunization coverage in the general population and the fact that in Italy the reporting of ADRs related to vaccines, at variance with other drugs, is compulsory [39]. The high number of ADRs due to NSAIDs, antihistamines and antineoplastic agents was instead in line with previous reports [24,25].

Among serious ADRs inducing drugs were psychotropic drugs, especially CNS stimulants and antidepressants. This finding is in line with a recent study showing that one-third of all ADRs reported in children were due to psychotropic drugs [40,41]. The prescribing of psychotropic medicines to the pediatric population is rapidly increasing in many countries, in Italy from 0.8 to 6‰ [42], despite regulatory authorities having issued various warnings about risks associated with use of these products in childhood [43]. Data concerning safety and efficacy of these drugs in pediatric settings are still limited, and further studies are needed to guarantee evidence-based therapeutic approaches with these drugs.

Finally, our study highlighted that off-label prescribing is still a serious cause of ADRs, as already documented [44] and that also in this aspect antipsychotic drugs are significantly involved.

## 5. Conclusion

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The MEAP project proves that active post-marketing pharmacovigilance programs are a valid strategy to increase awareness

on pediatric pharmacology, reduce underreporting and provide information on drugs in the pediatric setting that cannot otherwise be obtained due to the lack of pre-authorization studies. In particular, the study identifies previously unknown ADRs, some of which are serious and highlight significant safety issues concerning off-label use of drugs in particular of psychotropic drugs. The information on specific serious and previously unknown ADRs will be made the subject of dedicated short reports that will be conveyed to the participating regions as a tool to ameliorate pediatric clinical practice.

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## Declaration of interest

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