*Original Research* *Parul University Journal of Health Sciences and Research*
*ISSN: 2583-990X (E)*
*https://doi.org/10.62373/PUJHSR.2024.113*

# A Study on Pharmacovigilance in the Hospitalized Pediatric Patients at Tertiary Care Hospital

**Vedant Sheth *[1], Dhaval Chauhan [1], Ganesh Sharma [1], S P Srinivas Nayak [2].**

*[1] Department of Pharmacy Practice, Parul Institute of Pharmacy and Research. Parul University, Vadodara, Gujarat, India, 391760
[2] Assistant Professor, Department of Pharmacy Practice, Parul Institute of Pharmacy and Research. Parul University, Vadodara, Gujarat, India, 391760.

**Corresponding Author:** Vedant Sheth, Department of Pharmacy Practice, Parul Institute of Pharmacy and Research. Parul University, Vadodara, Gujarat, India, 391760 **E-Mail:** vsheth134@gmail.com

## ABSTRACT

Pharmacovigilance is a critical aspect of public health, aiming to detect, assess, understand, and prevent adverse effects and other drug-related issues. It plays a pivotal role not only in the development phase of medications but also in post-marketing surveillance, ensuring ongoing safety and efficacy. In India, the Pharmacovigilance Programme (PvPI) spearheaded by the All India Institute of Medical Sciences (AIIMS) aims to safeguard public health by collating and analyzing data to inform regulatory interventions and communicate risks to healthcare professionals and the public. The classification of adverse drug reactions (ADRs) based on types and severity provides a framework for understanding and managing these occurrences. Additionally, factors predisposing individuals to ADRs, such as drug-related, social, patient-related, and disease-related factors, are crucial considerations in pharmacovigilance efforts. Furthermore, understanding drug interactions, including pharmacokinetic and pharmacodynamic interactions, combined toxicity, additive effects, synergistic effects, and antagonistic interactions, is essential in optimizing therapy and minimizing risks to patients. Overall, pharmacovigilance is indispensable in ensuring the rational use of medicines and optimizing patient outcomes while safeguarding public health.
**KEYWORDS:** Pharmacovigilance, Pediatric, PvPI, Adverse drug reaction.

## INTRODUCTION

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problems [1]. The goal of pharmacovigilance is to enhance patient safety by ensuring that medicines are used appropriately and that any potential risks associated with their use are identified and minimized Pharmacovigilance is important not only during the development of new drugs but also after they have been approved for marketing and are being used in the general population. This ongoing monitoring is necessary to detect any previously unrecognized adverse effects and to determine the safety of the drugs in different patient populations, such as pregnant women, children, and the elderly [2]. To achieve its goals, pharmacovigilance relies on the collection and analysis of data from a variety of sources, including spontaneous reports of adverse drug reactions, observational studies, clinical trials, and registries [3].

Healthcare professionals play a crucial role in pharmacovigilance by reporting suspected adverse drug reactions to regulatory authorities, such as the FDA or EMA [4] Overall, pharmacovigilance is essential in ensuring the safety and efficacy of medicines and protecting public health. By identifying and minimizing the risks associated with drug use, pharmacovigilance helps to promote the rational use of medicines and to optimize patient outcomes.

The World Health Organization defines ADR as “a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.” [1,2] This definition, therefore, does not include drug misuse, accidental or purposeful overdoses, failed treatments, or mistakes in drug administration [2].

An adverse Drug Event [AE] is ‘any untoward medical occurrences that may present during the treatment with a medicine but does not necessarily have causal relationship with this treatment’ [5,7] An adverse drug event is any negative result that occurred while receiving therapy but wasn't necessarily brought on by the medication [6,7].

PHARMACOVIGILANCE PROGRAMME OF INDIA [PvPI] The All India Institute of Medical Sciences (AIIMS), New Delhi was designated as the National Coordination Center for the Pharmacovigilance Programme of India (PvPI), which was launched by the Indian government on July 14, 2010, with the goal of safeguarding public health. The Programme shall be coordinated by the IPC, Ghaziabad as a National Coordinating Centre (NCC). A Steering Committee will be in charge of running the center. [9] PvPI's goal is to protect the health of the Indian population by ensuring that the advantages of using a medicine outweigh any risks involved with it. The purpose of the PvPI is to collate data, analyze it and use the inferences to recommend informed regulatory interventions, besides communicating risks to healthcare professionals and the public. It also includes the detection of standard quality medicines as well as errors regarding prescribing, dispensing, and administration [10].

Adverse drug reaction (ADR) monitoring involves the following steps: 1. Identifying adverse drug reaction (ADR) 2. Assessing causality between drug and suspected reaction by using various algorithms. 3. Documentation of ADR in patient’s medical records. 4. Reporting serious ADRs to pharmacovigilance centers /ADR regulating authorities [11]. The effectiveness of drugs utilized in patients in an adult age group cannot be extrapolated to a pediatric age group. Many commonly used medications have pharmacokinetic and pharmacodynamic profiles that vary greatly between these two patient age groups [12,14]. Additionally, ADRs in children may have a more devastating impact than in adults. ADRs can therefore result in serious morbidity in children [13,14]. ADRs in children have been shown to have serious consequences, including lasting disability or even death, in addition to hospital stays or protracted hospitalization [15].

The risk of medication toxicity is higher in pediatric populations since many new drugs are launched without adequate pharmacovigilance studies. This makes them more vulnerable to rational drug prescribing [16].

**CLASSIFICATION OF ADR (Based on Williams and Brown)**

**TYPE A- Augmented [Dose-related]** These reactions usually exacexacerbations the pharmacological effect of the drugs and are dose dependent eg- insulin-induced hypoglycemia. These reactions are usually predictable due to their known pharmacology and are preventable. Incidence of type A reactions are high, they are associated with less mortality and morbidity.

**TYPE B- Bizarre [Non-dose-related]** These reactions are hypersensitivity reactions and are not dose dependent. Eg. penicillin-induced hypersensitivity reactions. These reactions are not predicted and are preventable in some cases. This type is associated with high mortality and morbidity, but its occurrence is quite low.

**TYPE C- Chronic [Dose-related and time-related]** These reactions are a disease that occurs at a higher frequency among exposed patients than those unexposed, the exact mechanism is unknown. Eg high frequency of CV event among patient exposed to COX-2 inhibitors.

**TYPE D- Delayed [Time-related]** These type of reaction become apparent past sometime after the use of medicine. The incidence is low and are difficult to diagnose.

**TYPE E- End of use [Withdrawal]** These type of reaction occur when the drug treatment is abruptly terminated. Eg withdrawal seizures on terminating anti-convulsant.

**TYPE F- Familial [Unexpected failure of therapy]** These type of reaction occur when the desired pharmacology target therapy is not achieved.

**Type G-Genotoxicity** These type of ADR occurs due human errors

**TYPE H- Hypersensitivity**

**TYPE U- Unclassified [17,18]**

ADRs are also classified based on their severity: [19,20]

| SEVERITY | DEFINITION |
|---|---|
| Mild | The drug can be continued without any treatment |
| Moderate | The drug was stopped and/or required treatment |
| Severe | The reaction caused hospital admission, permanent disability, delayed discharge, or was life-threatening |
| Lethal | Drug reactions directly or indirectly caused the death |

**Predisposing Factors**

These variables include social, patient, and disease-related variables as well as drug-related variables. [21,8]

1. Drug-related factors
   - Drug Dose and Frequency
   - Poly Pharmacy
2. Social factors
   - Race and Ethnicity
   - Alcohol

- Smoking

3. Patient-related factors
   - Age
   - Gender
   - Pregnancy
   - Fetal development
   - Renal function
   - Liver function
   - Allergy
4. Disease-related factors Patients are more likely to experience adverse drug reactions (ADRs) when multiple disease conditions are present at once. For instance, a rise in the incidence of idiosyncratic toxicity with antibiotics such as trimethoprim-sulphamethoxazole [22,8].

   When two or more medications, or a medication and another substance, interact with one another, it might affect how the drugs are metabolised, absorbed, or removed from the body. This is known as a drug-drug interaction. These interactions may limit the therapeutic benefits of one or both medications' effectiveness and safety, as well as increase the risk of side effects.

   **Drug interactions can be classified into several types:**

- Pharmacokinetic interactions: These interactions involve changes in how drugs are absorbed, distributed, metabolized, or excreted in the body. For example, one drug may inhibit or induce the enzymes responsible for metabolizing another drug, altering its concentration in the bloodstream.
- Pharmacodynamic interactions: In this type of interaction, two drugs with similar or opposing effects may be taken together, leading to an enhanced or reduced therapeutic effect. This can increase the risk of side effects or reduce the efficacy of one or both medications.
- Combined toxicity: Some drug combinations can increase the risk of adverse effects due to their shared toxicities. Taking multiple medications with similar side effects, such as drugs that can cause liver damage, can pose a higher risk to the patients.
- Additive or synergistic effects: When two drugs with similar pharmacological effects are combined, they may have an additive or synergistic effect, leading to a more potent response than expected. This can be beneficial if intended, but it may also increase the risk of adverse effects.
- Antagonistic interactions: On the other hand, antagonistic interactions occur when one drug counteracts the effects of another. This can lead to a reduced therapeutic effect or treatment failure.

## Methods and Materials

- Study Site: Parul Sevashram Hospital, Vadodara
- Duration of Study: Data was collected between February-April 2023
- Proposed Sample size: 100
- Study Criteria
  - Inclusion criteria:
    - Patients of age 0-18 groups
    - Patients of either sex

- Patients who are willing to take part in the study and willing to give written, signed, and dated informed consent to participate
- Patients who are prescribed any drug
- Patient presenting with any underlying disease
- Subjects and parent/legal guardian who is capable of giving a signed informed consent form
- Parent/legal guardian of the subject who is capable of giving a signed assent form
- The study is going to be conducted only with IPD pediatric patients

➢ Exclusion criteria:

- Patients not willing to take part in the study and not ready to sign the consent form
- The study excludes pediatric outpatients
- Patients who are above the age of 18

- Materials required:
  - ✓ Patient consent form
  - ✓ Assent form
  - ✓ Patient information leaflet
  - ✓ Data collection form
  - ✓ ADR report form

## RESULTS

### GENDER DISTRIBUTION

TABLE 1 shows gender distribution

| | |
|---|---|
| MALE | 53% |
| FEMALE | 47% |

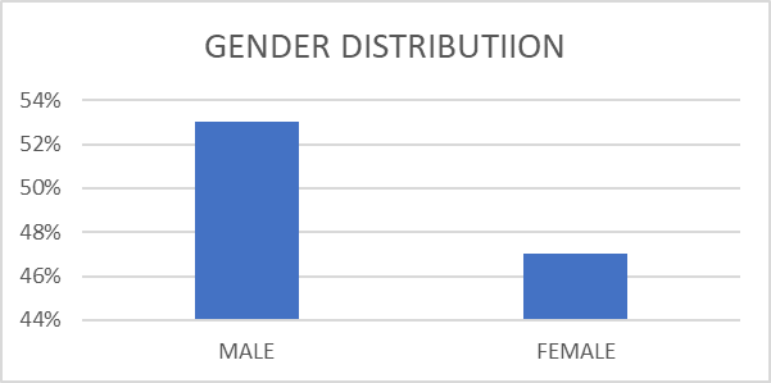


FIGURE 1 shows graphical representation of gender distribution

Out of the total patients, 53% of them were males and 47% of them were females.

### AGE DISTRIBUTION

TABLE 1.1 shows age distibution

| | |
|---|---|
| School age children | 30% |
| Adolescents | 30% |
| Toddlers | 20% |

| | |
|---|---|
| Infants | 15% |
| Neonates | 15% |

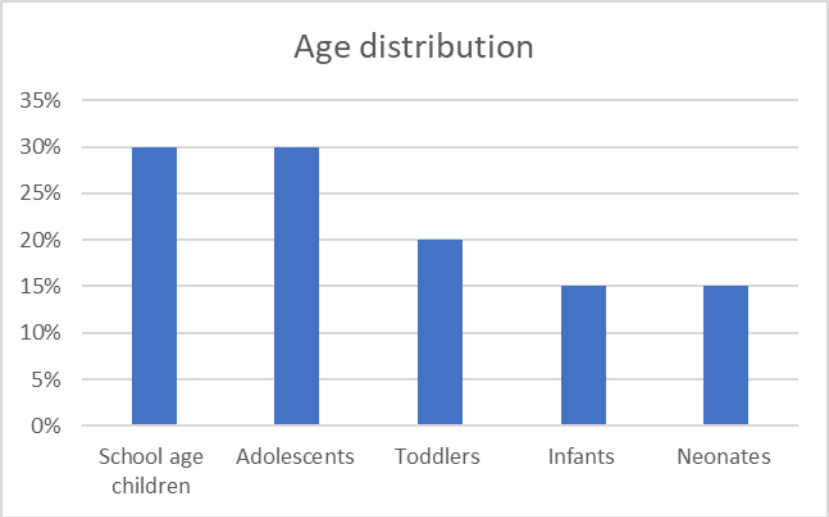


FIGURE 1.1 shows graphical representation of age distribution

According to the data, the school age children and adolescents were 30%, toddlers were 20%, infants and neonates were 15% each.

## COMMONLY PRESCRIBED DRUG CLASS

TABLE 1.2 shows commonly prescribed drug class

| | |
|---|---|
| Antibiotics | 45% |
| Analgesics | 25% |
| Analgesics | 25% |
| Others | 5% |

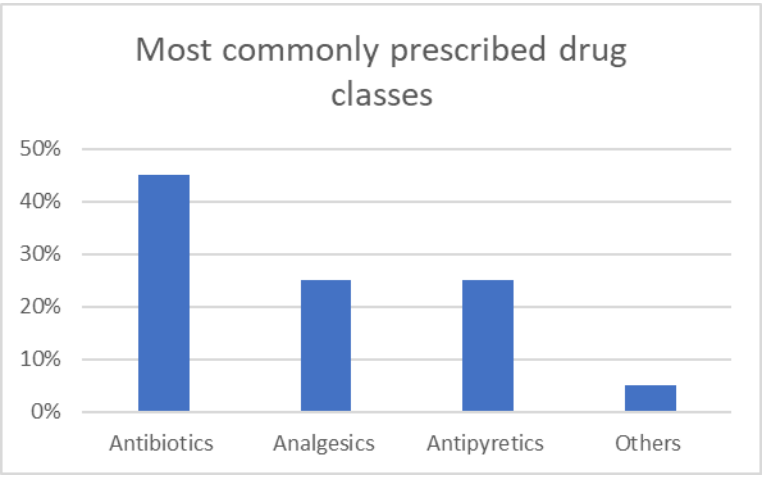


FIGURE 1.2 shows graphical representation of Most commonly prescribed drug classes

## AGE GROUP ASSOCIATED WITH ADR OCCURRENCE

TABLE 1.3 shows age group associated with ADR occurence

| | |
|---|---|
| Neonates | 2% |

| | |
|---|---|
| Infants | 5% |
| Toddlers | 10% |
| School-age children | 20% |
| Adolescents | 23% |

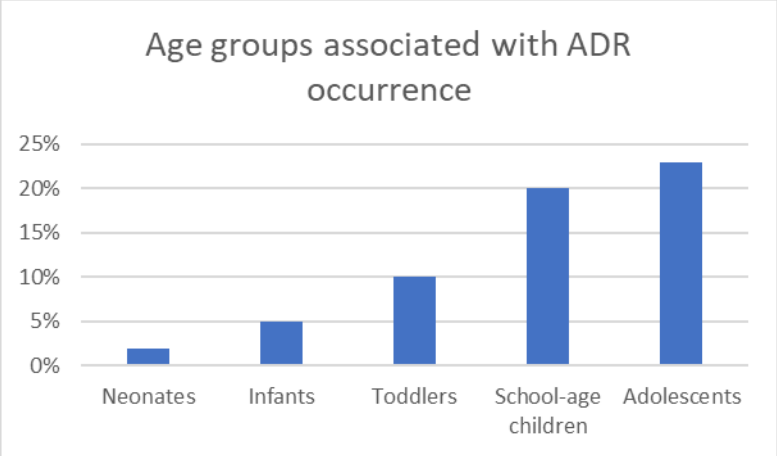


FIGURE 1.3 shows graphical representation of age group associated with ADR occurence

**BARRIERS OF ADR REPORTING**

TABLE 1.4 shows barriers of ADR reporting

| | |
|---|---|
| Lack of awareness | 70% |
| Uncertainty about ADR severity | 15% |
| Time constraints | 15% |

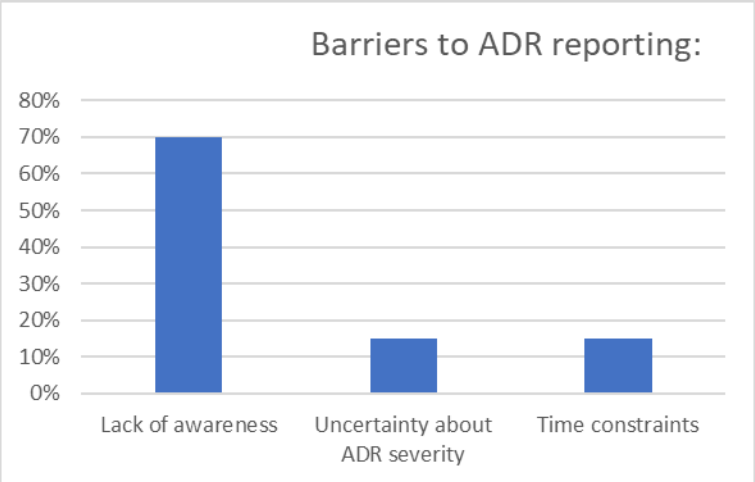


FIGURE 1.4 shows graphical representation of barriers to ADR reporting

**TYPES OF ADR**

TABLE 1.5 shows types of ADR

| TYPE OF ADR | FREQUENCY |
|---|---|
| TYPE A- Augmented | 68 |
| TYPE B- Bizarre | 26 |
| TYPE C- Chronic | 0 |

| | |
|---|---|
| TYPE D- Delayed | 0 |
| TYPE E- End of use | 0 |
| TYPE F- Familial | 0 |
| Type G-Genotoxicity | 0 |
| TYPE H- Hypersensitivity | 6 |
| TYPE U- Unclassified | 0 |

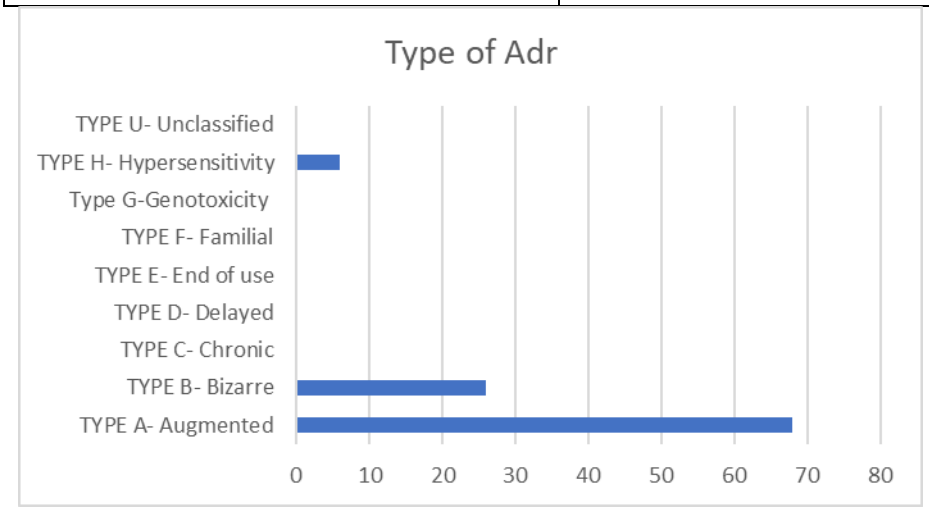


FIGURE 1.5 shows graphical representation of types of ADR

**SEVERITY OF ADR**

TABLE 1.6 shows severity of ADR

| SEVERITY | FREQUENCY |
|---|---|
| MILD | 55 |
| MODRATE | 45 |
| SEVERE | 0 |
| LETHAL | 0 |

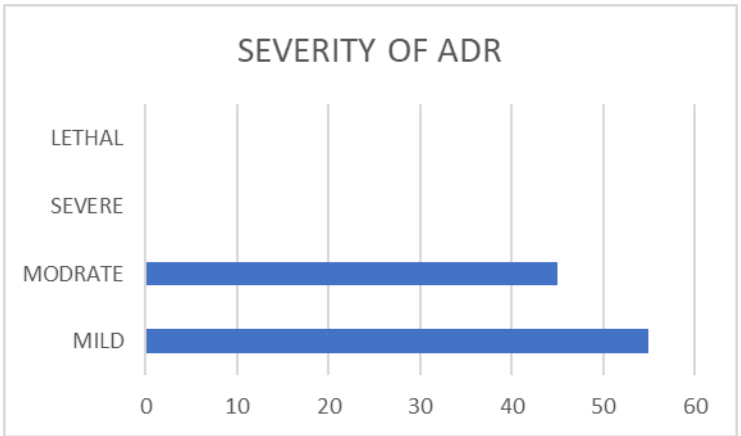


FIGURE 1.6 shows graphical representation of severity of ADR

**PREDISPOSING FACTOR**

TABLE 1.7 shows predisposing factor

| FACTORS | FREQUNECY |
|---|---|
| Drug-related factors | 93 |
| Social factors | 2 |
| Patient-related factors | 0 |
| Disease-related factors | 5 |

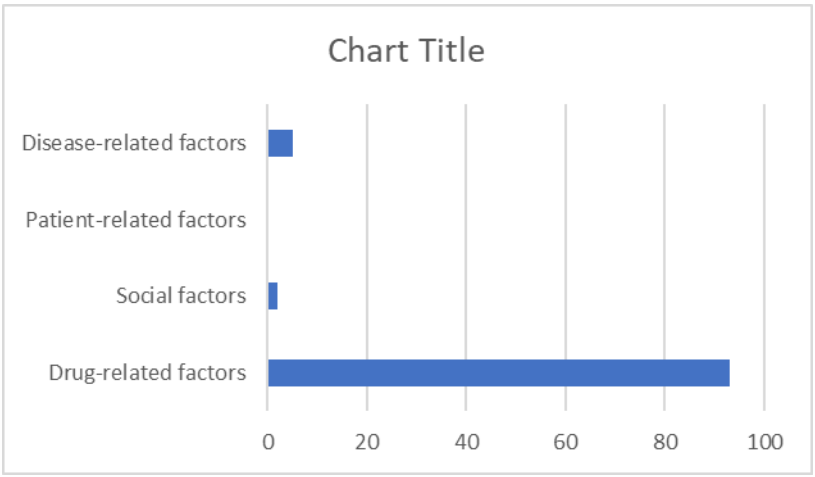


FIGURE 1.7 shows graphical representation of predisposing factor

**DRUG INTERACTION**

TABLE 1.8 shows drug interaction

| YES | 15 |
|---|---|
| NO | 85 |

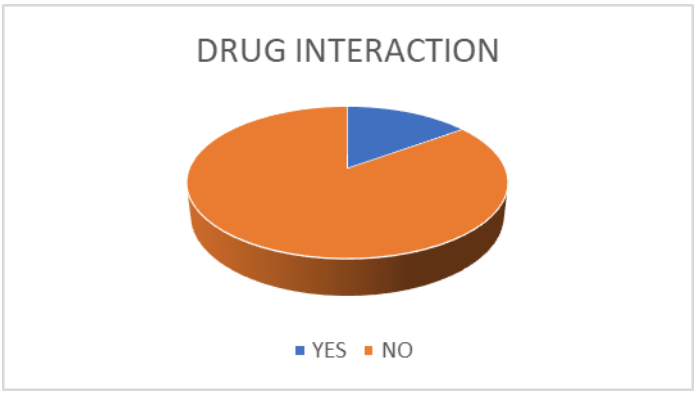


FIGURE 1.8 shows whether there was any drug interaction

**DRUG INTERACTION TYPE**

TABLE 1.9 shows drug interaction type

| MAJOR | 0 |
|---|---|
| MINOR | 90 |
| MODERATE | 10 |

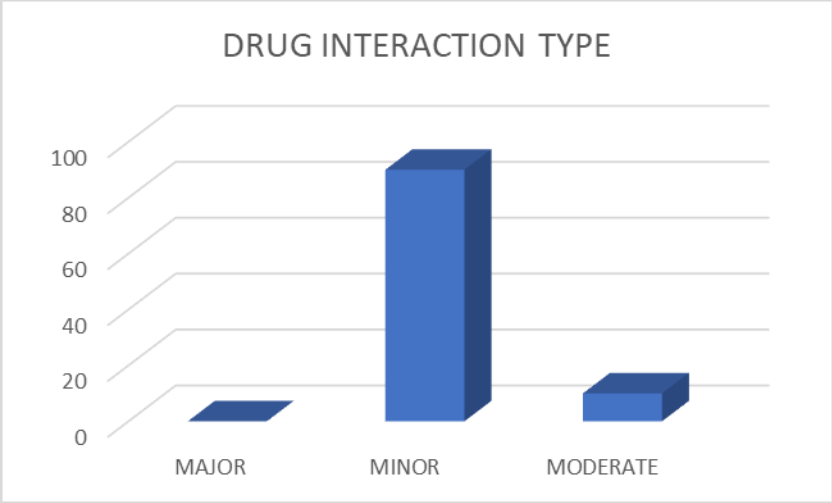

FIGURE 1.9 shows graphical representation of drug interaction type

The medication-related aspects of the study illuminated important prescribing trends. An average of 7 drugs were prescribed per patient, underlining the complexity of medical regimens in hospitalized pediatric cases. Antibiotics emerged as the predominant drug class, constituting 45% of prescriptions, followed by analgesics and antipyretics, each at 25%. The remaining 5% comprised other drug classes. Intriguingly, the overall incidence of adverse drug reactions (ADRs) was found to be 4%, underscoring the importance of vigilant pharmacovigilance efforts. Age-wise analysis unveiled a diverse ADR occurrence pattern: neonates exhibited a 2% incidence, infants 5%, toddlers 10%, school-age children 20%, and adolescents 23%. Moreover, only a minor fraction of patients (3%) were on polypharmacy (more than 5 drugs), with a mere 2% having underlying medical conditions.

The study also brought to light the significant barriers to ADR reporting. A staggering 70% of respondents reported a lack of awareness as a major obstacle, highlighting the urgent need for enhanced educational initiatives. Additionally, 15% cited uncertainty about the severity of ADRs, while the same percentage faced challenges due to time constraints. In conclusion, this study offers a comprehensive view of pharmacovigilance dynamics in hospitalized pediatric patients, emphasizing the need for tailored interventions to address age-specific vulnerabilities, improve reporting practices, and mitigate ADR-related challenges.

These findings demonstrate the strikingly high occurrence of adverse drug reactions (ADRs) among pediatric hospital patients at the tertiary care facility. The characteristics of the affected individuals highlight how different age groups are susceptible to ADRs, with newborns and young children being especially at risk. The frequent prescription of analgesics, antipyretics, and antibiotics points to the possible risk involved with types of drugs that are often used.

Additionally, the low number of formally reported ADRs suggests that pharmacovigilance procedures in the context of pediatric treatment need to be enhanced. The study's findings highlight how critical it is to educate healthcare professionals about the need of ADR reporting, especially in light of obstacles including ignorance, ambiguity, and time restraints.

This study highlights the need for pharmacovigilance to increase patient safety in hospitalized pediatric patients. It emphasizes the significance of tracking and disclosing ADRs,

particularly in high-risk age groups, and suggests focused efforts to strengthen reporting procedures and eventually increase patient outcomes.

## DISCUSSION

The study aims to understand the pharmacovigilance in the hospitalized pediatric patients.
Out of 100 patients 53 of them were males and remaining 47 were females.
The study underscores the critical importance of pharmacovigilance in ensuring the safety and efficacy of medications, particularly in hospitalized pediatric patients. By shedding light on prescribing trends and adverse drug reaction (ADR) occurrences, the research emphasizes the need for tailored interventions to address age-specific vulnerabilities and improve patient outcomes.

One notable finding is the high prevalence of ADRs among pediatric patients, with certain age groups showing increased susceptibility. This highlights the need for healthcare professionals to be vigilant in monitoring for adverse reactions, especially in newborns and young children who may be more vulnerable.

Moreover, the study reveals significant barriers to ADR reporting, including a lack of awareness, uncertainty about ADR severity, and time constraints. Addressing these barriers is crucial for enhancing reporting practices and ensuring timely detection and management of ADRs.

In conclusion, the study underscores the importance of pharmacovigilance in pediatric care settings. Healthcare providers can improve patient safety and optimize treatment outcomes by tracking and disclosing ADRs. Strengthening reporting procedures and enhancing healthcare professionals' awareness of ADRs are essential steps toward achieving this goal.

## CONCLUSION

Several key findings have emerged in this study focusing on pharmacovigilance among hospitalized pediatric patients at a tertiary care hospital with a sample size of 100. These findings shed light on the importance of monitoring and addressing adverse drug reactions (ADRs) in the pediatric population. The study revealed that a significant proportion of pediatric patients (7%) experienced at least one ADR during their hospitalization. Age was identified as a crucial factor influencing ADR occurrence, with varying percentages observed among different age groups: neonates (15%), infants (15%), toddlers (X%), school-age children (23%), and adolescents (20%). This underscores the importance of tailoring pharmacovigilance efforts to different age categories to ensure timely detection and appropriate management of ADRs.

Polypharmacy, defined as the prescription of more than five drugs, was associated with an increased risk of ADRs in 3% of cases. This finding highlights the potential risk posed by complex medication regimens in pediatric patients and underscores the importance of rational drug prescribing. The study's exploration of barriers to adverse drug reaction (ADR) reporting in the context of pediatric care yielded insightful findings. It was evident that a substantial barrier lay in the lack of awareness, with a significant 70% of respondents acknowledging this challenge. This lack of awareness points to a critical need for educational initiatives informing healthcare providers about recognizing and reporting ADRs. Moreover, uncertainty about the severity of ADRs emerged as another impediment, affecting 15% of

participants. This uncertainty highlights the complexity of assessing ADRs, especially in a pediatric population with subtle or ambiguous symptoms. The study also illuminated time constraints as a significant factor, impacting 15% of respondents. The demanding nature of healthcare environments often leaves clinicians with limited time for detailed ADR assessment and reporting. In addressing these barriers, it becomes evident that targeted efforts to improve awareness, provide tools for assessing ADR severity, and streamline reporting processes are crucial to enhancing pharmacovigilance practices and ensuring the safety of pediatric patients.In conclusion, this study provides valuable insights into the realm of pharmacovigilance in hospitalized pediatric patients. The high incidence of ADRs among this population, coupled with the underreporting of these events, calls for immediate attention from healthcare professionals, policymakers, and regulatory bodies. Enhanced education and awareness campaigns addressing ADR reporting, along with targeted interventions to mitigate associated risks, are imperative steps toward ensuring the safety and well-being of hospitalized pediatric patients. Continued research and collaborative efforts are essential to optimize pharmacovigilance practices and minimize the impact of ADRs in the pediatric healthcare landscape.

## REFERENCES


[1]. World Health Organization. (2002). The importance of pharmacovigilance: Safety monitoring of medicinal products. Retrieved from https://www.who.int/medicines/services/inn/en/Pharmacovigilance.pdf

[2]. European Medicines Agency. (2012). Guideline on good pharmacovigilance practices (GVP) Module I – Pharmacovigilance systems and their quality systems. Retrieved from https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-module-i-pharmacovigilance-systems-their-quality_en-0.pdf

[3]. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. (2018). ICH E2D(R1) Guideline for Postapproval Safety Data Management: Definitions and Standards for Expedited Reporting. Retrieved from https://database.ich.org/sites/default/files/E2D_R1__Guideline.pdf

[4]. Food and Drug Administration. (2022). Adverse Event Reporting System (FAERS). Retrieved from https://www.fda.gov/drugs/surveillance-drug-safety/adverse-event-reporting-system-faers

[5]. Raghavender R, Rohit S, Srawan D, Vijay R. A prospective review on pharmacovigilance. Int J Pharm Sci Invent. 2014;2(2):653-8.

[6]. Sindhu AR, Sebastian M, Panicker PR, Muthusamy S, Nallasamy V, Ramanathan S, Perumal S. A study on adverse drug reactions in hospitalized pediatric patients in a Tertiary Care Hospital. Journal of Applied Pharmaceutical Science. 2019 Sep 1;9(9):072-6.

[7]. Morimoto T, Gandhi TK, Fiskio JM, Seger AC, So JW, Cook EF, Fukui T, Bates DW. Development and validation of a clinical prediction rule for angiotensin-converting enzyme inhibitor-induced cough. Journal of general internal medicine. 2004 Jun;19(6):684-91.

[8]. Abubakar AR, Simbak NB, Haque M. Adverse drug reactions: predisposing factors, modern classifications, and causality assessment. Research Journal of Pharmacy and Technology. 2014 Sep 1;7(9):14.

[9]. Kumar DA, Reddenna L, Basha SA. Pharmacovigilance Programme of India. https://pubs.lib.umn.edu/index.php/innovations/article/view/371/365

[10]. Pharmacovigilance Programme of India [Internet]. Gov.in. [cited 2022 Oct 21]. Available from: https://www.ipc.gov.in/PvPI/about.html
[11]. Ramya RS. Adverse drug reaction causality assessment. Int J Res Pharm Chem13. 2011; 606:611.
[12]. Chien JY, Ho RJ. Drug delivery trends in clinical trials and translational medicine: evaluation of pharmacokinetic properties in special populations. Journal of pharmaceutical sciences. 2011 Jan;100(1):53-8.
[13]. Aagaard L, Hansen EH. Adverse drug reactions reported for systemic antibacterials in Danish children over a decade. British journal of clinical pharmacology. 2010 Nov 1;70(5):765-8.
[14]. Priyadharsini R, Surendiran A, Adithan C, Sreenivasan S, Sahoo FK. A study of adverse drug reactions in pediatric patients. Journal of Pharmacology and Pharmacotherapeutics. 2011 Dec;2(4):277-80.
[15]. Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over 10 years. Pediatrics. 2006 Aug;118(2):555-62.
[16]. Dash M, Jena M, Mishra S, Panda M, Patro N. Monitoring of Adverse Drug Reactions in Pediatric Department of a Tertiary Care Teaching Hospital: A Hospital Based Observational Study. Int J Pharm. 2015;4(4):69-76.
[17]. Lodhi H, Thompson J. Adverse drug reactions. Anaesthesia & Intensive Care Medicine. 2020 Apr 1;21(4):212-6.
[18]. Sundaran S, Udayan A, Hareendranath K, Eliyas B, Ganesan B, Hassan A, Subash R, Palakkal V, Salahudeen MS. Study on the classification, causality, preventability, and severity of adverse drug reaction using spontaneous reporting system in hospitalized patients. Pharmacy. 2018 Sep 29;6(4):108.
[19]. Yu D, Sheets J, Suppes S, Goldman J. Characterization of severe adverse drug reactions at a free- standing children's hospital. The Journal of Clinical Pharmacology. 2019 Dec;59(12):1569-72.
[20]. Smith Marsh DE. The severity of Adverse Drug Reactions [Internet]. MSD Manual Consumer Version. [cited 2022 Oct 12]. Available from: https://www.msdmanuals.com/en-in/home/drugs/adverse-drugreactions/severity-of-adverse-drug-reactions
[21]. Alomar MJ. Factors affecting the development of adverse drug Reactions. Saudi Pharm J, 22: 83–94.
[22]. Hanses F, Zierhut S, Schölmerich J, Salzberger B, Wrede CE. Severe and long-lasting cholestasis after high-dose co-trimoxazole treatment for Pneumocystis pneumonia in HIV-infected patients—a report of two cases. International Journal of Infectious Diseases. 2009 Nov 1;13(6):e467-9.
[23]. Bailey DG, Dresser GK. Interactions between grapefruit juice and cardiovascular drugs. Am J Cardiovasc Drugs. 2004;4(5):281-97.

**Article information**

**Manuscript Submitted:** 13-05-2024 **Manuscript Revised:** 02-09-2024
**Manuscript Accepted:** 24-11-2024 **Manuscript published:** 20-12-2024

**Scan here to access this article online**