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PHARMACOVIGILANCE IN PEDIATRICS: A NOVEL REVIEW

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ABSTRACT

The methodical observation of the safety of medications used in children and adolescents is known as pediatric pharmacovigilance. Because children are a diverse population with constantly changing growth, organ maturation, body composition, and developmental pharmacology, it is especially crucial. Drug exposure, responsiveness, and the clinical manifestation of adverse drug reactions (ADRs) can all be impacted by these variations. Furthermore, off-label and unlicensed medication use, age-inappropriate dosage forms, and weight-based dosing are still often used in general practice, and children clinical studies are frequently smaller than adult trials. These elements may raise the possibility of medication errors and fail to address crucial safety concerns at the time of marketing. [1–4]

The burden of medication-related damage is not fully captured by spontaneous reporting alone, according to data from pediatric pharmacovigilance research. Electronic medical-record triggers found 280 adverse drug reactions (ADRs) in a pediatric hospital study, but only 21 ADRs were voluntarily reported in the same year. A further comparison of spontaneous EudraVigilance reports and systematic KiDSafe surveillance revealed significant disparities in the kinds of safety issues recorded, with 845 reports compared to 697. [5, 6] Signal detection is also aided by large databases. 1,198,560 pediatric reports, including 1,585 death incidents, were found in a WHO VigiBase review between 2010 and 2019; the majority of these reports included children between the ages of 28 days and 23 months. [7]

The significance of pediatric pharmacovigilance, developmental factors, ADR patterns, off-label use, medication errors, spontaneous and active surveillance, electronic health records, real-world evidence, signal detection, causality assessment, serious cutaneous reactions, the role of caregivers and healthcare professionals, underreporting, neonatal safety, adolescent pharmacovigilance, and emerging digital approaches are all covered in this review. An integrated, age-sensitive strategy is anticipated to offer a more comprehensive view of medication safety and assist in translating safety data into workable risk-reduction strategies.

KEYWORDS: *Pharmacovigilance for children, adverse drug reactions, medication safety, off-label usage, medication errors, spontaneous reporting, active surveillance, VigiBase, electronic health records, and signal detection.*

1. Objectives

• To discuss the significance of pharmacovigilance for kids and teenagers.

• To outline the clinical and developmental aspects that affect the safety of pediatric medicine.

• To examine the prevalence and trends of adverse drug reactions in children.

• To talk about the use of unlicensed and off-label medications and how it relates to safety monitoring.

• To investigate medication errors as an avoidable aspect of damage associated with pediatric medicine.

• To contrast electronic, active, and spontaneous ADR detection techniques.

• To explain the function of signal identification techniques, real-world evidence, and pharmacovigilance databases.

• To talk about the duties of doctors, nurses, pharmacists, parents, and youth.

• To determine pediatric pharmacovigilance's present difficulties, unmet research needs, and potential future developments.

2. INTRODUCTION

The research and practices pertaining to the identification, evaluation, comprehension, and avoidance of side effects or other medication-related issues are commonly referred to as pharmacovigilance. The same fundamental ideas hold true for children, but the approaches must be modified to take into account the traits of a developing population. The physiological reactions of a newborn, infant, school-age child, and adolescent to the same medication can differ significantly. Therefore, without sufficient evidence, a drug's safety profile in adults cannot be simply extrapolated to children. [1, 2]

When a medication is first used in clinical settings, the pediatric evidence base may likewise be small. Rare effects may not be detected by smaller clinical studies, and medications may continue to be used off-label due to the lack of suitable pediatric formulations or reasons. Frequent off-label usage, inappropriate dosage forms, and ongoing dose adjustment can raise the risk of medication errors and preventable adverse drug reactions, according to the 2018 review by Bouquet and colleagues.[1]

For this reason, post-marketing pharmacovigilance is especially crucial in pediatrics. While active surveillance, electronic records, registries, and record linkage can offer more details regarding frequency and clinical context, spontaneous reporting can produce early alerts. Throughout the medication life cycle, the c4c pediatric pharmacovigilance expert group advises taking into account various complementing techniques, such as benefit-risk evaluation, safety data collection, risk-management planning, and signal detection.[2]

Recent research demonstrates the usefulness of these methods. In one facility, Joyner and colleagues discovered that 280 pediatric adverse drug reactions (ADRs) were detected via computerized triggers followed by chart inspection, as opposed to 21 volunteer reports. Similarly, Leitzen and associates showed that distinct safety profiles were recorded by systematic and spontaneous reporting. [5, 6]

3. Why Pharmacovigilance is Important in Pediatrics

Due to their exposure during times of rapid biological change, children may be especially susceptible to the negative effects of medications. Drug clearance can be affected by developmental variations in renal and hepatic function, and pharmacodynamic responses can be altered by changes in body composition and receptor systems. These variations are clinically significant throughout development and adolescence, but they are most noticeable during infancy. [1, 2]

Strong pediatric pharmacovigilance is also necessary due to the potential for child-specific side effects. Studies on adults may not accurately anticipate the effects on growth, neurodevelopment, endocrine function, and other developmental processes. In particular, the 2018 pediatric pharmacovigilance review emphasized the importance of keeping an eye on symptoms that can manifest preferentially in children as well as the potential long-term effects of exposure during pregnancy. [1]

Better future prescribing is also supported by safety surveillance. Accurately recording and reporting a suspected response can help with regulatory examination, reduce recurrent exposure, and influence the selection of an alternative medication. In a 2024 study, a pharmacovigilance team's explanation of pediatric adverse drug reaction (ADR) paperwork enhanced the likelihood of appropriately re-prescribing antibiotics when prior responses had been misdiagnosed as definite allergies. [8]

4. Unique Factors Affecting Pediatric Drug Safety

The use of pediatric medications has a number of features that make pharmacovigilance more difficult. First, dosages are frequently customized based on clinical condition, body weight, age, and body surface area. Second, a child's needs might not be met by the current formulation. It could be necessary to measure a concentrated liquid in a tiny volume or to divide, compress, or distribute a tablet. Third, a lot of medications are prescribed in ways that deviate from their marketing authorization. [1, 3]

Another element is communication. While a young child might just become agitated or refuse meals, an adolescent can frequently experience headaches, dizziness, or nausea. Children who are really sick or newborns may not be able to express their symptoms at all. As a result, pharmacovigilance systems rely significantly on accurate clinical interpretation, nursing documentation, caregiver reporting, and observation. [2]

Lastly, determining causality may be made more difficult by the baseline rate of illness. Rather than being signs of a drug reaction, fever, vomiting, rash, or abnormal test findings could be signs of an

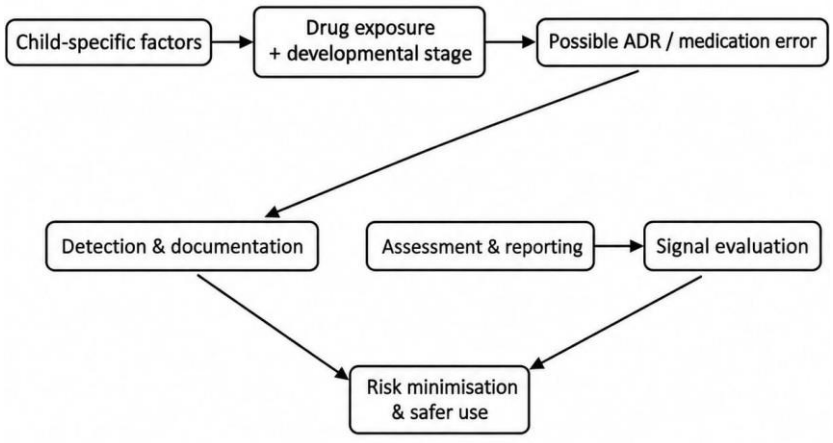
infection or the underlying illness. In order for assessors to differentiate a suspected adverse drug reaction (ADR) from an expected symptom of sickness, high-quality reports must provide sufficient clinical context.

5. Pediatric Age Groups and Developmental Considerations

Because safety patterns might vary significantly between developmental stages, age should be accurately reported in pediatric pharmacovigilance. The metabolic and excretory systems of newborns are underdeveloped. Organ function and body composition change quickly in infants. While teenagers undergo significant hormonal and behavioral changes that may affect medication exposure, adherence, and side effects, school-age children continue to develop physiologically. [1, 2]

A helpful example is given by a WHO pharmacovigilance analysis. 1,585 of the 1,198,560 pediatric reports that were filed between 2010 and 2019 were fatal. The majority of fatal reports involved boys, especially those between the ages of 28 days and 23 months. [7] These results highlight the significance of age-stratified analyzes, but they do not imply that every infant getting medication is at high risk

Age and sex variations were also seen in a 2020 Portuguese study of teenage ADR reports. Eighty percent of the 782 teenage complaints were deemed serious; the most common drug group was vaccinations, followed by systemic antibacterials. [9] Therefore, age-specific surveillance can identify trends that would be hidden if all patients under the age of eighteen were examined collectively.



6. Adverse Drug Reactions in Children

There is a broad range of clinical symptoms associated with pediatric ADRs. Pharmacovigilance datasets frequently include skin and subcutaneous reactions, gastrointestinal symptoms, neurological events, fever, and general illnesses. Anti-infectives and vaccinations are among the medications that are regularly prescribed to youngsters. [1,10]

Studies conducted in hospitals offer more context. 64 adverse drug reactions (ADRs) were found in 54 pediatric patients in an Indian prospective observational study, resulting in an incidence of 4.99% among the population under review. Patients who were receiving four or more medications and infants were identified as groups that needed extra care. [11]

The reported prevalence of ADRs among hospitalized children in the literature varied from 0.6% to 16.8%, according to an Odisha pharmacovigilance-center research published in 2021. This variation was attributed to variations in study design, location, and detection techniques. [12]Such diversity is crucial: without taking into account the methods used to gather the data, a high rate in a hospital under active monitoring should not be immediately compared to a low rate obtained via voluntary reporting.

Attention must also be given to rare but severe responses. 7,342 pediatric SJS-TEN records and statistically significant signals for 165 medications were found in a 2024 VigiBase investigation of pediatric Stevens-Johnson syndrome/toxic epidermal necrolysis, with antiepileptic and anti-infective medications being the two main classes. [13.]

7. Common Drug Classes and Pediatric Safety Concerns

Due to the widespread usage of anti-infective medications in children, several safety reports are produced. They may be linked to skin responses, hypersensitivity, and gastrointestinal issues. Due to their widespread usage and the rigorous monitoring of even infrequent suspicious occurrences, vaccines are also commonly included in reporting systems. [1,10]

Because children may exhibit neurological or behavioral symptoms that are hard to differentiate from underlying disorders, central nervous system medications need to be closely monitored. Neuropsychiatric events were the most commonly reported category, followed by gastrointestinal and hepatobiliary reactions, according to a French pharmacovigilance study of antidepressant exposure in children and adolescents, which found 1,366 reports including 2,922 adverse drug reactions. [14.]

Another significant category is immunomodulatory and antineoplastic medications. Nervous system medications and antineoplastic/immunomodulating drugs are common in pediatric reports, according to FDA adverse-event reporting analyzes, although the kinds of reactions differ by age group. [15.]

Additionally, the safety profile may vary depending on the medication. 2,203 reports and signals from 24 organ systems were found in a 2025–2024 FAERS analysis of azithromycin in children, demonstrating how big spontaneous-reporting databases can be leveraged to look at specific medications in actual pediatric populations. [16.]

8. Off-label and Unlicensed Medicine Use

When a medication is taken in a way that deviates from its approved labeling, such as in terms of age, indication, dose, method, or formulation, this is known as off-label prescribing. Off-label use may be required in pediatrics since not all age groups have access to evidence and formulations. Therefore,

off-label use shouldn't always be seen as improper prescribing. Rather, it pinpoints a domain where safety monitoring and proof generation are especially beneficial. [1, 2]

An off-label medication may have fewer age-specific data regarding dosage, formulation, interactions, or uncommon side effects, which presents a safety risk. Pharmacovigilance databases are important sources of real-world safety information because many medications are supplied to children without a specific pediatric license due to the lack of pediatric clinical trials, according to a 2022 pediatric pharmacovigilance study from Calabria. [17.]

The risk of drug errors may potentially interact with off-label use. Errors in preparation and administration are more likely when a formulation needs to be changed or a dose needs to be determined from adult-strength items. This danger can be decreased with the aid of caregiver education, computerized dose verification, standardized concentrations, and clear directions.

9. Medication Errors in Pediatrics

While medication errors are not the same as adverse drug reactions (ADRs), their potential to produce avoidable adverse drug events makes them extremely pertinent to pediatric pharmacovigilance. Erroneous dosage, concentration, frequency, decimal-point errors, route, preparation, and timing of administration are common issues. [3, 18]

Due to variations in definitions and detection techniques, a 2019 systematic review and meta-analysis revealed significant heterogeneity in the prevalence of medication mistakes among pediatric inpatients. [19]. The susceptibility of critically sick children and the incidence of avoidable adverse medication events were highlighted in another systematic analysis that focused on pediatric and neonatal intensive care settings. [20]

Risk can be decreased by interventions. Strategies for enhancing pediatric medication safety have been investigated, including electronic prescribing, clinical decision support, standardized concentrations, barcode medication administration, smart infusion pumps, and staff education. The need for pharmacokinetic and pharmacodynamic individualization has a significant impact on pediatric prescribing mistakes, according to a systematic assessment of prescribing-error strategies.[21]

The useful lesson is that even after an adverse drug reaction (ADR) is discovered, pharmacovigilance should continue. The system ought to inquire as to whether the incident was inevitable or whether there is a way to modify the medication-use procedure to stop it from happening again.

10. Methods of Pediatric Pharmacovigilance

When multiple approaches are combined, pediatric pharmacovigilance is most effective. The traditional basis is spontaneous reporting since, with extensive use, it can identify uncommon and unexpected situations. Nevertheless, imprecise clinical data, encouraged reporting, and underreporting are threats to spontaneous systems. [1, 2]

Active surveillance is more methodical. To find potential adverse drug reactions (ADRs), a pharmacovigilance team may examine admissions, emergency room visits, prescription orders, lab results, and clinical notes. In a seven-year active pharmacovigilance study, Nasso and colleagues examined 75,935 admissions in a pediatric emergency room; 120 admissions were linked to suspected adverse drug reactions (ADRs), and the admission rate for patients with ADRs was significantly higher than that of patients without ADRs. [22]

Another current technique is the use of trigger tools. To find records that need to be reviewed, they employ predetermined clues such antidote usage, sudden medicine withdrawal, changes to the allergy list, or particular laboratory abnormalities. Although each trigger still needs clinical validation, their ability to effectively screen a large number of people is a strength.

Signal detection across populations is supported by large datasets like VigiBase, FAERS, and EudraVigilance. Rather than being viewed as evidence of

causation, the results are most valuable when understood in conjunction with clinical knowledge, exposure patterns, and other data sources.

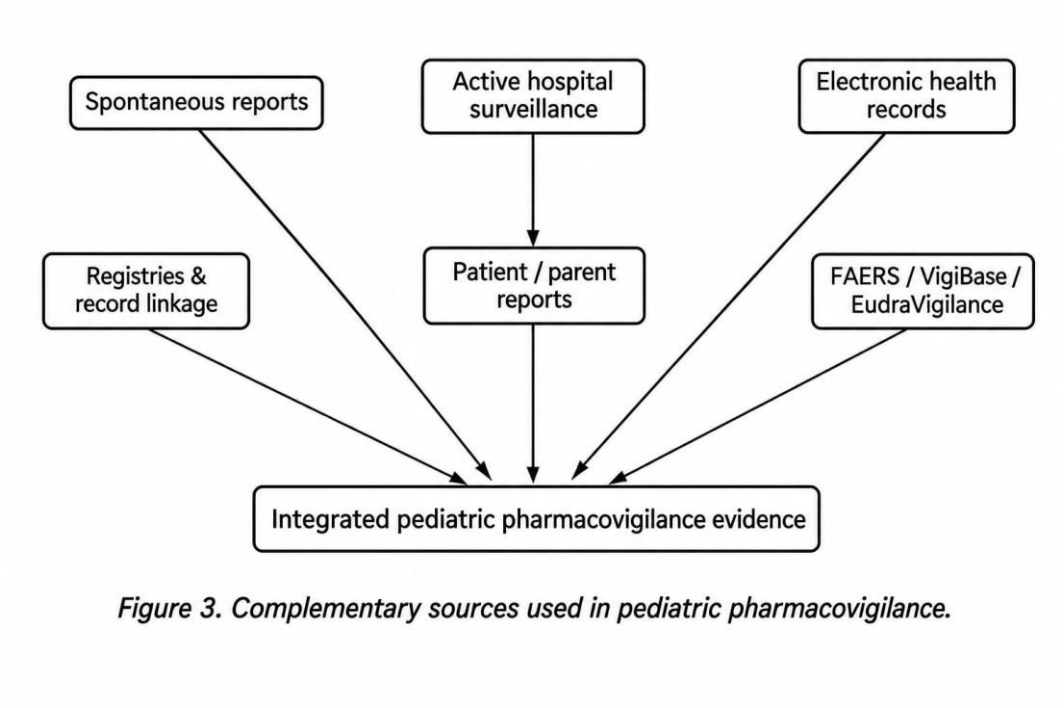


Figure 3. Complementary sources used in pediatric pharmacovigilance.

11. Active Surveillance and Trigger Tools

In pediatrics, the distinction between active and passive reporting is particularly crucial. In 2019, Joyner and associates looked at a children's hospital where 21 ADRs had been freely reported. They found 280 ADRs using electronic triggers based on changes in allergy profiles, ICD coding, and record inspection. In comparison to voluntary reporting alone, the study reported a 13-fold increase. [5]

Previous research from a tertiary children's hospital also demonstrated the importance of a comprehensive Drug Safety Service. ADR detection more than quadrupled from 10 to 41 cases per

10,000 admissions following the adoption of electronic triggers, consistent nomenclature, a streamlined reporting system, and staff training. Just 9% of the ADRs found in that study were the result of voluntary reporting alone. [23.]

The kind of safety information gathered is also altered by systematic gathering. 845 deliberately gathered ADR reports and 697 spontaneous EudraVigilance reports from the same time period were included in the KiDSafe study. In the methodically gathered dataset, medication mistakes and other medication-safety problems were more prevalent. [6]

These results lend credence to a hybrid model: active surveillance offers richer and frequently more comprehensive clinical data, while spontaneous reporting is still useful for generating broad signals.

Figure 4. Selected evidence showing the contribution of active or systematic surveillance

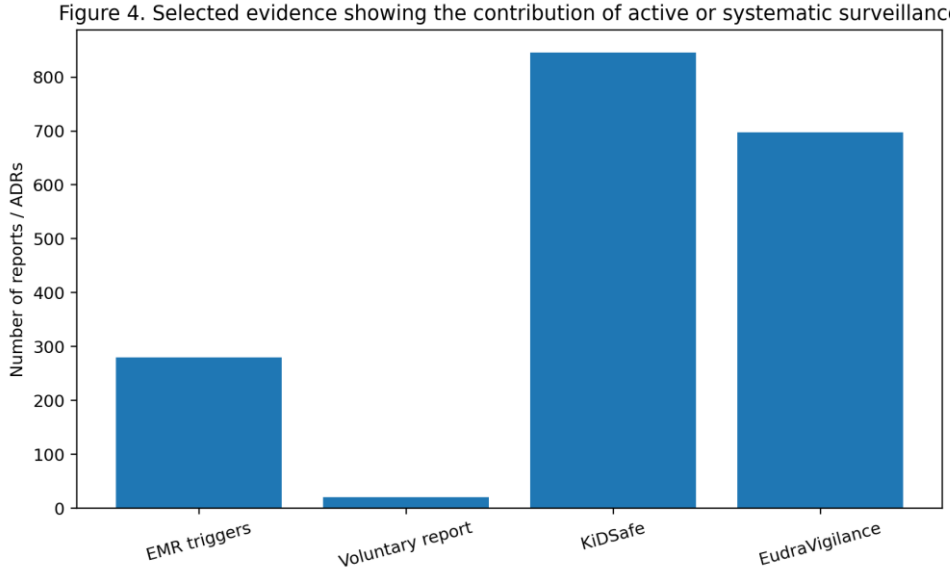


Figure 4. Selected evidence showing the contribution of active or systematic surveillance.

12. Electronic Health Records and Real-World Evidence

By linking medication exposure with diagnoses, test findings, clinical notes, allergy lists, and outcomes, electronic health records (EHRs) can assist pediatric pharmacovigilance. 71 studies with study populations ranging from less than 1,000 children to more than 10 million were found in a systematic review that used electronic healthcare data to identify possible pediatric adverse drug reactions.[24]

EHR-based surveillance has the benefit of being able to detect occurrences that are never reported as official ADRs. Additionally, it can offer denominator data, which enables researchers to compare rates between exposed and unexposed groups. However, as pharmacovigilance is not the primary purpose of EHR data collection, interpretation may be impacted by coding mistakes, missing data, modifications to documentation procedures, and inadequate information regarding over-the-counter or externally prescribed medications.

Because randomized clinical trials may be limited or challenging to undertake for every medication and every age group, real-world data is especially important in pediatrics. Its potential for assessing pharmaceutical safety and efficacy in everyday practice was highlighted by a comprehensive evaluation of real-world evidence in children. [25.]

Unstructured EHR data is being investigated in more recent study. After reviewing 984 records, a recent scoping assessment discovered only nine qualified studies, suggesting that this field is still in its infancy. Although adverse-event data may be extracted from clinical notes using natural language processing, there are still significant issues with generalizability and clinical context interpretation. [26.]

13. Signal Detection and Causality Assessment

Finding a potential new or altered link between a medication and an adverse event is the goal of signal detection. The Reporting Odds Ratio (ROR), Proportional Reporting Ratio (PRR), Information Component (IC), and empirical-Bayes methods are common approaches to disproportionality. These methods can assist in prioritizing occurrences for additional evaluation by comparing the observed reporting pattern with a reference backdrop.

Age stratification is frequently necessary for pediatric analyzes since the background incidence of illnesses and symptoms varies with development. Reporting odds ratios were employed in the WHO fatal-ADR study to examine variations by continent, age, and sex. [7] 165 medication signals were found in a 2024 VigiBase investigation of pediatric SJS-TEN using Information Component-based signal identification. [13.]

An independent clinical step is the judgment of causality. The temporal link, known pharmacology, alternative reasons, dechallenge, rechallenge when available, dose-response, and concurrent medications are all taken into account by the assessor. Therefore, a statistical signal should not be taken as proof that a medication caused the occurrence, but rather as a call to action for further research.

Efficient documentation facilitates the evaluation of causality. Whenever feasible, the suspected medication, dose, route, treatment dates, onset date, pertinent laboratory results, concurrent medications, and outcome should be documented.

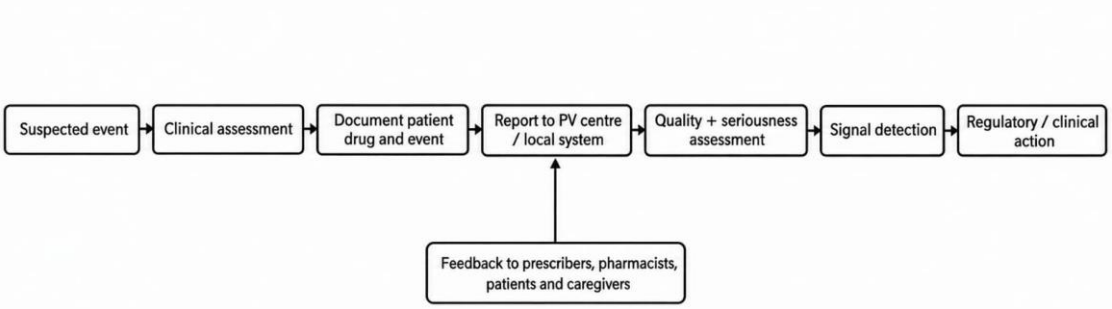


Figure 2. Practical workflow for pediatric ADR reporting and follow-up.

14. Serious and Rare Pediatric Safety Signals

Even if their absolute incidence is minimal, rare occurrences can have a significant clinical impact. One example is severe adverse responses to the skin. 7,183 pediatric SCAR reports were found in a 2026 publication that used FAERS data up to the second quarter of 2024. Hospitalization occurred in 64.5% of cases, and 6.3% of cases resulted in death. DRESS accounted for 32.5%, SJS for 27.9%, and toxic epidermal necrolysis for 19.0%. [27].

The study also discovered that positive signals were observed for a number of antiepileptic and anti-infective medications, and that 82.7% of cases with known onset information occurred within 30 days of exposure. These results highlight the significance of prompt identification and reporting when there may be serious clinical repercussions.

An alternative viewpoint is offered by the WHO fatal-ADR research. 1,585 of the almost 1.2 million pediatric reports were fatal. Fatal reports were concentrated in specific age groups and medical classifications, although making up only 0.13% of all pediatric reports in that collection. [7] These findings highlight the need for pharmacovigilance to look at incidents' severity, preventability, and potential clinical significance in addition to their frequency.

15. Role of Healthcare Professionals and Caregivers

The key players in pediatric pharmacovigilance include doctors, pharmacists, and nurses. Prescribers are able to assess potential causes and identify suspected reactions. Pharmacists are able to examine medication history, interactions, formulation, and dosage. Because they closely monitor patients, nurses can spot early clinical changes. [2,15]

Important reporters include parents and other caregivers. After a child leaves the medical facility, they can notice changes in their hunger, sleep, behavior, skin, respiration, or digestive system. Adolescents may notice reactions that adults do not immediately notice and may occasionally report symptoms directly.

A 2020 study that especially looked at pharmacovigilance reports from kids and teens emphasized how crucial it is to give them the information they need to report medication-related issues. [28.]

Documentation is just as vital. Thirty-one percent of the 3,065 ADRs that required medical attention in a 2020 pediatric hospital study were not properly recorded in the electronic medical record before to discharge. The presence of prospective pharmacovigilance oversight improved documentation. [29].
Therefore, a pharmacovigilance service can have two related objectives: identify the event and ensure that the data is still relevant for future prescriptions.

16. Under-reporting and Reporting Quality

One of the most enduring issues with spontaneous pharmacovigilance is underreporting. Uncertainty regarding whether a symptom is brought on by the medication or the underlying condition, time constraints, lack of familiarity with reporting protocols, and the belief that a recognized reaction does not require reporting can all exacerbate the issue among youngsters. [1, 2]

132 probable adverse drug reactions (ADRs) were discovered among 301 evaluated patients in a Dutch pediatric hospital study; of these, 55% were not specifically recorded as ADRs by treating physicians, and none had been reported to the national pharmacovigilance center. Thirty The result highlights the potential discrepancy between formal reporting, documentation, and clinical incidence.[30]

Reporting quantity and quality are equally crucial. Patient age and weight, when applicable, suspected medication, indication, dosage, method, start and stop dates, beginning of reaction, clinical description, result, and concurrent medications should all be included in a useful report. If at all possible, the reporter should additionally mention whether the incident necessitated hospitalization, posed a risk to life, or left the victim disabled.Simplified reporting procedures and education can be beneficial. The 2022 quality-comparison research showed how a support team could be notified by doctors with very little preliminary information while the team finished the comprehensive pharmacovigilance report from the medical record. [31].

17. Pharmacovigilance in Neonates and Infants

Because the organ systems involved in processing medications are still growing, neonates and young babies need extra care. Exposure may be influenced by factors such as gestational age, postnatal age, birth weight, current weight, and renal or hepatic function. Because the absolute therapeutic dose may be very small, slight numerical variations in dosage can be clinically significant.

According to the WHO fatal-ADR analysis, the first two years of life constituted a significant age group. The majority of fatal cases were youngsters between the ages of 28 days and 23 months. [7] This highlights the significance of age-specific surveillance but does not prove a causal risk for all medications.

Patients in neonatal intensive care frequently receive numerous medications, infusions, and highly customized care, which adds to the complexity. In pediatric and neonatal intensive care settings, medication mistakes and avoidable adverse drug events are significant issues. [20]

Pharmacokinetic data, gestational and postnatal age, weight, organ function, and long-term developmental outcomes should all be integrated into future neonatal pharmacovigilance whenever possible.

18. Pharmacovigilance in Adolescents

A new set of safety concerns arises during adolescence. Patients may use medications for acute infections, dermatological ailments, mental health issues, chronic diseases, or contraception. Additionally, they can start using medications or self-medicating without consulting their parents.

Vaccines and systemic antibacterials were among the most commonly reported groups in a Portuguese pharmacovigilance analysis of 782 adolescent complaints, which revealed that 80% of them were deemed serious. [9] Neuropsychiatric side effects like drowsiness, agitation, and suicidal thoughts or behaviors were among the most commonly reported reactions in a French study of antidepressant-related pediatric reports. [14].

Therefore, adolescent pharmacovigilance must ensure proper safety communication while respecting privacy. Clear information about anticipated effects, warning signs, and how to report suspected responses should be given to young people. Instead of taking the role of professional reporting, patient involvement can enhance it.

19. Prevention and Risk-Minimisation Strategies

Reducing harm is the ultimate goal of pharmacovigilance. Practical risk-minimization measures, such as changing prescribing information, limiting usage in specific age groups, adding warnings, enhancing formulations, instituting monitoring requirements, or educating healthcare professionals, may be implemented after a signal is sufficiently substantiated.

Accurate patient identification, weight measurement, allergy history, medication reconciliation, and dose calculation are the first steps in clinical prevention. Electronic prescribing methods and standardized pediatric concentrations help minimize preventable variation. In hospitals, barcode administration and smart infusion technology might offer extra security. [18, 21]

Documentation should make a clear distinction between a verified allergy and an unknown or non-allergic adverse impact when an ADR has already happened. Clarifying ADR reporting can stop needless avoidance of antibiotic classes and promote safer future prescribing, as the 2024 pediatric pharmacovigilance team study showed. [8]

Another inexpensive strategy is caregiver counseling. Parents should be aware of the medication's name, dosage, mode of administration, anticipated side effects, warning signs, and what to do in the event of an adverse response or missing dose.

20. Digital Pharmacovigilance and Artificial Intelligence

From basic electronic reporting to automated case discovery and signal prioritization, digital pharmacovigilance is growing. While natural language processing may scan clinical records for symptoms, probable medications, and outcomes, EHR triggers can flag patients who require review. [5, 24, 26]

In the future, machine learning techniques might be able to identify pediatric adverse drug reactions in big databases. Using a pediatric pharmacovigilance dataset from FAERS, a recent study found that a machine-learning method could find both known and perhaps new pediatric-specific ADR correlations. [32.] Because pediatric safety records are frequently sparse, these approaches show promise, but thorough validation is required.

False positives, hidden bias, inadequate data, and loss of clinical context are the primary dangers. A model that was trained in one facility might not work well in another. Therefore, rather than being employed as independent causality engines, digital technologies should be used as decision-support systems alongside human clinical review.

Future systems might integrate patient-generated data, EHRs, registries, and spontaneous reports into a single surveillance architecture. Early detection should be the aim without compromising clinical responsibility, privacy, or interpretability.

21. Challenges and Research Gaps

There are still significant gaps in pediatric pharmacovigilance. First, utilizing traditional clinical trials to evaluate unusual incidents is challenging. Second, in many evidence bases, neonatal and infant populations are still relatively underrepresented. Third, it may be challenging to consistently categorize exposure across studies due to off-label use. Fourth, direct comparisons are limited because different reporting systems employ different definitions and levels of data.

Additional difficulties are brought about by electronic data. According to a comprehensive review, pediatric pharmacovigilance studies frequently documented data-source quality and electronic health-record linkage inadequately. [24]. Only nine relevant studies were found out of 984 records in a single scoping review, demonstrating the continued scarcity of research utilizing unstructured EHR data. [26].

Long-term follow-up is another gap. Short-term use of a medication may make it seem safe, but long-term exposure or subsequent development may reveal its consequences. Thus, well-designed longitudinal investigations are necessary for pediatric pharmacoepidemiology. International cooperation could be beneficial by standardizing terminology and expanding the sample size for uncommon results. However, data sharing needs to be matched with ethical, governance, and privacy constraints.

22. Future Perspectives

Pediatric pharmacovigilance is probably going to become more data-driven and integrated in the future. Due to its accessibility and potential to produce unexpected signals, spontaneous reporting will continue to be significant. While electronic records might offer exposure denominators and clinical context, active hospital surveillance can enhance completeness. Longer-term follow-up can be supported via registries and record linkage. [2, 24, 25]

Additionally, signal detection is probably going to become more age-specific. Future analyzes can take into account developmental phases, disease context, medication formulation, and exposure intensity rather than considering all children under the age of eighteen as a single group. This could uncover patterns in aggregated data that are clinically significant.

Natural language processing, pattern identification, and case prioritization may all benefit from artificial intelligence, but transparent validation will be crucial. Human review should continue to be crucial, particularly for uncommon and significant pediatric incidents.

Above all, pharmacovigilance in the future should be more patient-centered. It should be easy for kids, teens, parents, and caregivers to describe possible reactions. Pharmacovigilance should be seen as a regular part of safer medication use and prescription practices, in addition to being a regulatory activity.

Table 1. Developmental considerations relevant to pediatric pharmacovigilance.

Age group	Key developmental issue	Common safety concern	PV focus
Neonates	Immature hepatic/renal function	Dose accumulation, sensitivity	Age, gestation, weight, organ function
Infants	Rapid maturation	Dose changes, formulation issues	Weight and developmental stage
Children	Changing body composition	Weight-based dosing, medication errors	Dose, formulation, adherence
Adolescents	Puberty and behavioral changes	Psychiatric/neurologic effects, self-medication	Privacy, direct reporting, chronic use

Table 2. Selected evidence from pediatric pharmacovigilance studies.

Study / source	Population or data	Key finding	Practical implication
Joyner et al., 2021 [5]	Children's hospital, 2019	280 ADRs by EMR triggers vs 21 voluntary reports	Active electronic surveillance detects more events
Leitzen et al., 2023 [6]	KiDSafe vs EudraVigilance	845 vs 697 reports; different safety profiles	Combine methods
Montastruc, 2023 [7]	WHO VigiBase, 2010–2019	1,198,560 pediatric reports; 1,585 fatal	Age-specific signal evaluation
Balcı et al., 2021 [12]	Pediatric ADR monitoring centre	Reported literature incidence 0.6–16.8%	Detection method affects estimates
VigiBase SJS-TEN, 2024 [13]	31,376,783 total ADRs; 2,248,727 pediatric	7,342 pediatric SJS-TEN; 165 drug signals	Rare severe events need large databases
FAERS SCAR, 2026 [27]	Children/adolescents	7,183 SCAR reports; 64.5% hospitalized	Serious rare events require rapid review

Table 3. Common pediatric pharmacovigilance challenges and possible solutions

Challenge	Why it matters	Possible response
Under-reporting	Safety signals may remain hidden	Education, simplified reporting, active surveillance
Off-label use	Evidence may be limited for age/formulation	Document exposure and monitor outcomes
Weight-based dosing	Calculation and concentration errors	Standardized concentrations and electronic dose checks
Poor ADR documentation	Future prescribing may be affected	Prospective PV review and clear EMR entries
Age heterogeneity	Signals can differ across developmental stages	Age-stratified analyses
Rare severe events	Too uncommon for small trials	Large databases and international collaboration
Unstructured clinical data	Useful information is difficult to query	NLP/AI with human validation

23. CONCLUSION

Because children's development, physiology, drug exposure, and clinical presentation of side effects differ from those of adults, pediatric pharmacovigilance is crucial. Important safety problems may remain unsolved due to limited pediatric trial populations, off-label and unlicensed use, age-dependent dose, formulation constraints, and medication errors.

Evidence from electronic health records and active surveillance shows that a significant percentage of pediatric adverse drug reactions may be missed by spontaneous reporting alone. A complementing surveillance paradigm is supported by the difference between 21 voluntarily reports and 280 ADRs found using electronic triggers in one pediatric hospital, as well as the distinct signals seen in systematic KiDSafe and spontaneous EudraVigilance reports.[5, 6]

An additional layer of evidence is provided by extensive pharmacovigilance databases. While subsequent VigiBase and FAERS investigations have found significant signals for severe cutaneous reactions and medication-specific adverse events, the WHO's review of 1,198,560 pediatric reports revealed 1,585 death occurrences.[7, 13, 16, 27]

Better reporting, age-sensitive analyzes, active surveillance, high-quality electronic data, empirical evidence, and meticulously vetted digital technologies will be essential to the future of pediatric pharmacovigilance. The ultimate goal is pragmatic: identify critical safety issues early, stop preventable injury, enhance future prescribing, and guaranty that children receive medications with the best possible risk-benefit ratio.

Additional Discussion: Practical Pediatric ADR Reporting Checklist

Prior to filing a pediatric ADR report, the reporter ought to make an effort to record the following:

• Patient: age, weight, sex, and any pertinent gestational or developmental data.

• The generic name, strength, formulation, method, dose, frequency, and indication of the suspected medication.

• Exposure: start and end dates of therapy, as well as any recent dose adjustments.

• Reaction: a detailed account of the clinical severity, laboratory results, onset time, and symptoms.

• Concomitant medications: any pertinent exposures to prescription, over-the-counter, and vaccinations.

• Recovered, recovering, not recovered, continuing, hospitalized, incapacitated, or deadly are the possible outcomes.

• Management: if the suspected medication was stopped or resumed, as well as the treatment administered for the reaction.

• Causality information: when available and morally acceptable, alternative causes, dechallenge, and rechallenge.

It is not necessary to demonstrate causation before submitting a report. Pharmacovigilance systems are intended to gather suspected reactions and evaluate them based on the information at hand. Simply said, having clear and comprehensive information increases the usefulness of that assessment.

Additional Discussion: Evidence Summary

The benefits of using different surveillance approaches are demonstrated by a few quantitative data from recent pediatric safety studies. In the same pediatric facility, Joyner et al. found 280 adverse drug reactions (ADRs) utilizing electronic triggers as opposed to 21 voluntarily reported ADRs. Leitzen et al. discovered significant variations in the kinds of incidents and medication-safety concerns recorded when they compared 697 spontaneous EudraVigilance reports with 845 methodically gathered KiDSafe reports. [5, 6]

From 2010 to 2019, the WHO fatal-ADR investigation found 1,198,560 pediatric complaints, of which 1,585 were fatal. 7,183 pediatric SCAR reports with hospitalization in 64.5% and a fatal outcome in 6.3% were found in the 2026 SCAR analysis using FAERS data through the second quarter of 2024. [7,27]Because spontaneous-reporting databases include reporting bias and do not have a straightforward denominator of exposed children, these figures should not be simply taken as population incidence. They are most helpful in illustrating the scope of safety data that is currently accessible and the capacity of various techniques to spot patterns that are clinically significant.

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