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Pharmacovigilance in Pediatric Populations: A Comprehensive

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Abstract: *Pharmacovigilance (PV) plays a pivotal role in ensuring the safety of medications in pediatric populations, a group particularly vulnerable to adverse drug reactions (ADRs) due to physiological differences, immature metabolic pathways, and limited clinical trial data. This comprehensive review examines the current state of pediatric pharmacovigilance, highlighting the unique challenges faced in this population, existing surveillance methods, global regulatory frameworks, and strategies for improvement. A systematic analysis of recent literature reveals that children experience ADRs at significantly higher rates than adults, with ADRs accounting for approximately 9.5% of pediatric hospital admissions, including 2.1% of all hospitalizations. The review synthesizes evidence from multiple databases and regulatory authorities to provide healthcare professionals, regulatory agencies, and pharmaceutical stakeholders with current insights into pediatric drug safety monitoring. Key findings indicate that allergic reactions are the most common type of ADR (40%), followed by gastrointestinal disturbances (25%), central nervous system effects (15%), respiratory issues (10%), and metabolic/electrolyte imbalances (10%). Furthermore, antibiotics account for 40% of ADRs, followed by antipyretics and analgesics (30%), vaccines (15%), and other drugs (15%). This review emphasizes the critical need for enhanced pharmacovigilance practices, improved reporting mechanisms, advanced technological integration, and international collaboration to minimize preventable adverse drug reactions in children worldwide.*

Keywords: Pharmacovigilance, pediatric patients, adverse drug reactions, drug safety, children, risk management

I. INTRODUCTION

Pharmacovigilance represents a crucial component of healthcare systems worldwide, serving as the scientific and operational foundation for detecting, assessing, and preventing adverse drug reactions and other medication-related problems. [1,2] For the pediatric population, this role becomes exponentially more critical given the unique physiological, developmental, and pharmacological characteristics that distinguish children from adults.

The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems".[2] However, the application of this definition in pediatric medicine requires special consideration, as children are not simply "small adults" with proportionally reduced drug requirements.[3]

Defining the Pediatric Population

The pediatric population comprises individuals aged 0-18 years, further subdivided into neonates (0-28 days), infants (28 days to 23 months), young children (2-11 years), and adolescents (12-16-18 years depending on regional definitions).[5] This broad age spectrum encompasses profound physiological and developmental changes that significantly impact medication efficacy and safety profiles.

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Epidemiology of Adverse Drug Reactions in Children

The prevalence of ADRs in pediatric patients (9.5%) is substantially higher than in general adult populations, with ADRs representing a significant cause of hospital admission (2.1%) and accounting for 39.3% of life-threatening events.[1] In hospitalized pediatric populations, serious ADRs account for up to 4% of admissions and occur in up to 18% of hospitalized pediatric patients.[8]

Rationale for Specialized Pediatric Pharmacovigilance

The impetus for dedicated pediatric pharmacovigilance stems from multiple factors:

- **Limited Clinical Trial Data:** Historically, pediatric populations have been systematically excluded from clinical drug trials, leading to a paucity of specific data on pediatric drug safety and efficacy.[2] This exclusion, while ethically justified to protect vulnerable populations, has created a significant knowledge gap.
- **Off-Label Medication Use:** Nearly 50-90% of drugs prescribed to children are not explicitly approved for pediatric use, increasing the risk of unexpected ADRs.[6] In hospitalized settings, approximately 40% of ordered medications in pediatric patients and more than 50% in neonates remain off-label, while in outpatient settings, approximately 20% of pediatric and more than 80% of neonatal visits result in one or more off-label drug prescriptions.[8]
- **Physiological Distinctiveness:** Children's developing organ systems, immature metabolic pathways, and evolving physiological functions create unique pharmacokinetic and pharmacodynamic profiles that differ fundamentally from adult populations.

II. PHYSIOLOGICAL DIFFERENCES AND THEIR IMPACT ON DRUG METABOLISM

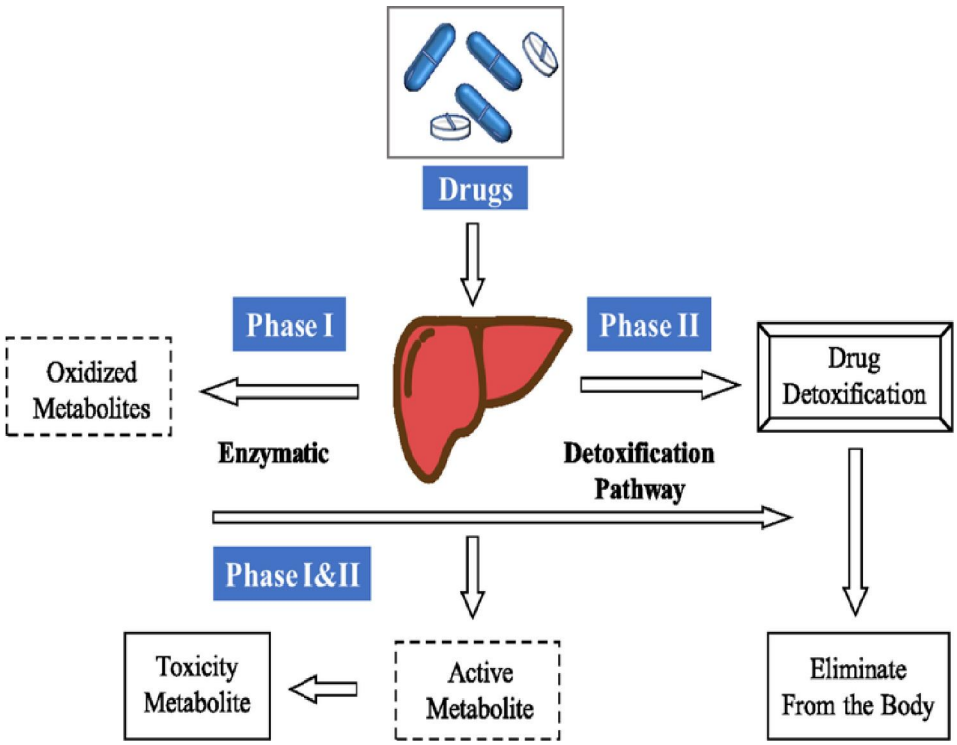

Fig 01. Biotransformation of drugs

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Drug Absorption

Neonates and infants exhibit significantly different drug absorption patterns compared to adults due to multiple factors, including higher gastric pH (less acidic) due to immature acid secretion, delayed gastric emptying and slower intestinal motility, and reduced enzyme activity in the gut.[3]

The higher gastric pH in newborns alters drug solubility and ionization, affecting absorption. For instance, weakly acidic drugs such as aspirin and phenytoin are less ionized in the stomach of adults, leading to better absorption; however, in neonates, their ionization is increased due to higher gastric pH, resulting in reduced absorption.[3]

Drug Distribution

Neonates demonstrate a higher total body water content (approximately 75-80%) compared to adults (approximately 55-60%), affecting drug distribution patterns.[3] This physiological difference has profound implications for hydrophilic drugs such as aminoglycosides, which require higher initial doses in neonates to achieve therapeutic plasma concentrations.

Conversely, neonates have lower fat stores than adults, resulting in reduced distribution of lipophilic drugs such as diazepam and barbiturates, leading to prolonged drug effects due to slower accumulation in fat tissues.[3]

Drug Metabolism

The liver is the primary site for drug metabolism, occurring in two phases. Phase I reactions (oxidation, reduction, hydrolysis) are mediated by immature cytochrome P450 enzyme systems in neonates, leading to slower metabolism of many drugs. For example, drugs such as theophylline and caffeine have prolonged half-lives in neonates due to deficient CYP1A2 activity.[3]

Phase II reactions, particularly glucuronidation, are underdeveloped in neonates, which explains why drugs like chloramphenicol can cause "gray baby syndrome" due to inadequate glucuronidation, leading to toxic drug accumulation.[3]

As children mature, hepatic enzyme activity increases, often exceeding adult metabolic rates by ages 1-9 years, resulting in faster drug clearance and shorter half-lives, requiring higher or more frequent doses in older children.[6]

Drug Excretion

The kidneys play a key role in drug elimination through glomerular filtration, tubular secretion, and reabsorption. Neonates have immature renal function, with glomerular filtration rate (GFR) approximately 30-40% of adult levels at birth, maturing over the first year of life.[3] This physiological immaturity prolongs elimination half-lives for drugs primarily excreted by the kidneys, such as aminoglycosides and penicillin, necessitating extended dosing intervals.

Pharmacodynamic Differences

Beyond absorption, distribution, metabolism, and excretion differences, children may exhibit altered drug sensitivity due to immature receptor systems. For instance, neonates exhibit increased sensitivity to opioids such as morphine, due to immature blood-brain barrier function and higher receptor affinity.[3]

III. CURRENT CHALLENGES IN PEDIATRIC PHARMACOVIGILANCE

Underreporting of Adverse Drug Reactions

One of the most significant obstacles to effective pediatric pharmacovigilance is the systematic underreporting of ADRs. Healthcare professionals often fail to report ADRs due to lack of awareness, time constraints, or the perception that ADRs are expected side effects of medication use.[6]

Moreover, caregivers and parents may not recognize or report ADRs, further complicating data collection and analysis, particularly because children may be unable to communicate their symptoms effectively.[3] This communication

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barrier is especially pronounced in very young children who cannot articulate subjective symptoms such as dizziness, nausea, or mood changes.

Ethical Limitations in Clinical Research

Ethical concerns often limit the inclusion of children in clinical trials, leading to a lack of pediatric-specific safety data. Informed consent is a significant issue, as young children cannot provide consent, and parents may be hesitant to enroll their children in studies. Consequently, many drugs are approved based on adult clinical trial data, increasing the likelihood of unforeseen ADRs in pediatric use.[3]

Lack of Pediatric-Specific Drug Formulations

Many medications lack age-appropriate formulations, forcing healthcare providers to manipulate adult dosages (such as crushing tablets or diluting solutions) to administer them to children. This practice can result in inaccurate dosing and unanticipated drug effects.[3]

Polypharmacy and Comorbidities

Children with chronic conditions frequently require multiple medications, increasing the risk of drug-drug interactions and compounded adverse effects. These interactions can be particularly dangerous in pediatric populations because of the lack of established safety data for drug combinations in children.

Medication Errors and Off-Label Use

The high prevalence of off-label medication use in pediatric practice, combined with the need for individualized dose calculations based on age, weight, and developmental stage, creates multiple opportunities for medication errors. These factors collectively contribute to the higher incidence of preventable ADRs in pediatric populations, with studies documenting that up to half of ADRs in hospitalized pediatric patients are preventable.[8]

IV. METHODS OF ADVERSE DRUG REACTION DETECTION IN PEDIATRICS

Spontaneous Reporting Systems

Spontaneous reporting systems (SRS) are among the most widely used pharmacovigilance methods for detecting ADRs in real-world clinical practice. In this passive surveillance approach, healthcare professionals, patients, and caregivers voluntarily report suspected ADRs to national or international regulatory authorities, such as the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and the World Health Organization (WHO) Global Individual Case Safety Reports database (VigiBase).[7]

These systems have proven valuable in identifying rare and serious ADRs that clinical trials may not capture. However, spontaneous reporting suffers from inherent limitations, particularly in pediatric populations where underreporting is endemic.

Active Surveillance and Cohort Studies

Active surveillance refers to proactive methods of ADR detection, in contrast to the passive nature of spontaneous reporting. This includes cohort studies, which involve systematically monitoring a group of children exposed to a specific drug over time to assess its safety profile.[3]

Active surveillance approaches, including Prescription Event Monitoring (PEM) and Electronic Health Records (EHR)-based studies, have demonstrated superior ADR detection rates compared to passive systems. For example, an Italian active monitoring system of ADRs in children developed through a network of family pediatricians raised the rate of ADRs per 100,000 children reported to the mandatory Italian system from 4 to 15.1 reported ADRs per 1000 children after 1 year of operation.[3]

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Electronic Health Records and Big Data Analysis

Modern information systems enable real-time monitoring of ADRs through analysis of electronic health records. Data mining techniques and artificial intelligence applications can identify patterns and signals indicative of previously unrecognized adverse reactions, particularly those occurring rarely or with delayed onset.

Post-Marketing Surveillance Studies (Phase IV Trials)

Post-marketing surveillance, or Phase IV trials, involve monitoring the safety of a drug after it has been released to the market. Unlike pre-marketing clinical trials, Phase IV studies are more focused on detecting ADRs that may not have been identified earlier due to smaller sample sizes or the exclusion of certain population groups, including children.[7]

Case-Control Methodologies

Case-control studies comparing children who have experienced specific ADRs with matched controls can identify risk factors and drug-ADR associations with greater precision than spontaneous reports alone.

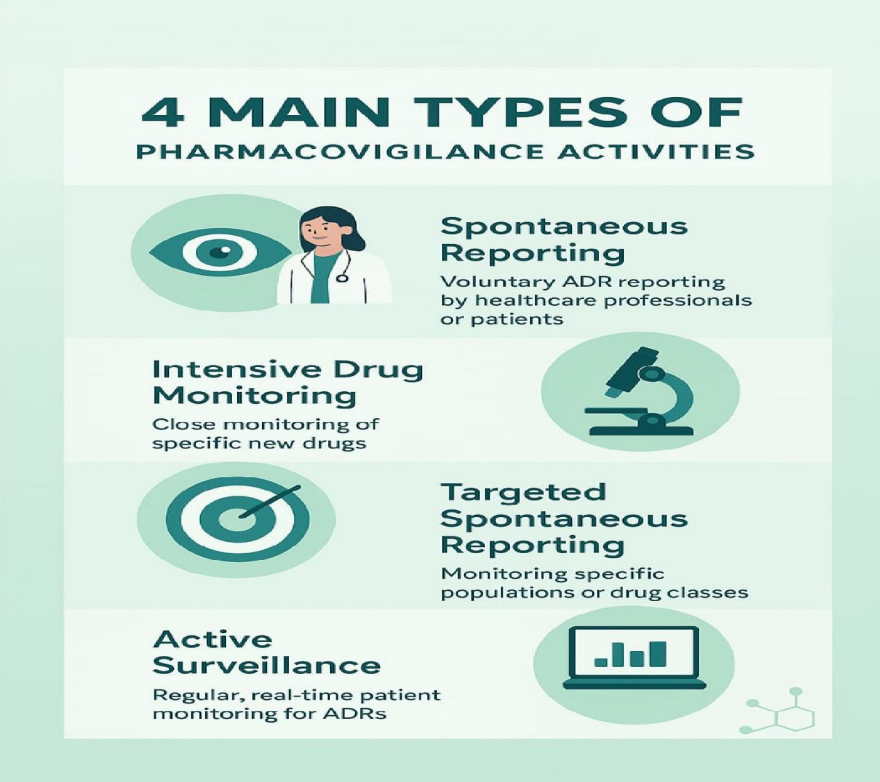

Fig 02. Types of Pharmacovigilance Activities.

V. GLOBAL REGULATORY FRAMEWORKS

European Union Regulatory Approach

The European Medicines Agency (EMA) established the Pediatric Regulation (EC No. 1901/2006), adopted in 2007, to address challenges of differing pharmacokinetic and pharmacodynamic profiles compared to adults, uncertainty about long-term drug riskbenefit profiles, and additional risks from off-label medicine use, with the goal of identifying research priorities and increasing the volume and quality of pediatric research.[5]

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The European Pediatric Regulation mandates that pharmaceutical companies develop and submit Pediatric Investigation Plans (PIPs) for all new medicines, ensuring that pediatric drug studies are integrated into the approval process. This regulation stipulates that, except for certain exemptions, marketing authorization applications for drugs must include research conducted in children.[5]

United States Regulatory Approach

The U.S. Food and Drug Administration has implemented several legislative and regulatory frameworks to promote pediatric drug safety. The Best Pharmaceuticals for Children Act (BPCA, 2002) encourages pharmaceutical companies to conduct pediatric drug studies by providing additional market exclusivity incentives. The Pediatric Research Equity Act (PREA, 2003) requires pharmaceutical companies to assess the safety and efficacy of new drugs in pediatric populations if the medication is likely to be used in children.[5]

The FDA also established the Pediatric Advisory Committee (PAC) to review safety problems found in the year following the granting of exclusivity and seek suggestions for action. The PAC consists of 14 voting members with experience in pediatric research, pediatric subspecialties, statistics, and biomedical ethics.[5]

Japanese Regulatory Approach

Under the Ministry of Health, Labour and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA) has established three systems to ensure drug safety and effectiveness after approval: a system for reporting adverse events, a system for re-reexamination using post-approval data, and a system for re-evaluation. The Pharmaceutical Affairs Law was updated in 2002 with majority of revisions, providing information on the

Good Vigilance Practice (GVP) and Good Post-Marketing Research Practice (GPSP) criteria.[5]

Since Fiscal Year 2012, the Network Implementation Project for Collecting Data on Pediatric Drug Safety has developed and maintained a system at the National Centre for Child Health and Development (NCCHD) to collect and analyze safety information in pediatric populations. By December 2019, 460,000 medical data from patients and 50,000 questionnaire data from patients had been processed and periodically updated in this framework.[5]

Indian Regulatory Approach

Pharmacovigilance in India was introduced in 1986 under the supervision of the drug controller with a standardized ADR monitoring system. In 1998, India joined the WHO's

International Drug Monitoring Program. In 2005, the program was renamed the Pharmacovigilance Program of India (PvPI), with the goal of safeguarding public health by ensuring that drug use is conducted safely and effectively.[5]

Paediatric pharmacovigilance

Paediatric pharmacovigilance is an ongoing process that begins with the first administration of a drug to a child, which can occur during clinical trials or in everyday clinical practice, and may involve off-label or unlicensed uses. This process assesses the existing knowledge of treatment-related risks for children—referred to as the current paediatric safety specification—against new data from clinical trials, spontaneous reports, non-clinical safety studies, and observational research. It also looks into potential risks, addressing gaps in safety information such as risk factors or outcomes.

Additionally, it encompasses routine paediatric pharmacovigilance issues such as the long-term effects of treatments, medication errors, non-compliance due to age-inappropriate formulations, ineffectiveness from underdosing, adverse reactions from excipients, and drug interactions (including interactions with food and between different excipients in co-medications). When relevant, it also considers challenges related to medical devices that are not well-suited for children.

Moreover, it incorporates traditional pharmacovigilance topics like designated medical events (DMEs), pharmacogenetics, and considerations for special populations (like individuals with renal or hepatic impairments). The

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paediatric safety specification and associated risk management strategies are periodically updated as new safety information is obtained, which may necessitate revisions to existing study protocols, informed consent forms, and product labels. Key components of the paediatric pharmacovigilance cycle are illustrated in Figure 2.

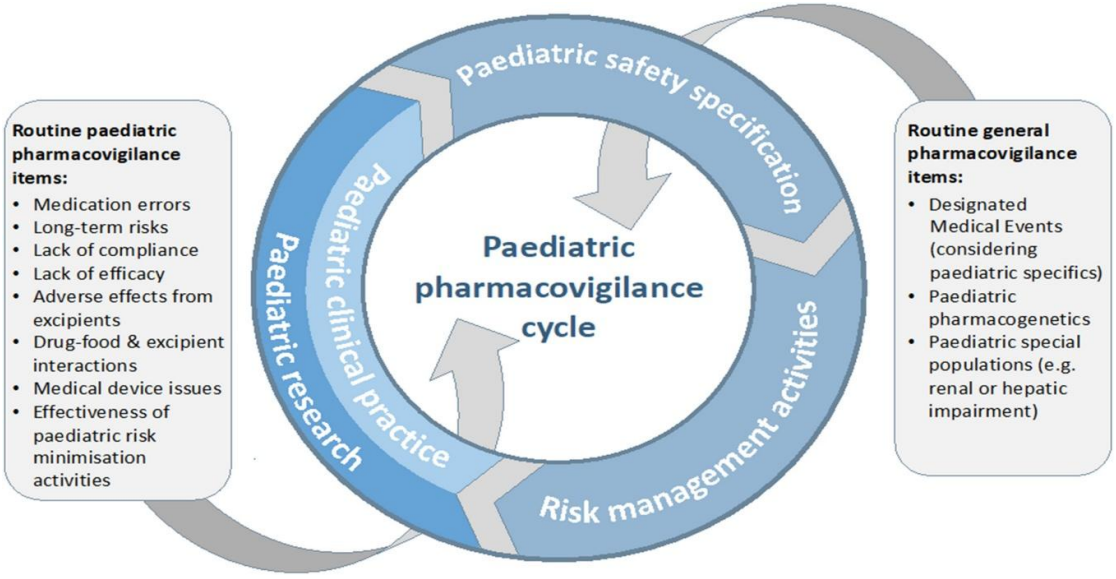

Fig 03. Paediatric Pharmacovigilance Cycle

VI. PATTERN OF ADVERSE DRUG REACTIONS IN PEDIATRIC POPULATIONS

Age-Related Incidence Patterns

Analysis of pediatric ADRs reveals a higher susceptibility among younger children, with those under 2 years experiencing the highest incidence rate (40%), followed by those aged 2-6 years (35%), children aged 7-12 years (20%), and teenagers aged 13-18 years (5%).[0]

Clinical Presentations and Affected Body Systems

The breakdown of ADR types revealed that allergic reactions were the most common, constituting 40% of reported ADRs and including manifestations such as rashes and urticaria. Gastrointestinal disturbances represented 25% of ADRs, followed by central nervous system effects at 15%, respiratory issues at 10%, and metabolic/electrolyte imbalances also at 10%.[0]

In a comparative study, the most commonly affected body system in pediatric patients was skin and appendages (31.60%), followed by gastrointestinal disorders (25.11%) and body as a whole (15.15%).[8]

Severity Classification

In terms of severity, 60% of ADRs were classified as mild, 30% as moderate, and 10% as severe.[0] In hospitalized pediatric populations, majority of ADRs (87%) were nonserious in nature, with serious ADRs requiring intervention to prevent damage (6.93%) and those resulting in prolonged hospitalization (3.89%).[8]

Causative Medications

Antibiotics were identified as the leading cause of ADRs (40%), followed by antipyretics and analgesics (30%), vaccines (15%), and other drugs (15%).[0]

In pediatric populations specifically, antimicrobial agents represented the most common drug group causing ADRs (33.46%), followed by blood products (14.12%), with antimicrobials including beta-lactam antibiotics (36.47%), macrolides (14.12%), fluoroquinolones (7.6%), antimalarials (7.6%), and vancomycin (7.6%).[8]

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VII. SPECIFIC DRUG CLASSES OF CONCERN IN PEDIATRICS

Antibiotics

Macrolide antibiotics, particularly azithromycin and erythromycin, carry significant risk of hypertrophic pyloric stenosis in infants, with erythromycin conferring higher risk than azithromycin. These agents should be avoided in infants younger than one month except for specific indications such as Bordetella pertussis or Chlamydia trachomatis pneumonia.[6]

Tetracyclines pose a well-established risk of tooth discoloration when administered before mineralization of permanent teeth is completed by 8 years of age, excluding third molars. Although tetracyclines should be avoided in children younger than 8 years, their use may be necessary in some children. Doxycycline, while structurally similar to tetracycline, demonstrates largely lacking in vivo reports of tooth discoloration, enamel hypoplasia, and bone growth retardation, making it recommended as first-line for short-term treatment (21 days or less) of susceptible infections.[6]

Antipsychotics

First-generation antipsychotics carry substantial risk of acute dystonic reactions (such as oculogyric crisis and torticollis) and hyperprolactinemia in pediatric populations. Youth are at increased risk for acute dystonic reactions due to sensitivity to potent D2 blockade within the nigrostriatal and tuberoinfundibular dopamine pathways. First-generation antipsychotics should be avoided in patients 18 years and younger, with alternative agents such as olanzapine available with reduced risk for adverse effects.[6]

Second-generation antipsychotics present metabolic risks including type 2 diabetes, weight gain, dyslipidemia, and metabolic syndrome, with clozapine and olanzapine conferring highest risk, while ziprasidone and lumateperone present lowest risk. Additionally, withdrawal-emergent dystonia/dyskinesia and hyperprolactinemia represent important considerations with second-generation antipsychotics.[6]

Opioids

Codeine carries FDA recommendations for avoidance in children younger than 12 years due to respiratory failure and death risk, with avoidance in 12-18-year-old patients after surgery to remove tonsils and/or adenoids, and caution in 12-18-year-olds with recommendation for pharmacogenetic testing.[6]

Meperidine should be avoided in children younger than one month and used with caution in patients 18 years and younger due to risk of acute neurotoxicity manifested as agitation, myoclonus, hyperreflexia, tremors, delirium, and seizures.[6]

Montelukast

In 2020, the FDA released a boxed warning regarding serious neuropsychiatric adverse effects associated with montelukast, including irritability, aggression, anxiety, and mood disorders. Sleep disturbances such as nightmares have been shown to occur more commonly in children. Thus, montelukast should be used with caution in children 18 years and younger, with close monitoring for neuropsychiatric effects.[6]

VIII. STRATEGIES FOR IMPROVING PEDIATRIC PHARMACOVIGILANCE

Pediatric-Specific Adverse Drug Reaction Databases

Establishing dedicated, globally-networked pediatric ADR databases would facilitate collection of broader ADR data that might be overlooked in general pharmacovigilance systems. Disease-specific registries for pediatric oncology, HIV treatment, and other specialized conditions enable long-term follow-up to detect delayed or long-term adverse reactions.

Education and Training Initiatives

Healthcare professionals, including pediatricians, nurses, and pharmacists, require thorough training on ADR detection in children, including identification of symptoms suggesting drugrelated issues, awareness of pediatric vulnerabilities, and proper ADR reporting procedures.

Training should emphasize how ADRs in children might differ from those in adults.[7] Educating parents and caregivers about potential medication side effects and encouraging them to report adverse reactions is critical. Parents

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should receive guidance on detecting ADR signs and receive clear instructions on reporting procedures to appropriate authorities.[7]

Regulatory Policy Enhancements

Strengthening regulatory guidelines globally to require pediatric drug testing and robust post-marketing pharmacovigilance practices for drugs prescribed to children is essential. While the Pediatric Research Equity Act (PREA) in the U.S. requires that new drugs and biologics be tested in pediatric populations, similar frameworks must be expanded globally to provide clearer understanding of drug effects in children.[5]

Pharmacogenomics Integration

Identifying genetic markers for ADR susceptibility, including variations in genes encoding drug-metabolizing enzymes such as CYP450 enzymes, enables identification of children at increased vulnerability for ADRs when administrating certain drugs. Integrating pharmacogenomics into clinical practice allows pediatricians to tailor drug treatments to individual children based on genetic makeup.[7]

Advanced Technology Implementation

Artificial intelligence (AI) and machine learning can enhance ADR signal identification and analysis, providing real-time insights into pediatric medication safety. AI-driven analytics can identify ADR patterns from large datasets more efficiently, while natural language processing can extract ADR reports from unstructured sources such as patient forums and medical notes.[7]

Cross-Sector Collaboration

Comprehensive pediatric pharmacovigilance requires collaboration among pharmaceutical companies, healthcare providers, researchers, parents, and regulatory bodies. Industry must invest in pediatric studies and post-marketing surveillance, while regulatory authorities should facilitate information sharing and standardization of reporting systems.

IX. FUTURE DIRECTIONS IN PEDIATRIC PHARMACOVIGILANCE

Real-World Evidence and Big Data Analytics

Future pharmacovigilance systems should leverage integration of multi-source data including clinical trial data, post-marketing surveillance, and patient-reported outcomes. Continuous, real-time surveillance using data streams from electronic health records can enable early warning signal detection for pediatric medication risks.

International Harmonization

Harmonization of regulatory standards through international collaboration between organizations like the FDA, EMA, and WHO can standardize pediatric pharmacovigilance guidelines globally. Development of centralized databases for pediatric ADR reporting can facilitate global data sharing.[7]

Enhanced ADR Reporting Mechanisms

Digital and mobile-based ADR reporting systems should be developed to improve accessibility for healthcare professionals, parents, and caregivers. Integration with EHR systems could streamline reporting by healthcare providers, while patient-reported ADR systems can encourage direct reporting from parents and older pediatric patients to improve

ADR detection rates.[7]

Personalized Medicine Approaches

Advances in pharmacogenomics combined with physiologically-based pharmacokinetic modeling will enable development of personalized medicine strategies tailored to individual pediatric patients, maximizing therapeutic benefit while minimizing ADR risk.

CASE STUDY :

The Coldrif Incident: Product Details

Coldrif is a cough syrup produced by Sresan Pharmaceuticals, located in Tamil Nadu, India. The tainted batch (SR-13) was created in May 2025 and is set to expire in April 2027. This commercial formulation includes typical ingredients

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found in pediatric cough syrups, such as paracetamol, phenylephrine hydrochloride, and chlorpheniramine maleate, which are commonly present in over-the-counter cold remedies.[9]

Fig 04. Coldrif Cough Syrup

Causes and Mechanisms of Contamination

Manufacturing and Supply Chain Failures

The disasters are primarily attributed to the unethical and illegal replacement of pharmaceutical-grade excipients with less expensive, hazardous industrial solvents.[10] Manufacturers implement cost-reduction strategies by substituting pharmaceutical-grade propylene glycol or glycerin with more affordable, industrial-grade DEG, which is commonly utilized in automotive brake fluid and antifreeze.[10]

Contaminated supply chains incorporate these detrimental substances due to the use of unreliable suppliers and the lack of necessary batch-wise testing of raw materials.[10]

Throughout various outbreaks, consistent underlying factors have been recognized: the adulteration or replacement of industrial glycols with pharmaceutical excipients often takes place as a result of financial pressures or insufficient supplier evaluation.[11], [12],[13]

Toxicological Mechanism

Diethylene glycol (DEG) and ethylene glycol (EG) are small, sweet-tasting solvents that are sometimes illicitly utilized as inexpensive substitutes for pharmaceutical glycols. Upon ingestion, these substances are metabolized into toxic metabolites—specifically oxalic and glycolic acids—which can lead to renal tubular necrosis, metabolic acidosis, and depression of the central nervous system.[14],[15]

Children are especially vulnerable due to their lower body weight and reduced capacity for renal clearance.[16] The clinical progression generally initiates with symptoms affecting the central nervous system and gastrointestinal tract, advancing over a period of 24 to 72 hours to acute kidney injury (AKI) and, if not treated, can result in death.[16]

Regulatory Response and Recommendations

In light of the incident that occurred in October 2025, India's regulatory authority, the Drugs Controller General of India (DCGI), has strengthened regulations mandating the testing of raw materials and finished products for DEG/EG,

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in addition to expedited sample testing. These actions are in accordance with WHO recommendations; however, they must be executed with strict adherence.[17]

Immediate Actions

Confiscation of stock and prohibition of products Focused examination of supplementary batches and producers Detention of accountable company staff when deemed necessary [18],[19]

Regulatory Strengthening Measures

1. Mandatory DEG/EG Examination: It is essential for all manufacturers of oral liquid formulations, especially those intended for children, to conduct testing of final products and excipients utilizing approved chromatographic methods (GC, LC-MS).[17]
2. GMP Audits: Enhance the capacity for regulatory inspections to scrutinize internal quality control documentation, glycol supply chains, and excipient suppliers, which should include unannounced audits of liquid formulation facilities.[17]
3. Centralized Reference Laboratories: Create or designate regional laboratories for chemical analysis and toxicology that are equipped with GC/MS or LC/MS technology for the independent testing of samples from manufacturers.[17]
4. Serialization and Traceability: Enforce the use of unique identifiers on all bottles and packaging units, along with digital records that trace product lots back to raw material suppliers, production dates, shipping, and distribution channels.[17]
5. Rapid Recall Procedures: Set legal timeframes for sample testing, public notifications, recalls of suspect lots, and compensation for affected individuals.[17]

Surveillance and Communication Systems

Continuous oversight of negative occurrences, especially within pediatric healthcare facilities
Real-time notification and alert platforms available to pharmacies and healthcare providers
Regular public education initiatives concerning the safe utilization of pediatric syrups [21],[17],[20]

International Coordination

The U.S. FDA, WHO, and European Medicines Agency have publicly monitored the situation and released recommendations for import/export surveillance.[20],[22] .
WHO has issued medical product alerts and requested member states investigate supply chains.[19]

Recommended international measures include:

Cross-border rapid-alert systems with standardized testing procedures.
Strict controls on import and export of liquid medications and excipients.
Capacity building for regional reference laboratories.
Criminal accountability mechanisms for manufacturers and suppliers [19],[22].
Clinical and Policy-Level Recommendations

For Healthcare Providers

Maintain a heightened level of suspicion for medication-related poisoning in pediatric acute kidney injury (AKI) cases.
Facilitate prompt triage and hemodialysis for children experiencing metabolic acidosis or oliguria.
Administer fomepizole when it is accessible.
Ensure effective communication with public health authorities concerning suspected lots [17],[22].

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For Supply Chain and Manufacturing

Mandatory screening for diethylene glycol (DEG) and ethylene glycol (EG) in all glycerine and propylene glycol lots, as well as finished oral liquids intended for pediatric use.

Vendor qualification must include documented supplier chains and certificates of analysis.

Conduct independent third-party testing through government laboratories to confirm compliance with industry standards [17],[22].

For International and Regulatory Bodies

Develop expedited alert systems that incorporate standardized testing protocols.

Harmonize national pharmacopoeia standards to enforce glycol limits.

Invest in the enhancement of analytical laboratory capabilities.

Integrate system reforms with mechanisms for legal and criminal accountability [18],[19].

Limitations of Current Evidence

Swift reporting of news and preliminary laboratory alerts deliver a substantial portion of immediate information concerning this incident; nevertheless, conclusive case numbers and forensic laboratory verification are still awaited in various nations.

Long-term studies evaluating the true global impact of medications contaminated with glycol are scarce.

This review emphasizes authoritative sources from the WHO, national regulatory bodies, and prominent news organizations, although specific aspects may evolve as the ongoing inquiries reach completion.[13],[23]

X. CONCLUSION

Pediatric pharmacovigilance represents a critical yet underdeveloped area of medication safety requiring urgent attention and substantial resource allocation. The unique physiological, developmental, and pharmacological characteristics of children create complex challenges for drug safety monitoring that cannot be adequately addressed through adult-focused systems alone.

Key findings from comprehensive analyses demonstrate that adverse drug reactions in pediatric patients represent a significant health burden, with allergic reactions being most common (40%), followed by gastrointestinal disturbances (25%), and CNS effects (15%), with antibiotics being the leading causative medication class (40%).

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