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ENSURING DRUG SAFETY IN CHILDREN: ADVANCING A COMPREHENSIVE PEDIATRIC PHARMACOVIGILANCE SYSTEM

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Abstract

Pediatric patients are especially susceptible to adverse drug reactions (ADRs) due to age-related pharmacokinetic variability and the frequent use of off-label medications that often lack adequate safety and efficacy data. Pediatric pharmacovigilance (PV) is essential for detecting, assessing, and preventing drug-related harm in this population. This study aims to explore the key concepts of pediatric pharmacovigilance, identify challenges and drugs most commonly associated with safety concerns in children, and suggest strategic and technological solutions to enhance drug safety monitoring in children. A comprehensive literature review was conducted using databases such as PubMed, ScienceDirect, and official regulatory sources. Key concepts and challenges were analyzed, including developmental pharmacology, limitations of ADR reporting, and the role of digital tools. Major challenges identified include underreporting of ADRs, limited pediatric-specific clinical data, lack formulations suitable for children, and ethical barriers to pediatric trials. Amoxicillin, as one of the most prescribed antibiotics in children, and Ibuprofen, as the most used NSAID, result in being the drugs with the highest frequency of ADR reports. Various strategies such as full implementation of regulatory measures, education and awareness raising on the importance of ADR reporting, data protection, international collaboration with incorporation of mobile applications and artificial intelligence (AI) are powerful opportunities to modernize pediatric pharmacovigilance. The implementation of these strategies will assist the healthcare system in better and timely management of ADRs with the aim of ensuring safe and effective pharmacotherapeutic treatment for the pediatric population.

Keywords: Pediatric pharmacovigilance, drug safety, adverse drug reactions, technological innovations, digital health.

1. Introduction

Drug safety in paediatric patients is a serious public health concern around the world (Khan *et al*, 2021).

The unique physiological and pharmacological characteristics of infants and children significantly differentiate them from adults, which increases the need for advanced methods and specialized considerations. Pediatric patients are not simply "small adults" (Macfarlane F *et al*, 2006), they have significant differences in physiology affecting drug absorption, distribution, metabolism, and elimination (Ku LC, Smith PB, 2015).

In addition, children constitute a population that, due to ethical barriers and the complexity of conducting research, is limited in its inclusion in clinical trials. Lack of sufficient and appropriate data contributes in using off-licensed drugs, which leads to an increased potential for the occurrence of ADRs, both in hospital and ambulatory care settings. Once a drug has been authorized to enter the market, it will become part of constant monitoring through the pharmacovigilance system. WHO (World Health Organization, 2002) defines Pharmacovigilance (PV), as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems". Segal ES *et al*, (2005) and Noda *et al*, (2020) in their study, suggest that spontaneous reporting of ADRs is critical for effective post-marketing drug surveillance and patient safety. In pediatrics,

pharmacovigilance aims in reducing harm, optimising paediatric pharmacotherapy and provide parents and prescribers with accurate descriptions of the benefit–risk balance of available treatment options, including potential long-term effects (Aurich B *et al*, 2022). Therefore, this review aimed to explore the key concepts of pediatric pharmacovigilance, identify the drugs most commonly associated with safety concerns in children, examine the multifactorial challenges involved, and propose structural and technological strategies to enhance drug safety in pediatric populations.

2. Materials and methods

The study is based on analysis of review and original articles, and official sources including the World Health Organization (WHO) and European Medicines Agency (EMA). A bibliographic research is done using databases such as PubMed, ScienceDirect, EBSCO, Scopus, Sage and Google Scholar. Articles and papers published within the past two decades were searched on the keywords: "pediatric pharmacovigilance," "adverse drug reactions in children," "drug safety monitoring in pediatrics," "off-label drug use in children" "technological innovations and digital health". Supplementary data were obtained from WHO's global individual case safety report database (VigiAccess).

3. Results and Discussion

The Beginning of Pharmacovigilance: Pediatric Implications

The beginning of PV is marked by the thalidomide disaster, a drug initially marketed as a sedative and later used to treat nausea in pregnancy. In the 1950s it was presented as a safe drug, but soon later, in early 1960s it was banned for its harmful effects. It caused widespread birth defects, resulting in over 12,000 cases of teratogenic malformations in newborns including phocomelia and limb agenesis. This catastrophe led to the establishment of the World Health Organization (WHO) Program for International Drug Monitoring and the creation of the Uppsala Monitoring Centre (UMC), marking the beginning of global PV as a scientific discipline.

Key concepts of pediatric pharmacovigilance

Paediatric pharmacovigilance is a continuous process, worldwide, multidisciplinary effort throughout the life cycle of pharmaceutical products administered to children, regardless of the local licensing status (Aurich B *et al*, 2022). It is a critical subset of drug safety that involves the monitoring, evaluation, and continuous improvement of medication use in children. Effective pediatric pharmacovigilance ensures that medicines are used safely and appropriately across all stages of development, from infancy through adolescence.

International agencies like World Health Organization (VigiBase®), the European Medicines Agency (EudraVigilance), and Food and Drug Administration (MedWatch) provide pediatric pharmacovigilance support through safety databases that include pediatric reports, pediatric-specific risk management strategies and regulatory incentives for pediatric drug trials. According to the WHO, an adverse drug reaction (ADR) is "A response which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function." (The Uppsala Monitoring Centre, 2011). The pharmacovigilance system in the Republic of North Macedonia defines an ADR as any unwanted and harmful response to a drug that occurs during its use. The national pharmacovigilance system defines ADRs not only as reactions from approved use but

also those resulting from misuse, overdose, medication errors, and off-label use. This system also defines off-label drug use as the use of a medicinal product that does not comply with the approved Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL), including administration in unauthorized pediatric age groups. This aligns with European pharmacovigilance standards and reflects the broader scope of ADR surveillance in pediatric populations.

Challenges in Pediatric Pharmacovigilance

Physiological differences

Pediatric PV is both essential and challenging due to the fact that children are particularly vulnerable to ADRs as a result of developmental and physiological differences. These differences in children compared to adults are critical in both clinical practice and pharmacovigilance. Immature physiological systems in children impact drugs pharmacokinetics (absorption, distribution, metabolism, excretion) and pharmacodynamics, requiring careful dosing and monitoring. Therefore, it is essential to consider not only the child's weight, height, and medication details, but also the child's exact age, as their development stage has a substantial impact on the safety and response to the drug. Some pharmacokinetic parameters such as bioavailability, volume of distribution, and clearance are age-related (Fernandez E *et al*, 2011).
In Table 1, are presented various physiological factors that differ between neonates and adults with clinical implications that can affect drug behavior and the occurrence of adverse drug reactions. As it can be seen from the table, several factors among which plasma protein binding, total body water and anzyme activity need to be considered when prescribing.

Table 1. Physiological Differences between children and adults

Physiological Parameter	Pediatric Population	Adult Population	Clinical Implications
Gastrointestinal pH	Elevated at birth (pH 6–8); gradually acidifies	Low (acidic)	Altered drug solubility and stability; increased absorption of acid-labile drugs (e.g., penicillin)
Gastric emptying time	Prolonged and variable in neonates and infants	Faster and more predictable	Delayed or erratic drug absorption
Intestinal enzyme activity	Immature at birth	Fully developed	Reduced first-pass metabolism; variable bioavailability
Bile salt production	Decreased in neonates	Normal	Reduced solubilization of lipophilic drugs; decreased absorption
Total body water	Higher (~70–80%)	Lower (~60%)	Larger volume of distribution (Vd) for hydrophilic drugs; may require higher weight-based dosing
Body fat	Lower in neonates, increases with age	Stable	Affects distribution of lipophilic drugs (e.g., diazepam)

Plasma protein binding	Lower albumin and α1-acid glycoprotein; reduced binding capacity	Normal binding proteins	Increased free (active) drug concentrations; higher risk of toxicity for highly bound drugs
Blood-brain barrier (BBB)	Immature and more permeable	Mature and selective	Increased CNS exposure to drugs
Hepatic metabolism (CYP enzymes)	Immature Phase I & II Immature CYP450 activity	Fully developed	Slower metabolism in neonates; altered clearance; risk of accumulation or toxicity
Renal excretion	Reduced GFR, tubular secretion, and reabsorption in neonates	Normal renal function	Decreased drug clearance; prolonged half-life for renally-excreted drugs (e.g., aminoglycosides)
Pharmacodynamic response	Receptor expression and function still maturing	Receptor systems stable	Altered drug sensitivity and effect profiles; paradoxical or exaggerated responses possible
Homeostatic regulation	Immature compensatory mechanisms	Mature regulatory systems	Greater susceptibility to adverse events affecting BP, glucose, temperature regulation

Off-Label Drug Use in Pediatrics

Children are frequently excluded from clinical trials as a result of ethical and regulatory constraints, which results in a relatively high incidence of off-label prescribing. Less than 50% of drugs entering the market are clinically evaluated in the pediatric age group (D'Errico, S *et al*, 2022). As a result, the efficacy and safety profiles of drugs in children are still not well understood, which in turn increases the risk of unpredictable adverse drug reactions in this population.

Underreporting of ADRs in Children

Underreporting is a significant challenge in pediatric pharmacovigilance. Healthcare professionals, particularly those in primary care, may not be aware of the reporting requirements or the importance of ADRs in children. Furthermore, caregivers may not always recognize or report ADRs. In some cases, healthcare providers may consider certain ADRs to be expected side effects of the drug or may attribute the reactions to a child's preexisting condition, leading to underreporting. Underreporting continues to be a prevalent issue, despite international initiatives to enhance ADR reporting. Other reasons could be related to work overload of staff, voluntary reporting systems possible conflict of interest, and lack of training (Vallano A *et al,* 2002).

Ethical and Legal Challenges

Pediatric research involves complex ethical considerations, particularly regarding informed consent and long-term safety monitoring. These challenges limit the inclusion of children in trials and contribute to the lack of pediatric pharmacovigilance data.

Lack of Pediatric-Specific Formulations

Formulations are hardly ever designed for an optimal use in children (Golhen, K. *et al*, 2023). Therefore, according to Ivanovska V *et al*, (2014) when there is no suitable commercially available pediatric specific formulation, either an adult dosage form or the active pharmaceutical ingredient (API) bulk powder must be manipulated to create the final product. Such manipulations can affect drugs pharmacokinetics and pharmacodynamics thus raising the possibility of the adverse drug effects occurring.

Global Inequities in Surveillance

Low- and middle-income countries (LMIC) face specific challenges with regard to pharmacovigilance (Kiguba R *et al*, 2023). Olsson S et al., have detected that among 55 low- and middle-income countries, in majority, the national pharmacovigilance systems have weak regulatory enforcement and minimal pharmacovigilance awareness, resulting in very low reporting rates (Olsson S *et al*, 2010). According to Khan et al., lack of awareness, communication channels, trained staff, language barrier, infrastructure, and facilities, are additional challenges of the ADR reporting system (Khan MAA *et al*, 2022). To ensure that drug safety monitoring processes are implemented and supported, Alomar *et al*., 2019 proposed that national drug regulatory mechanisms should be designed to include pharmacovigilance measures, but at the same time it is necessary to increase international cooperation, to create pharmacovigilance models with particular emphasis on those adapted to pediatric populations.

The most frequent class of drugs in pediatric ADRs and Pharmacovigilance Reporting

Children and adolescents are at particular risk for adverse drug reactions (ADRs) (Martina P. Neininger *et al*, 2022). Angamo, M. T *et al*, (2016) in their study have concluded that ADRs are responsible for approximately 5% of all hospital admissions in children, while according to Khan, Z *et al* (2020), the overall average incidence of ADRs in pediatric patients ranges from 9.52% to 9.53%. Several studies show that anti-infective agents are among the most frequent classes of drugs associated with ADRs, which mainly occur in the form of gastrointestinal symptoms such as nausea, vomiting, and diarrhea, as well as dermatological reactions like skin rashes (Smyth RM *et al*, 2012). In a 10-year safety surveillance of adverse drug reaction of pediatric drugs, Leporini et al., showed that anti-infective agents for systemic use and skin disorders were, respectively, the most frequently adverse drug reaction category in pediatric population (Leporini, C *et al*, 2022).

According to the majority of Uppsala Monitoring Centre (UMC) reports, different antibiotics are shown to present different frequencies of ADR reporting. Among them, data from reports show that amoxicillin, in addition to being considered the most prescribed antibiotic in children, is also the antibiotic that contributes the most to adverse drug effects (Nasso, C *et al*, 2020). Table 2 presents a summary of different antibiotics and ADR frequencies in children.

Table 2. Frequency of antibiotic ADRs in children

	0–27 days	**28 days to 23 months**	**2-11 years**	**12-17 years**	**Total**
Amoxicillin	435	12005	21634	7626	41700
Amoxicillin/ clavulanic acid	719	8145	21497	6776	37137
Phenoxymethyl penicillin	18	993	3519	1468	5998
Cephalexin	35	1157	2874	1123	5189

Cefpodoxime	60	576	1383	273	2292
Cefixime	51	1074	2804	634	4563
Cefaklor	67	2814	6426	1030	10337
Azithromycine	165	3017	14296	3753	21231
Trimethoprim / Sulfamethoxazole	107	3864	9313	4433	17717

Source: vigiaccess.org. Accessed: 30.05.2025

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in infants (children < 2 years of age), children, and adolescents worldwide (Trajanovska M et al, 2010; Ferreira TR and Lopes LC, 2015), for pain relief, fever control, and inflammation. Several studies (Paul IM et al, 2018; Etminan M et al, 2017) suggest that cold medicines and opioids also pose significant risks of adverse drug reactions (ADRs), particularly in younger children. Notably, some studies have reported that the incidence of ADRs related to NSAIDs may exceed those associated with beta-lactam antibiotics, especially in the context of severe reactions (Liew WK et al, 2013; Gabrielli S et al, 2018; Jares EJ et al, 2015). As illustrated in Table 3, the majority of ADR reports submitted to the Uppsala Monitoring Centre (UMC) are linked to ibuprofen, which may be due to its widespread use in the pediatric population.

Table 3. Frequency of NSAIDs ADRs in children

	0–27 days	**28 days to 23 months**	**2-11 years**	**12-17 years**	**Total**
Ibuprofen	882	4986	20109	10656	36633
Acetylsalicylic acid	226	851	2930	2476	6483
Naproxen	56	297	1248	2512	4113
Ketoprofen	75	69	536	1249	1929
Indomethacin	245	136	178	327	886
Diclofenac	111	345	1674	3689	5819

Source: vigiaccess.org. Accessed: 29.05.2025

Technological and Strategic Recommendations for Enhancing Pediatric Pharmacovigilance

Advancing pediatric pharmacovigilance requires the integration of modern technologies alongside coordinated policy and system-level interventions. As children represent a unique and vulnerable population, strategies must address both the limitations in traditional reporting mechanisms and the gaps in pediatric-specific safety data. The following technological and strategic recommendations aim to improve the detection, analysis, and prevention of adverse drug reactions (ADRs) in pediatric populations (Sienkiewicz K et al, 2021).

Technological Innovations

Emerging digital tools and computational technologies offer powerful opportunities to modernize pediatric pharmacovigilance. These innovations have the potential to improve the responsiveness of drug safety management, enhance data accuracy, and facilitate real-time monitoring.

Mobile applications based on the Internet are convenient and fast and have significantly improved ADR reporting by enabling real-time data submission, which reduces the risk of errors and missing information (PH. et al, 2025). Based on studies of Tomašev N, et al (2019)

and Danysz K, et al (2019), artificial intelligence (AI) is considered as an example of a specialized reporting mechanism with technological advancements, which analyses large datasets to detect potential ADRs earlier and more efficiently.
Few of web applications of AI are accessible to public like “VigiAccess” for data of ADRs (Murali K. et al, 2020).

Strategic Recommendations

Various strategies need to be implemented for the strengthening and proper functioning of pediatric pharmacovigilance. Advanced technology together with the full implementation of regulatory measures and improvement of reporting mechanisms, education and awareness raising of healthcare personnel in general and parents in particular, data protection and international collaboration for earlier detection of international safety signals are essential.

4. Conclusions

Pediatric pharmacovigilance represents a multifactorial approach with a tragic historical background and an imperative that needs improvements and advancing. Many are the challenges faced by this essential system in ensuring the safe and effective administration of drugs in children. Physiological differences between children and adults are evident, requiring a professional dosing approach and drug monitoring. The limited inclusion of children in clinical trials, mainly due to ethical barriers, has resulted in the use of off-licensed drugs in the form of manipulated formulations. This in itself constitutes an increased potential for the occurrence of ADRs. Healthcare professionals may not be fully aware of the importance of reporting ADRs, which directly affects underreporting. Parents, not being informed, also neglect reporting ADRs, considering them insignificant or as expected side effects of the drug. Improving reporting mechanisms for ADRs in children will improve real-time monitoring and reporting, while international collaboration can lead to global improvements in pediatric drug safety. In addition, significant improvements in ADR detection and reporting are expected from the implementation of technological advances, including artificial intelligence and mobile health tools.
The full and comprehensive implementation of these strategies can help advance and build safe health care systems, especially for children, ensuring that they receive effective treatments with minimized risks.

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