

REVIEW

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# Pharmacovigilance and incidence of adverse drug reactions in hospitalized pediatric patients: a mini systematic review

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## Abstract

**Background:** Pharmacovigilance is an identifying and responding process against an adverse drug reaction (ADRs) problem encountered in the drug administration. ADRs are among the common reasons for morbidity and fatality in pediatrics throughout the globe.

**Main body:** A systemic review of the previous 10 years (2010–2019) published studies were taken into consideration to describe observational studies on ADRs and to determine the incidence and characteristics of ADRs in pediatrics. Electronic relevant literature was searched in PMC, PubMed, Google Scholar, and OvidSP databases using MESH heading and text words. The titles, text, and abstracts were checked for patients below 18 years of age, nature of ADRs, observational studies (prospective or retrospective), and maximum information was recorded to count their frequency. The studies which discussed specific or particular drug exposures were not selected in this review. Of the 36,689 titles retrieved, 27 studies were selected for full-text review. Ten observational studies were added in the final review. Observational studies on pediatric were carried out in seven distinct nations. The predominant study design within observational methodological studies was prospective ( $n = 5$ , 50%). The overall average occurrence of ADRs incidence was 9.52%. ADRs reporting in male patients (54.6%) were more than females (45.4%). The severe types of ADRs were reported in four studies. Anti-microbials were the most common class of drugs related to ADRs.

**Conclusion:** This systematic review reveals that ADRs in pediatrics are serious public health problems. Periodic drug surveillance studies are mandatory for the safe and appropriate usage of medicines in pediatrics.

**Keywords:** Pediatrics, Adverse drug reactions, Pharmacovigilance, Hospital, Review

## Background

Pharmacovigilance is an identifying and responding process against a problem encountered in the drug administration [1]. The advancement of drugs in the previous decades has brought surprising benefits for the patients, concurrently the incidence of adverse drug reactions (ADRs) has also increased notably [2]. World

Health Organization (WHO) describes ADR as “a response to a drug which is harmful, unintended and occurs at normal doses used for the treatment, diagnosis, and prophylaxis of a disease” [3]. ADRs are among the common reasons for morbidity and fatality throughout the globe [4]. Ultimately, these issues have a major impact on public health due to imposing a significant economic load on society and already stretched healthcare systems [5].

The safety of medicines in pediatrics is a global issue and proper knowledge about pharmacovigilance and spontaneous reporting of ADRs is the most essential measure to boost the safe use of therapeutic agents [6,

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7]. The very early case of a safety issue that drives to a pharmacovigilance reflection, published in 1877 in the *British Medical Journal*, was the chloroform issues. In 1898, the commercialization of diacetylmorphine was the second issue that occurred, latterly called heroin, which started to be addictive at the start of the 1910s (Only in the USA, almost 0.5 million dependent patients were reported) [8]. Amid the 1960s, numerous babies were born with agenesis of the limbs and phocomelia as an adverse effect of thalidomide. In 1957, Thalidomide was launched into the market as a safe over-the-counter hypnotic/sedative drug; latterly, it was used to control nausea in pregnant women. This was afterward confirmed in the same year that thalidomide usage was responsible for 20% of the increase in phocomelia and agenesis of the limb's defects [7].

In reply to the thalidomide tragedy, in 1968, the WHO earlier built up its plan for International Drug Monitoring. Later on, a WHO collaborating center in 1978 named "Uppsala Monitoring Centre (UMC)" was designed to support the specified program [7]. Worldwide, pharmacovigilance studies are the basic demand of the time for an invariable audit of unwanted effects in community and hospitals. Healthcare professionals, i.e., physicians, pharmacists, nurses, and other paramedical staff are all guided about the reporting ADRs, which consequently leads to high medicine safety for the population [6, 9–11].

Obtaining, ordering, reproducing, checking, handling, distributing, and managing are the medication stages manner, and mistakes/errors in pediatric medicine may occur at any stage [6, 7]. Medication errors are any preventable action that may injure the patient [9]. Pediatric populations are at greater risk than adults for medication errors as they have immature physiology and developmental disabilities that impair their ability to communicate and self-administer medications. Studies reported that medication errors in pediatrics were 3 times higher than in adult populations. Pediatrics poses a complex and unique set of risks, mainly due to the large differences in body mass, which require doses to be measured individually based on patient age, weight or body surface area, and clinical condition [7, 8]. Such variations raise the probability of errors, particularly dosing mistakes. Additionally, drug formulations are frequently extemporarily formulated to meet the requirement for low doses in such patients, and there is a lack of information on pediatric doses and indications [7]. The possible types of medication errors in pediatric populations are wrong drug, wrong route of administration, an error of use, incorrect or out-of-time, incorrect frequency, incorrect dosage, incorrect case, drug interfaces, intravenous conflict, ignoring mistakes, and incorrect rate of intravenous drug administration [2, 3, 5, 7]. Medication error ultimately leads to an acute to severe ADRs [2, 7, 12].

Previous studies have revealed that almost 5% of all hospital admissions are as a result of ADRs, and that 5% of hospital-admitted children will face an ADR within their stay in hospital and 5% of all acute hospitalizations originated from ADRs [7, 12–14]. Children are more prone to ADRs as they rarely express their own drug therapy experiences [15]. Therefore, medications in children have a high risk of developing different types of ADRs [16]. When compared to adults, children can have somewhat more severe side effects. Hence, ADRs can be a major reason for morbidity and mortality in children [17]. Furthermore, very low attentiveness has been given to ADRs in newborns, toddlers, children, and teenagers [18, 19]. Therefore, the basic purpose of the current study was to perform a systematic review of observational studies on ADRs in hospitalized children during the previous decade and to determine the frequency and characteristics of ADRs.

## Main text

### Search strategy

A comprehensive and systematic search in different databases, i.e., PubMed, PMC, Google Scholar, and OvidSP-related published English literature was identified from 1 January 2010 to 31 December 2019. These databases were searched to identify existed literature of Pharmacovigilance and ADR in hospitalized admitted pediatric patients. Basic search terms were "Pharmacovigilance OR drug therapy/adverse effects OR adverse drug reaction reporting system OR adverse effects/pharmaceutical preparations" AND "child OR pediatrics OR child-preschool" AND "Observational studies." The basic search strategy and keywords were modified as appropriate according to the searched database (Supplementary file 1).

### Eligibility criteria

Basic screening of search results was carried out by the first author then the second and third reviewers independently reviewed and examined the titles and abstracts to find out potential studies with full texts. Only those papers were included if they referred to ADRs in pediatrics of age 0 to 18 years, observational studies (prospective or retrospective), and maximum information was reported to calculate their frequency while those studies were excluded which contained ADRs referred to adult-only or a mixture of adults and children, and studies that discussed specific or particular drug exposures and did not separate the results. We searched and screened those studies and electronic bibliographic articles that were similar to the already described inclusion criteria and were selected and counted in the final analysis.

**Data extraction**

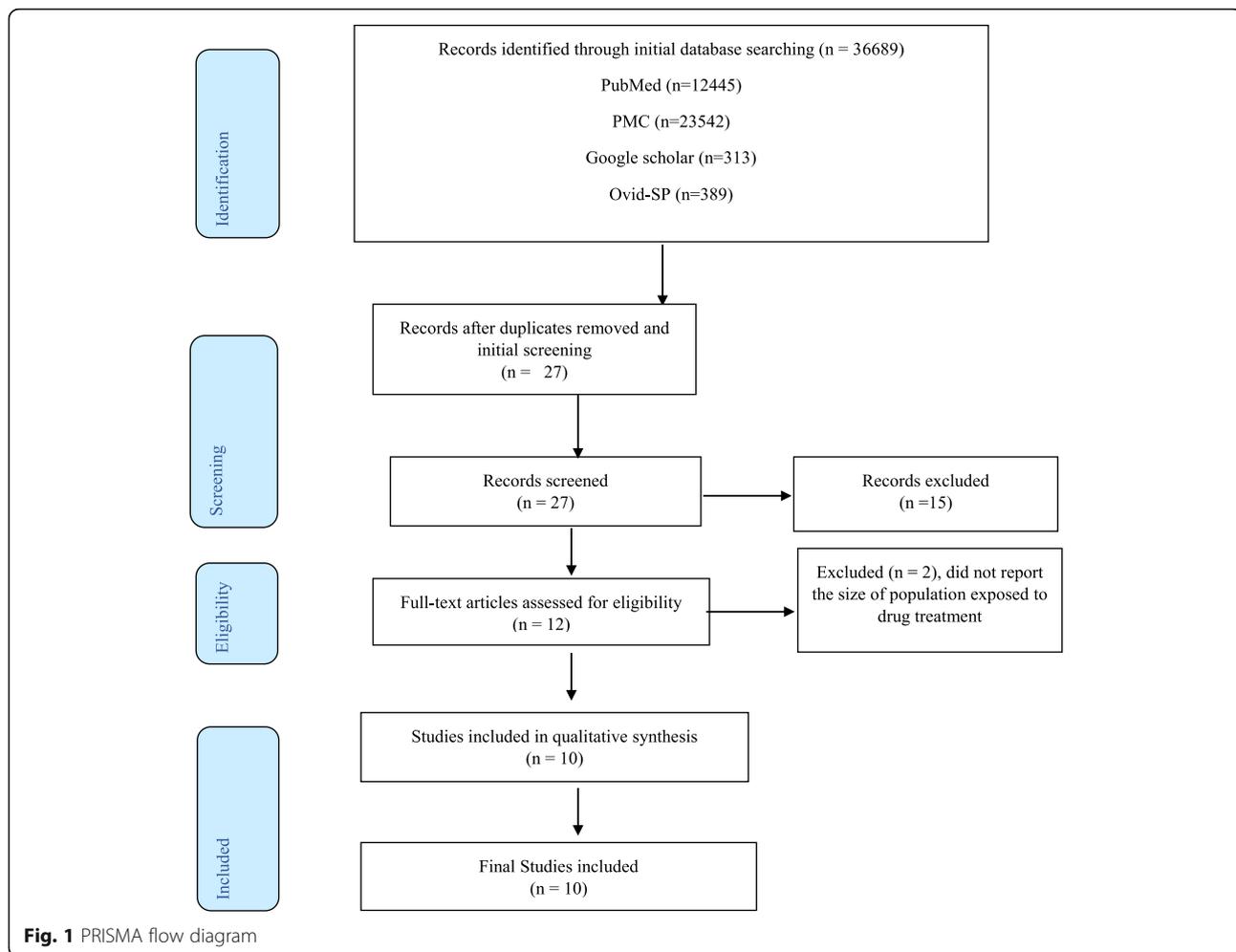
All eligible studies were assessed to meet inclusion criteria. Any discrepancies at each stage of selection were discussed by a reviewer and resolved by consensus. All the investigators separately analyzed the methodology, results, and criteria of every study by using standard data extracted proforma. The information related to the proportion of pediatrics who showed ADRs was obtained from the selected studies. The details about ADRs severity and probability were taken into consideration, and ADRs were categorized as severe if they were serious or mortal. Other information included in the analysis contains the study design, country, year, study setting, duration of the study, population studied, mean age, most commonly reported ADRs, and drugs. The final results of the review were summarized narratively, and major characteristics of the study were arranged in tabular form.

Of the 36,689 titles retrieved by the basic electronic initial search strategy, 27 studies were selected for complete text review. After the removal of 15 research

articles that were found irrelevant to a primary research question, 12 full-text publications were retrieved. Two more studies [20, 21] were excluded because they did not report the amount of the population disclosed to drug therapy, causing the calculation of ADR frequency inadequate. Finally, 10 studies were evaluated for eligibility in the final review (Fig. 1).

Observational studies on pediatric were carried out in seven distinct nations. The predominant study design within observational methodology was prospective ( $n = 5, 50%$ ) [22–26], retrospective-prospective ( $n = 1, 10%$ ) [16], cross-sectional ( $n = 1, 10%$ ) [27], and cohort ( $n = 3, 30%$ ) [28–30]. All of the reports concerning the ADR incidence in hospital admitted pediatrics. The recorded ADR frequency ranged from 1.7 to 25.4% amid the studies (Table 1). The estimated total average incidence rate was 9.52%. Further details about the final included studies are summarized in Table 1.

The overall ADRs reporting in male patients were more than females. The causality assessment of ADRs in included studies revealed that the most common types



**Fig. 1** PRISMA flow diagram

**Table 1** Summary of observational studies (n=10) and ADRs incidence rate

Studies (year) (reference)	Country	Study design	Pediatrics population studied (n)	Duration of study	Incidence of ADRs % (n)
Gallagher RM et al. (2011) [22]	UK	Prospective	822	2 weeks	3.3% (27)
Gallagher RM et al. (2012) [23]	UK	Prospective	6821	1 year	3.6% (249)
Khan LM et al. (2013) [16]	Saudi Arabia	Retrospective-Prospective	1200	1 year	6.3% (76)
Dash M et al. (2015) [29]	India	Prospective cohort	500	1 year	25.4% (127)
Gholami K et al. (2015) [24]	Iran	Prospective	658	6 months	4.1% (27)
Rivas AB et al. (2016) [28]	Spain	Prospective cohort	313	1 year	17.2% (116)
Salas Rdl et al. (2016) [30]	Colombia	Prospective cohort	772	6 months	20.2% (156)
Kurian J et al. (2016) [25]	India	Prospective	1082	6 months	5.9% (64)
Vázquez-Alvarez AO et al. (2017) [27]	Mexico	Prospective cross-sectional	1083	6 months	1.7% (19)
Sindhu AR et al. (2019) [26]	India	Prospective	200	6 months	7.5% (15)

of ADRs were probable followed by definite/certain and possible. The severity of ADRs was observed in seven studies and showed the highest percentage of ADRs were mild and moderate. Severe types of ADRs were also expressed in four studies. Amid the studies, the severity rate of ADRs was from 5.6 to 42% (Table 2).

The most commonly affected system due to ADR were skin ( $n = 5$ ), the digestive system ( $n = 3$ ), and the circulatory system ( $n = 2$ ). The most frequently reported ADRs were urticaria/rashes, vomiting, diarrhea, and neutropenia. Almost 70% ( $n = 7$ ) of the studies were showed severe ADRs to anti-microbials. Anti-epileptic, anti-convulsants, and anti-neoplastic agents were the next frequently reported therapeutic classes (Table 2).

## Discussion

The findings observed from this systematic review are obtained from a geographically variegated sample of observational drug surveillance studies. This information offers to understand the healthcare team about the major influence of ADRs in hospitalized pediatric patients in various healthcare settings. Furthermore, the results of this review might have a significant impact on the reporting, management, and design of pediatric surveillance studies.

Our results reveal that the estimated average ADR incidence in all selected studies was 9.52%. The difference in ADRs rate among the studies is due to the variation in the selected settings, data collection methods, and methodologies used. The previously published meta-analyses about the incidence of ADRs in the pediatric patients found that the reported ADR incidence rate was in the range of 4.37 to 16.78% amid the studies and meta-analytic estimated average was 9.53% [18]. According to the study which was conducted in 38 different Italian hospitals and recruited 1332 hospitalized patients reported that the onset of at least 1 ADR was associated with a median of 4-day stay prolongation [31].

ADR reporting in male patients were more than females in included studies. It is stated that the difference in susceptibility to ADRs between gender is due to physiological features, such as weight, fat percentage, intestinal transit velocity, genetic, and hormonal variations [32].

The severe types of ADRs were also reported in four studies included in this systematic review. These results suggest that ADRs are a serious public health problem in the pediatric population. The assessment of ADR severity is crucial to undertake substantial steps against the drug continuation decision. It is stated that severe ADRs are responsible for the increased duration of stay and also impose a financial load on patients [18, 33, 34].

The majority of the studies observed that anti-microbials were the most frequent class of drugs related to ADRs. Anti-microbials are prescribed to half (50%) of all hospitalized patients and it is also one of the costliest categories of drug expenditure [35]. Higher usage of anti-microbials for prophylactic and therapeutic purposes may be a reason for ADRs in hospitalized patients [2]. Inappropriate usage of anti-microbial is associated with high ADRs incidence and ADRs-related admissions in hospitals [36, 37].

The results of ADRs are almost always biased by the rate of actual reporting. Some relevant information related to ADRs, such as prolongation of stay, financial burden information, ADR ratio in general intensive care units (ICUs) or wards, intravenous or oral drugs, night dose, or day dose were not evaluated by the studies included in this systematic review. Such types of data are important to emphasize on the careful collection of information while performing ADR reporting and help prevent ADRs in the first place. These important points should be included and need to be evaluated in future studies for the meticulous collection of data.

Despite many advantages, our systematic review also had some limitations. Firstly, we selected only those

**Table 2** Details of observational studies on ADRs in pediatric hospitalized patients ( $n = 10$ )

Study/year (reference)	Gender	Age group	Mean age of population	Types of ADRs/ causality assessment (n, %)	Severity	Most common drug class involved in ADRs	Most common reported ADRs
Gallagher RM et al/2011 [22]	Not reported	Not reported	Not reported	Probable ADR (17, 63%) and definite/probable (10, 37%)	Not reported	Anti-neoplastic agents	Neutropenia, vomiting, and diarrhea
Gallagher RM et al/2012 [23]	Male = 52.8% Females = 47.2%	Age not reported	3 years 1 month	Definite (94/249, 37.8%)	Severe 14 (5.6%)	Cytotoxic drugs	Neutropenia, thrombocytopenia and anemia.
Khan LM et al/2013 [16]	Male = 48.7% Female = 51.3%	0–15 years	Not reported	Possible ADRs (36, 47.3%), probable (34, 44.7%), and definite (6, 7.9%)	Not reported	Anti-microbials	Skin-associated ADRs
Dash M et al/2015 [29]	Male = 37.8 % Females = 62.2 %	< 14 years	Not reported	Probable (101, 80%) and possible category (26, 20%)	Mild 88 (69.3%), moderate 30 (23.6%), and severe 9 (7%)	Anti-epileptic and anti-microbial drugs	Skin-associated ADRs
Gholami K et al/2015 [24]	Male = 59.2% Females = 40.8%	≤ 18 years	40.6 ± 36 months	Probable (23, 85.2%), possible (3, 11.1%), and definite (1, 3.7%)	Not reported	Anti-microbials and central nervous system agents	Skin-associated ADRs, diarrhea, and vomiting
Rivas AB et al/2016 [28]	Male = 63% Females = 37%	Age not reported	0.9 ± 2.9 days	Probable ADRs (66, 57%), possible (37, 32%), and definite (13, 11%)	Moderate (49, 42%), mild (47, 41%), and severe (20, 17.2%)	Anti-microbials and caffeine citrate	Feed intolerance, phlebitis, and tachycardia
Salas Rdl et al/2016 [30]	Male = 50.9% Females = 49.1%	< 6 years	20.8 ± 17.3 months	Probable (153, 98.1%), possible (2, 1.3%), and definite/certain (1, 0.6%)	Mild (103, 66.0%), moderate (53, 34 %), and no severe case	Anti-microbials	Diarrhea, vomiting, rash, and phlebitis
Kurian J et al/2016 [25]	Male = 68.5% Females = 31.5%	≤ 18 years	Not reported	Probable category (56, 87.5%) followed by possible (8, 12.5%)	Mild (53, 82.8%), moderate (11, 17.2%), and no severe case	Anti-microbials and anticonvulsants	Diarrhea vomiting, rashes, and somnolence
Vázquez-Alvarez AO et al/2017 [27]	Male = 57.6% Females = 42.4%	1 day to 18 years	7.2 (± 5.9) years	Probable (13, 68.4%), definite (4, 21%) and possible (2, 10.6%)	Severe (8, 42%)	Anti-microbials and anti-epileptic drugs	Skin-associated ADRs and anxiety
Sindhu AR et al/2019 [26]	Male = 53.3% Females = 46.7%	0 to 12 years	Not reported	Probable (10, 66.6%), possible (4, 26.6%), and definite (1, 6.6%)	Mild (9, 60%), moderate (6, 40%) and no severe case	Anti-microbials and anti-convulsants	Skin-associated ADRs, hypotension, and diarrhea

observational studies which recruited hospitalized pediatric populations and were observed ADRs via prospective or retrospective approach. Secondly, yet, even amid the methodologically sound and most homogeneous research papers, there is considerable variation in the reported ADRs incidence. Present heterogeneity is just partially described by the various number of medications administered to pediatrics in every study. Thirdly, we performed a keen search, but this resulted in a high number of titles and abstracts for review. To reduce uncertainty, we used comprehensive exclusion and inclusion criteria and selected a traditional approach of selecting studies for full-text review where ambiguity is there. Fourthly, the other predictors such as diagnosis and prescription patterns of drugs could not be measured in the analysis as they were not properly and homogeneously reported in selected studies. Fifthly, the findings of this review are hard to confidently extrapolate to an international level because most of the studies were carried out in a few countries. Sixthly, the current systematic review mainly analyzed the studies of hospitalized pediatric patients who admitted in different wards and thus should not necessarily be generalized to all pediatric populations. Finally, for compelling causes associated with the feasibility of the review, we did not consider evidence taken from grey literature. This error may have raised a question about the accuracy of the calculated estimated average incidence rate [38] but not the relevance of findings and the implications for practice.

## Conclusion

Adverse drug reactions of medications are the main causes of morbidity and mortality around the world. This mini systematic review describes that ADR in hospitalized pediatrics patients is a potential public health problem. The drug surveillance studies, prescription patterns audits, and clinical data in pediatric patients should be recorded in a logically accepted way for better analysis in the future. This will help the statistical technique of metanalysis to produce effective information for the proper prevention of ADRs in pediatrics. Pediatric physicians, pharmacologists, pharmacists, and other healthcare personals involved in the treatment of pediatrics should make all efforts to provide proper information, logical communication, and appropriate education regarding the rational use of medicines. The future studies for the appropriate assessment of prescribing practices in various healthcare settings and collaborative efforts for the avoidability of ADRs are needed for better pharmacovigilance activities and patient safety.

## Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s43054-020-00038-8>.

**Additional file 1.** Electronic search strategy.

### Abbreviations

ADRs: Adverse drug reactions; MESH: Medical Subject Headings; WHO: World Health Organization; USA: United States of America; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; UK: United Kingdom

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### Authors' contributions

ZK and YK were involved in the concept, design, and data collection of the study. KM, CB, FK, and FUK carried out the critical evaluation and interpretation of the data. ZK, KM, and YK wrote the first draft of the manuscript, and all authors contributed to subsequent drafts. All authors revised the manuscript and approved the final version for submission.

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### Competing interests

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