Online ISSN: 2588-3526

Journal of Wildlife and Biodiversity

Volume 7 (Special Issue): 13-37 (2023) (http://www.wildlife-biodiversity.com/)

Research Article

Enhancing Adverse Drug Reaction Reporting in Pediatrics and Its Impact on Public Health: A Systematic Review and Meta-Analyses

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Received: 30 September 2023 / Revised: 16 October 2023 / Accepted: 30 September 2023/ Published online: 25 November 2023.

How to cite: Salih, **B**., Allela O. (2023). Enhancing Adverse Drug Reaction Reporting in Pediatrics and Its Impact on Public Health: A Systematic Review and Meta-Analyses, Journal of Wildlife and Biodiversity, 7 (Special Issue), 13-37. **DOI**: https://doi.org/10.5281/zenodo.10206795

Abstract

Adverse drug reactions (ADRs) pose a significant public health concern, especially in paediatrics. ADRs are defined as any undesirable or unintended response to a drug, ranging from mild and self-limited to severe and life-threatening. It is estimated that ADRs affect up to 25% of hospitalized children, making them a leading cause of morbidity and mortality in this population. This study aimed to comprehensively review available evidence regarding the effectiveness of different interventions in enhancing ADR reporting in pediatric populations. In October 2023, we conducted a search on the electronic database Medline PubMed without imposing limitations on the publication date or geographic area, excluding all secondary and tertiary literature. Data were extracted from identified studies using a structured data extraction form in Microsoft Office Excel® 2016. The systematic search yielded a total of 108 records. After removing seven duplicate records, 101 distinct records underwent title and abstract screening. Six were excluded due to language restrictions or irrelevance to the research topic. Subsequent full-text assessment for eligibility resulted in the exclusion of an additional 79 records, primarily due to the absence of intervention in the study design. Ultimately, 16 studies were deemed suitable for quantitative synthesis. This systematic review and meta-analysis revealed that interventions aimed at improving adverse drug reaction detection and reporting increased identification compared to

standard practice in children. However, concerns about significant issues related to bias and heterogeneity threaten the reliability of our results.

Keywords: Adverse Drug Reaction, Hospitalized children, Meta-analysis, Pediatrics.

Introduction

Adverse drug reactions (ADRs) represent a significant public health concern, particularly in pediatrics (Aagaard et al., 2010). ADRs are defined as any undesirable or unintended response to a drug, ranging from mild and self-limited to severe and life-threatening. They are estimated to impact up to 25% of hospitalized children, emerging as a leading cause of morbidity and mortality in this special population (Andrade et al., 2017; Tripathy et al., 2021). Nevertheless, the underreporting of ADRs remains a major challenge in the field of pharmacovigilance and safety surveillance. Several reports estimated that only 5-10% of ADRs are reported, especially in the pediatric populations (Hazell & Shakir, 2006). Elsewhere, a large review published in 2001 found that the reporting rate of ADR does not exceed 20% of the ADR events that occurred among the study paediatric patient population (Impicciatore et al., 2001).

The defective process of reporting adverse drug reactions (ADRs) in children can be complex and time-consuming due to various factors. These include a lack of awareness of pharmacovigilance, insufficient time for reporting, and fear of retaliation, particularly if the ADR is perceived to result from a medication error (Dittrich et al., 2020; Leitzen et al., 2023). Additionally, diagnosing ADRs in children can be challenging, especially at a very young age, as they may struggle to articulate their symptoms, and these symptoms may resemble those of many other conditions.

One major consequence of such underreporting is the delayed identification of safety issues related to drugs or medical interventions. This delay may lead to higher rates of re-hospitalizations and longer lengths of stay (Lombardi et al., 2020; Pirmohamed et al., 2004). Furthermore, underreporting hampers the effectiveness of post-marketing surveillance efforts, translating into inadequate tracking and assessment of the long-term safety of drugs. This, in turn, prevents the identification of rare or delayed ADRs that might be life-threatening in some circumstances (Mejía et al., 2020; Pirmohamed et al., 2004; Walsh et al., 2015). Therefore, improving the quality and quantity of ADR reporting, especially in pediatrics, is critically essential for ensuring the highest level of safety for children exposed to drugs (Thiesen et al., 2013).

Numerous interventions have been meticulously implemented and assessed across various healthcare settings, demonstrating their effectiveness in influencing the reporting behavior of healthcare providers and patients (Li et al., 2020). For instance, educational interventions play a crucial role in enhancing healthcare professionals' awareness of pharmacovigilance and the importance of reporting adverse drug reactions (ADRs). These interventions can take diverse formats, including workshops, online courses, and peer-to-peer training (Reumerman et al., 2018). In a randomized clinical trial, an educational intervention on pharmacovigilance resulted in a statistically significant increase in the ADR reporting rate per 1,000 physicians per year, rising from 28.1 to 39.6. Furthermore, in the intervention arm, ADR reporting significantly surged by 65.4% (95% confidence interval [CI]: 8.2-15.3) throughout the study period (Lopez-Gonzalez et al., 2015). Another study found that a web-based educational intervention on ADR reporting for nurses substantially improved the nursing staff's capability in ADR monitoring and self-efficacy (Jin Kim & Hwang, 2022).

Moreover, technological interventions, such as electronic reporting systems and mobile apps, can enhance the ease and convenience for healthcare professionals to report ADRs (Li et al., 2020). In contrast to the educational pathway, electronic reporting systems were more commonly implemented as the interventional strategy, with a point estimate increase of 13.7-fold (−5.29–32.68, 95% CI), compared to 4.5-fold (0.66–8.19, 95% CI) for traditional educational methods (Li et al., 2020).

Besides, policy-related interventions, such as mandatory reporting requirements and financial incentives, can significantly contribute to improving the quality and quantity of ADR reporting. In a general Chinese hospital, the implementation of an incentives-based policy showed a significant increase in the reporting rates by more than 30% (Fang et al., 2017).

However, data regarding ADR identification, reporting, and monitoring, as well as quality interventions in pediatric populations, are still considered sporadic and limited. Therefore, this systematic review and meta-analysis aim to screen all available evidence on the effectiveness of different interventions in improving the quantity of ADR reporting in such pediatric populations.

Martial and methods

Search Strategy

The systematic review adhered to the Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines (PRISMA) (Moher, Liberati, Tetzlaff, Altman, & Group*, 2009). Following a database search, duplicate results were removed. After independently reviewing the titles and abstracts of the papers identified in the search, two reviewers (Bootan A. Salih, Omer Allela) determined which studies qualified for full-text review. Subsequently, the two reviewers (Bootan A. Salih, Omer Allela) completed the full-text review to determine the studies that would ultimately be included in the systematic review.

Information Sources

In April 2023, a search was conducted on the electronic database Medline PubMed. No limitations were placed on the date of publication or geographic area, and all secondary and tertiary literature were excluded.

Search Method

The following search terms, including suspected ADR, adverse drug reaction, adverse event, intervention, paediatrics, quality, and improvement, were appropriately combined throughout the search process. These terms were utilized as single entities or in combination through Boolean logic (AND, OR) and proximity techniques in the aforementioned database, with the term pediatrics as a fixed term.

Eligibility Criteria

The inclusion criteria for the systematic review comprised studies that (i) focused specifically on patients aged <18 years, (ii) provided a quantitative output in the results section, and (iii) offered a clear description of the intervention/quality initiative. On the other hand, the exclusion criteria for this systematic review included (i) all systematic reviews and meta-analyses, (ii) qualitative studies, and (iii) studies that did not describe any new interventions to improve reporting.

Risk of Bias Assessment

Data quality was assessed using the Good ReseArch for Comparative Effectiveness (GRACE) checklist for observational studies (Dreyer, Velentgas, Westrich, & Dubois, 2014). The reviewers selected this checklist because it was specifically developed for evaluating the quality of observational, and non-interventional studies, and all the studies identified in the review followed this design.

Meta-analysis

A meta-analysis was conducted on studies identified in the systematic review that reported differences between the intervention and control arms. Additionally, only studies assessed as being of good to high quality by the GRACE tool were included in the meta-analysis.

Statistical Analysis

The incidence rate ratio (IRR) was employed to compare adverse drug reaction (ADR) incidence rates, expressed as the number of ADRs per person-years, between the intervention and comparator groups. Pooled IRRs across the studies were calculated using the Mantel-Haenszel method. Statistical heterogeneity was assessed using the I2 statistic. The choice between the random vs. fixed effects model was based on the statistical significance of the calculated p-value for heterogeneity. Random effects models were implemented for the calculation of the pooled IRR estimates whenever a statistically significant heterogeneity estimate was obtained; otherwise, fixed effects models were employed. Subgroup analyses based on the type of intervention were conducted. Sensitivity analysis was implemented using the leave-one-out approach, excluding individual studies one by one to evaluate their influence on pooled IRRs. Publication bias was explored through visual inspection of funnel plots and Egger's test. Meta-regression was performed to assess the relationship between effect sizes and study-level characteristics, such as the type of intervention and length of follow-up. Statistical analyses were conducted using R software (Version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). All tests were two-sided, with $p < 0.05$ considered significant. Data extraction was performed using a structured data extraction form in Microsoft Office Excel® 2016.

Results

Study selection

The systematic search yielded a total of 108 records. After the removal of seven duplicate records, a total of 101 distinct records underwent title and abstract screening. Six of these were excluded due to language restrictions or irrelevance to the research topic. Subsequent full-text assessment for eligibility resulted in the exclusion of a further 79 records. The primary reasons for these exclusions were the absence of intervention in the study design. Ultimately, 16 studies were found suitable for quantitative synthesis. Out of these, nine studies met the stringent criteria for inclusion in the meta-analysis. Importantly, seven studies, although included in the

quantitative synthesis, were not considered for the meta-analysis because they lacked a control or second arm, which is pivotal for comparative statistical evaluation (Figure 1).

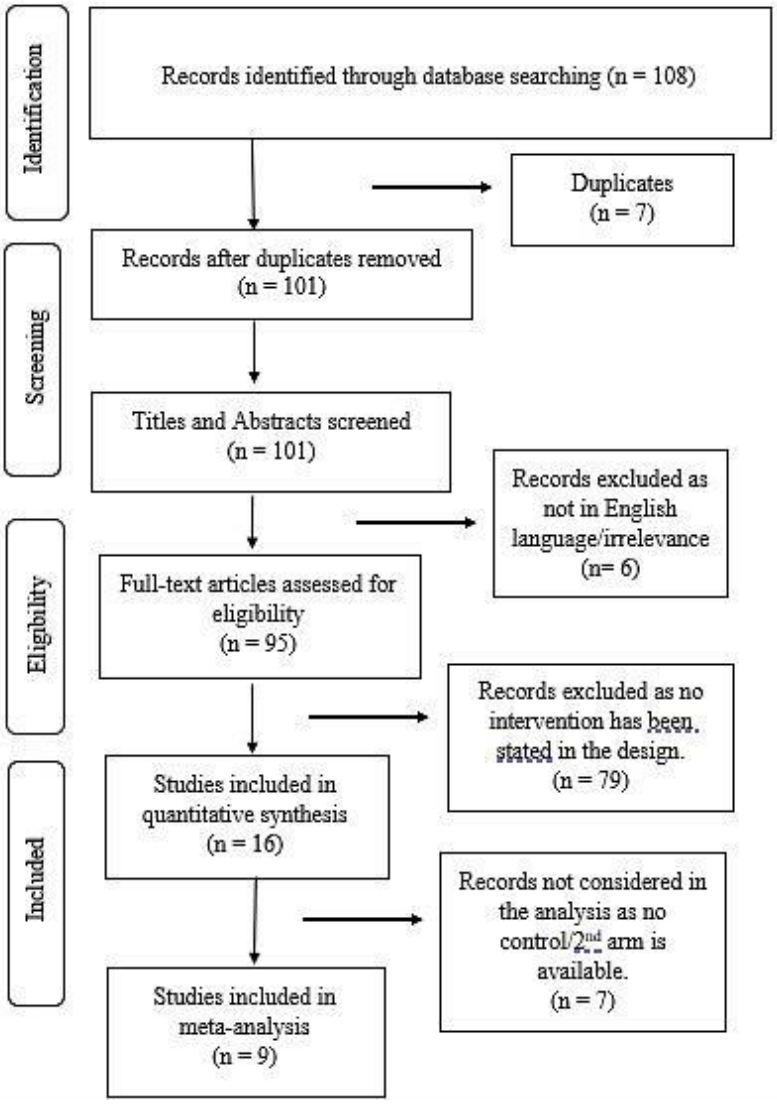

Figure 1. PRISMA flow chart

Summary of the included studies

The main characteristics of the 16 included studies are summarized in Table 1. These studies were conducted in various countries, including Mexico (n=1), the USA (n=3), Israel (n=1), Korea (n=1), Canada (n=2), the Netherlands (n=1), Germany (n=1), Italy (n=1), and India (n=1). The study designs encompassed quasi-experimental (n=1), open-label trials (n=2), retrospective

studies (n=3), prospective studies (n=2), surveys (n=2), cohort studies (n=1), and a pilot observational study (n=1). Sample sizes ranged from 16 to 3,753 participants..

Table 1. Methodological Characteristics of the included studies

Study	Country		Study Design	Study Setting	Sample Size
Clarkson, 2001	UK		Pilot observational	Hospitals	-
Neubert, 2006	Germany		A prospective, 6-month pharmacoepidemiologic survey	Children's University Hospital	396
Carleton, 2009	Canada		Cohort	Children's hospital	-
Goldman, 2013	USA		Before and After study	Tertiary care pediatrics hospital	672
Morales, 2016	Mexico		Quasi-experimental pre-post-test study	Tertiary care paediatrics hospital	1,136
Beak, 2016	Korea		Retrospective chart review	Tertiary care paediatrics hospital	-
Hui, 2016	Canada		Retrospective analysis	Tertiary care paediatrics hospital	115
Hawcutt, 2016	UK		Retrospective review of a database	UK national medicines regulator (Medicines and Healthcare products Regulatory Agency (MHRA))	-
Patel, 2017	India		Prospective, cross-sectional study	Teaching hospital	-
Cammack, 2019	USA		open-label clinical trial	Tertiary care paediatrics hospital	124
Kronenfeld, 2019	Israel		open-label clinical trial	Tertiary care paediatrics hospital	3,753
Soyer, 2019	CANADA		Descriptive retrospective study	Teaching hospital	-
Tillman, 2021	USA		Retrospective study	Regional hospital campus	-
Dittrich, 2022	Netherlands		Retrospective chart review	University Teaching Hospital	552
Balsam, 2022	Italy		Cohort	Teaching hospital	210
Hawcutt, 2022	UK		Before & and after guide-based SURVEY	UK national medicines regulator	234

Intervention Characteristics

The interventions evaluated to improve ADR detection included pharmacist education and feedback (n=3 studies), implementation of monitoring tools (n=3), computerized systems (n=2), student reporting (n=1), guideline implementation (n=1), pharmacogenomics approaches (n=1), and regional monitoring centers (n=1). Comparators were standard practice or control groups without the specific intervention. The study periods ranged from three months up to eight years of follow-up. ADR identification and reporting were the primary outcomes assessed in all studies. The specific ADRs reported and classification systems used varied across studies, with common ADRs including rash, allergies, gastrointestinal disorders, and effects on the nervous system (Table 2). Neonate-related ADRs were considered in only one study.

Table 2. Characteristics of interventions vs. comparison/control in the included studies, (N=16)

Study	Quality Initiative/ Intervention Vs Comparator if available	Total ADR Reported N=	Outcome	Study Period (months)	Most common causative disease	Most common causative drug
Clarkson, 2001	A monthly reminder letter and presentations to staff in the identified hospitals IN Paediatric Regional Monitoring Centre (PRMC) Vs before the system implementation	135	The existence of the PRMC resulted in an increase of reports when compared with previous data from the same region and in comparison, to a region with a similar population of children	12	Localized skin reaction	Topical local anesthetics
Neubert, 2006	a computerized monitoring system (CMS) based on laboratory test results for the detection of adverse drug reactions (ADRs) in a pediatric ward	73	This study demonstrates that, using CMS, different kinds of mild adverse events were detected compared to the observation by the treating physician	6	Nervous system manifestations	Anti-infectives for systemic use
Carleton, 2009	genotype-specific approaches to therapy in childhood (GATC)	1836	Active and targeted surveillance of ADRs coupled with pharmacogenom	36		Anthracyclines Cardiotoxicity

	national ADR network		ics can address specific drug safety concerns in children. High quality ADR reports, site-specific surveillance approaches, and effective communication are necessary for network success.			
Goldman, 2013	integrative Drug Safety Service (DSS): extensive hospital staff education	A significant increase was observed (slope, 6.01; P <.001) in ADR detection after implementation of the DSS, with a greater than 4-fold increase to 41 cases per 10,000 admissions	Implementation of a multifaceted, interdisciplinary DSS was more effective in detecting ADRs than voluntary reporting alone	12	Allergies to Medications	-
Morales, 2016	the pharmacist gave talks on Pharmacovigilance and on the program for electronic capture of data, took part in patient visits, left reminders, improved accessibility to ADR report format and performed feedback activities		Physicians do identify ADRs but fail to report them. The intervention increased ADR correct identification and reporting. The effect was maintained after the intervention.	6	-	-
Beak, 2016	QA programme including Pharmacist. Vs the routine of the Physician reporting	931	A multi-disciplinary approach would improve spontaneous ADR reporting at the pediatric OPD.	12	Rash or urticaria	Anticonvulsant

Hui, 2016	ADR documentation transfer throughout the implementation of a comprehensive EHR system	155	identified discrepancies in ADR documentation within hospital systems, which need to be addressed as healthcare institutions transition to EHRs	18	Allergies to Medications	-
Patel, 2017	Trained Medical students on reporting. Vs the routine physician reporting	449	Students reported valuable and clinically relevant ADRs. Medical students should be exposed to ADR reporting during their clinical teaching posting and should be actively involved in pharmacovigilance program to improve the detection rate	12	GI disorders	Diclofenac
Cammack, 2019	a bedside monitoring tool	28	The use of a bedside monitoring tool improves ADR detection	12	Hypertension	Hydrocortisone
Kronenfeld, 2019	The interventional program included: placing posters in medical team rooms and nurse stations; supplying nurses with forms requiring them to fax reports of ADRs including minimum information (patient's name, ID number and a short description of the suspected ADR);	112	important to periodically encourage healthcare professionals to report any ADRs in order to increase knowledge about medication safety and prevent fatal harm.	3	Neurological disorders	Antiepileptic medication

	presenting a 45-minute lecture about the importance of pharmacovigilance to doctors and nurses in the Pediatric Division; distributing papers summarizing the main topics of the lecture to the medical team and nurses and; inserting a reporting paper into the patient's medical record					
Soyer, 2019	Medical technicians Vs PV team	364	A total of 343 ADRs were identified, accounting for 2.33% (343/14,693) of total hospitalizations over 7 months.	6	-	-
Tillman, 2021	a DSS was developed to perform hospital-wide pharmacovigilance: A dedicated DSS pediatric clinical pharmacist. Vs. no DSS	3065	The identification of factors such as specific medications, ADR types, and clinical treatment settings associated with decreased ADR documentation may help to identify targeted areas and provide support for increased pharmacovigilance efforts.	96	rash	antimicrobials
Dittrich, 2022	Active reporting based on Education	232	an active reporting system has the potential to increase our knowledge about ADRs in pediatric patients	24	-	-

Balsam, 2022	a hospital pharmacist has been involved and has taken a lecture on the definition of ADRs and medication errors and their correct reporting	927	active pharmacovigilance and health care personnel sensitization are associated with improved ADR detection, providing valuable information about drugs' safety profile in pediatric patients.	36	-	Vaccines
Hawcutt, 2022	New education guide for Children and young Pediatrics		The new guide for Children and Young Pediatrics to inform them about how to report a suspected ADR to the MHRA was well received and increased the knowledge, and confidence to report, in those who responded.	6		

ADR; adverse drug reactions, CMS; computerized monitoring system , DSS; Drug Safety Service, EHR; electronic health record, GATC; genotype-specific approaches to therapy in childhood, MHRA; Medicines and Healthcare products Regulatory Agency, OPD; outpatient department, PRMC; Paediatric Regional Monitoring Centre, PV; pharmacovigilance, QA; quality assurance.

Pooled ADR Reporting Rates

A total of 8 studies reported the effects of different interventions on the change in ADR reporting rates (Figure 2). These studies applied healthcare-led interventions (N=5) and technology-driven interventions (N=3). The pooled analysis of interventions demonstrated a statistically significant increase in the ADR reporting rate (IRR 2.81, 95% CI 1.58 to 5.0). Subgroup analysis was conducted based on the type of intervention. Healthcare professional (HCP)-led interventions (5 studies) had a pooled IRR of 3.18 (95% CI 1.30 to 7.78) compared to the comparator/control arm using the random effects model. Similarly, technology-driven interventions (3 studies) resulted in an IRR of 2.18 (95% CI 1.33 to 3.58). Comparing both intervention types, there was no significant difference in terms of ADR reporting rates (p=0.47).

Notably, there was substantial heterogeneity across the studies (I2=95%, p<0.001), and this significant between-study variation was consistently seen within both intervention types (I2 = 97%, 84% for HCP-led and technology-driven interventions, respectively; p<0.01 for both).

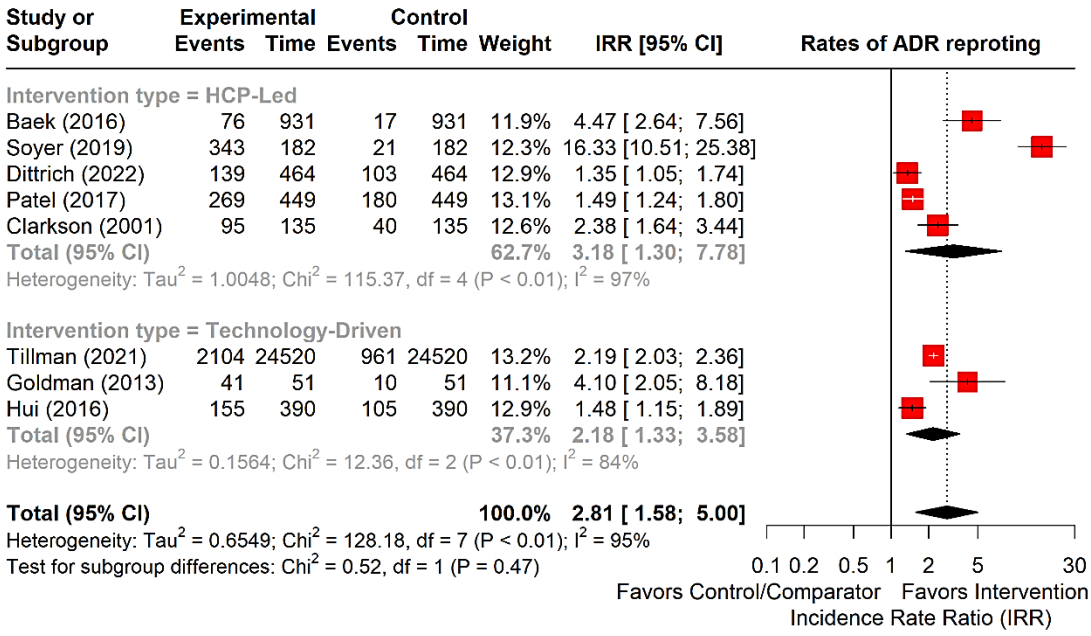

Figure 2. Forest plot demonstrating the effects of interventions on ADR reporting rates.

Sensitivity Analysis

Leave-one-out sensitivity analyses were conducted by excluding each study individually and recalculating the pooled effect size. The resulting incidence rate ratios ranged from 2.10 to 3.13 across the analyses. Importantly, all 95% confidence intervals continued to exclude the null value (IRR of 1). No single study significantly altered or skewed the pooled results when omitted. The sensitivity analyses support the robustness of the overall meta-analysis findings, as the effect sizes remained relatively consistent within the confidence intervals whether each study was included or excluded (Figure 3).

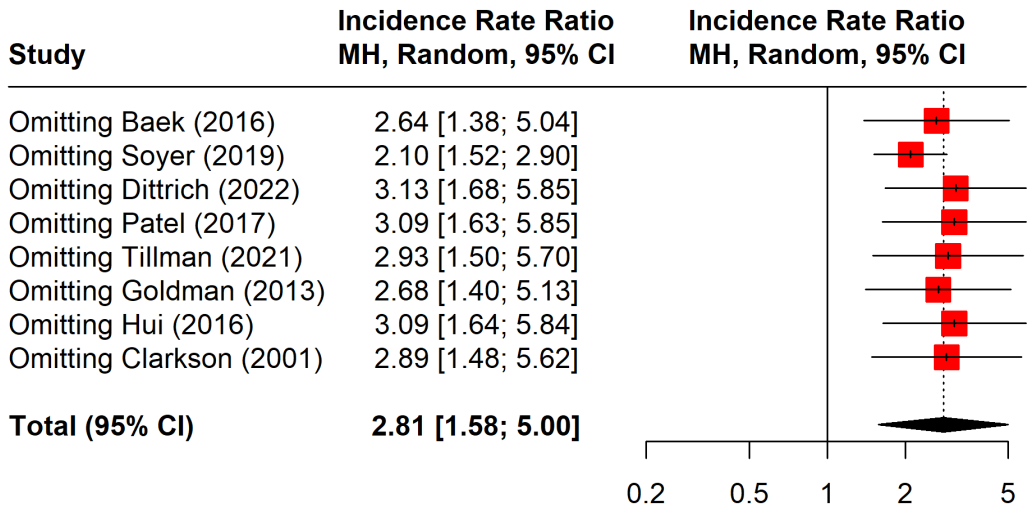

Figure 3 Sensitivity analysis of the included studies (N=8)

Publication Bias

Funnel plots of the included studies demonstrated some asymmetry, indicating potential publication bias (Figure 4). However, quantitative evaluation using Egger's regression test (Table 3) found no statistically significant evidence of small-study effects (p = 0.501). This suggests that the visual asymmetry observed in the funnel plots is unlikely to significantly influence the risk of publication bias in the overall results.

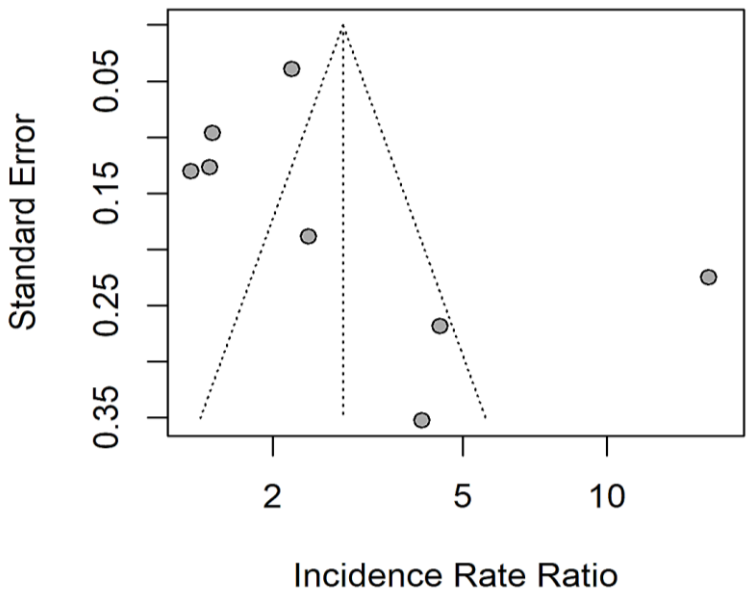

Figure 4 Funnel plot of the included studies assessing the publication bias.

Table 3 Eager's test results investigating the publication bias in the studies assessing the effects of interventions on ADR reporting rates (N=8)

Egger's test	Intercept	SE (Intercept)	t	P
	0.62	0.23	0.72	0.501

Meta-Regression

A meta-regression analysis was conducted to examine potential predictors of the adverse drug reaction (ADR) reporting rate, including follow-up duration and type of intervention (Table 2). The outcome was the incidence rate ratio (IRR) of ADR reporting. The coefficient for follow-up duration was 1.21 (95% CI -2.56 to 4.98), suggesting that for each additional year of follow-up, the IRR of ADR reporting increased by a factor of 1.21. However, this association was not statistically significant (p = 0.51). Similarly, the coefficient for the type of intervention was -0.32 (95% CI -1.65 to 1.01) for technology-driven versus healthcare professional-led interventions. This translates to a 0.32-unit lower IRR of ADR reporting for technology-driven interventions compared to HCP-led interventions. Nevertheless, this difference was also not statistically significant (p = 0.625). There was substantial heterogeneity among studies for both follow-up duration (I2 = 96.56%) and the type of intervention (I2 = 97.24%), suggesting the limited ability of these predictors to account for the large between-study variability.

Table 5. Meta-regression predictors of ADR reporting rate

Variable	Coefficient	Standard error	I2	P-Value
Follow-up duration (Years)	1.21	0.41	96.56%	0.51
Type of intervention				
HCP-led	Reference Category			0.625
Technology-Driven	-0.32	0.65	97.24%	

Discussion

To the best of our knowledge, this study is the first to systematically review and synthesize quantitative evidence regarding the impact of various interventions on adverse drug reaction (ADR) reporting rates in the pediatric population. Specifically, our objective was to evaluate the effectiveness of different healthcare professional (HCP)-led and technology-driven interventions in improving ADR identification and reporting in pediatric settings, compared to standard practice or controls. We conducted a thorough search across multiple databases and trial registries for relevant studies published up to September 2023. Included studies assessed interventions targeting improved ADR reporting versus routine practice or control in diverse pediatric settings. The outcome measured was ADR reporting rates, expressed as the number of ADRs per person-years. Study-specific incidence rate ratios (IRR) were pooled using random-effects models.

Eight studies, including 5478 participants, were included for the quantitative synthesis of the current evidence. Our findings suggested that different interventions were associated with a significantly increased incidence rate ratio (IRR) of ADR reporting (IRR 2.81, 95% CI 1.58 to 5.0). However, a substantial variability in the estimated pooled IRR rates was observed ($I2=95\%$, $p<0.01$), which could not be attributed to either different interventions implemented within each study or different follow-up durations. Consistent with our findings, several systematic reviews have suggested that educational interventions, monitoring systems, computerized tools, and multifaceted approaches can enhance adverse drug reaction (ADR) detection and reporting in adults, with a range of reported effect sizes. For instance, Paudyal et al. (2020) conducted a systematic review and meta-analysis aiming to evaluate the effectiveness of various interventions in improving ADR reporting by healthcare professionals (HCPs) and patients. The study analyzed data from 28 studies, primarily targeting HCPs and employing a range of intervention strategies, such as educational, technological, policy-based, financial, or a combination of these.. A meta-analysis of five randomized controlled trials (RCTs) demonstrated a statistically significant 3.5-fold increase in adverse drug reaction (ADR) reporting in the intervention groups compared to controls, with a pooled risk ratio (RR) of 3.53 and a 95% confidence interval (CI) of 1.77-7.06. However, the authors reported the generally low quality of the included studies and the absence of theory-based and sustainable interventions in the designs. They argued for the

need for more robust, theory-based interventions, a focus on patient reporting, and further research in low- and middle-income countries.

Similarly, Li et al. (2020) conducted a systematic review of 13 studies investigating the impact of various strategies on the underreporting of ADRs in healthcare systems. The results showed that multifaceted strategies led to a 9.26-fold point estimate increase in ADR reporting (95% CI: -2.21-17.11), compared to a 7.19-fold increase (95% CI: -5.29-32.68) for single interventions. Among the strategies, electronic reporting tools emerged as more effective, with a 13.69-fold point estimate increase in ADR reporting (95% CI: -5.29-32.68) versus 4.42-fold (95% CI: 0.66-8.19) for traditional educational methods. However, the authors also cautioned that the majority of the studies included in the review were of low quality. They explicitly highlighted the role of digital technology over the past decade in improving ADR reporting. Earlier, a systematic review of 43 studies assessing the impact of different interventions on ADR reporting rates suggested a particular benefit of multiple interventions compared to single interventions in enhancing ADR reporting (Gonzalez-Gonzalez et al., 2013). Interestingly, we observed a consistent improvement in ADR reporting rates despite the wide diversity of tools implemented to enhance ADR reporting across different clinical pediatric settings in the included studies. The role of healthcare professional (HCP) education was particularly highlighted by Kronenfeld et al. (2019), who conducted a 3-month prospective intervention study involving 3,753 pediatric patients and 1,323 prescriptions. Aiming to compare ADR reporting rates during the intervention period with those from the year prior, which served as the control period, HCPs were encouraged to report adverse drug reactions. Notably, the ADR reporting rate was zero in the period before the intervention. During the intervention, healthcare professionals were encouraged to use a newly implemented ADR reporting system, leading to the collection of an additional 46 ADR reports. Clarkson et al. utilized a straightforward method involving monthly reminders and staff presentations, which increased ADR reporting related to topical local anesthetics (Clarkson et al., 2001). Two studies (Baek et al., 2016; Ríos et al., 2016) engaged the healthcare team through pharmacist-led talks and quality assurance programs, respectively. Concurrently, educational initiatives involving medical students (Patel et al., 2017) and healthcare personnel (Balsamo et al., 2022) were associated with enhancing ADR reporting concerning gastrointestinal adverse effects from diclofenac and vaccine safety, respectively. Moreover, Goldman et al. showed the power of staff

education through an integrative Drug Safety Service, resulting in a more than four-fold increase in the detection of medication-related allergies (Goldman, 2013).

The importance of electronic health records (EHR) for accurate ADR documentation was underscored by Hui et al. (2016). In the context of ADHD in children, EHR-based decision support improved the likelihood that children with ADHD had visits for, as well as care related to, managing their condition (Co et al., 2010). Neubert et al. adopted a computerized monitoring system, identifying primarily nervous system-related ADRs within six months (Neubert et al., 2006).

The role of proactive surveillance was presented in two studies through bedside monitoring tools in neonatal intensive care units (NICUs) (Cammack et al., 2019) and a dedicated Drug Safety Service clinical pharmacist (Tillman et al., 2021). The latter was particularly noteworthy for its extended study period of 96 months and its focus on adverse drug reactions (ADRs) related to rashes from antimicrobials. Targeted surveillance coupled with pharmacogenomics was further highlighted by Carleton et al., generating high-quality ADR reports focused on anthracyclines and cardiotoxicity (Carleton et al., 2009). Importantly, we found a significant increase in the ADR reporting rate in different pediatric settings through the adoption of either healthcare professional (HCP)-driven or technology-driven interventions. However, we found no differences between both types of interventions in the increased ADR reporting rates, as evidenced by the results of subgroup analysis ($p=0.47$) and the meta-regression findings ($p=0.63$). In contrast to our findings, Paudyal et al. (2010) found that different interventions have varying effects on ADR reporting rates in their meta-analysis. Their results indicated that financial and face-to-face educational interventions were particularly effective in improving both the quality and quantity of ADR reporting, as opposed to interventions that did not involve face-to-face interactions. It should be noted that our findings cannot be directly compared to Paudyal et al., 2010, due to the inclusion of different populations (adults and pediatrics vs. pediatrics only in the current study), study designs (RCTs vs. observational in our study), and effect size (risk ratio [RR] vs. incidence rate ratio [IRR] per person-life year in this meta-analysis).

Another key finding from the current analysis is a substantial amount of between-study variability in the reported effect sizes of interventions on adverse drug reaction (ADR) reporting rates ($I2 = 95\%$). Subgroup analyses, as well as the findings of the meta-regression from the current study, failed to attribute this variability to either the different nature of interventions

(healthcare professional [HCP]-led vs. technology-driven) or the different follow-up durations adopted within each study. This suggests the influence of unaccounted factors, including country setting, healthcare system differences, patient population specifics, outpatient vs. inpatient setting, and the multitude of ways the interventions were implemented at each site. Insufficient reporting of intervention details in many of the included studies prevented the assessment of the impact of component variations on the pooled incidence rate ratio (IRR) in the current study.

Several factors were previously reported to influence ADR reporting rates in clinical practice settings. In their systematic review, Lopez-Gonzalez et al. (2009) included 45 studies with the aim of investigating the factors associated with underreporting rates of ADR. Medical specialty emerged as the most significant professional factor influencing ADR reporting in 76% of the studies that included physicians. Additional personal factors, including ignorance (believing that only severe ADRs need to be reported), were observed in 95% of studies, followed by diffidence (72%), lethargy (77%), indifference (67%), insecurity (67%), and complacency (47%). The authors concluded that while personal and professional factors exhibited a moderate influence, it was the knowledge and attitudes of health professionals that were most strongly associated with ADR reporting rates. The existence of a dedicated pharmacovigilance center within hospital settings is another factor that was shown to enhance ADR reporting rates (Nam et al., 2015). The attitude of HCPs within practice settings is also deemed to have a significant role (Musdar, 2019). The channel of reporting ADRs demonstrated a significant preference for telephone and computerized approaches (Potlog Shchory et al., 2020). Payment for reporting showed minimal impact on enhanced ADR reporting in a survey-based study of 91 nurses (Pulford & Malcolm, 2010).

The nonsignificant effect of the follow-up time presented in the results of meta-regression in the current analysis ($p=0.51$) suggests a consistent time-effect of different interventions on the increasing rate of adverse drug reaction (ADR) reporting. In contrast to this finding, Figueiras et al. (2006) conducted a cluster-randomized controlled trial aimed at enhancing the reporting of ADRs through a multifaceted continuing medical education intervention. This intervention included an outreach visit, a reminder card, and a report form. At baseline, the intervention group had lower ADR reporting rates compared to the control group, measured by reports per 1,000 physician-years, although these differences were not statistically significant. However, post-intervention data demonstrated a remarkable increase in ADR reporting in the intervention

group, from a baseline of 7.6 (95% CI, 4.0-12.6) to 100.2 (95% CI, 85.2-116.4), compared to a modest increase in the control group from 11.3 (95% CI, 8.9-14.1) to 14.5 (95% CI, 12.0-18.0) ($P < 0.001$). The relative risk (RR) for total ADR reporting in the first four months post-intervention was an astonishing 27.78 (95% CI, 8.36-92.23; $P < 0.001$). While the magnitude of this effect decreased over time, it remained statistically significant for up to 12 months following the intervention. The authors suggested that their multifaceted intervention was highly effective in increasing ADR reporting among physicians, although the effect diminished over time, suggesting the need for ongoing interventions. In a similar context, McGettigan et al. (1997) looked into the outcomes of an interventional program that involved putting yellow reporting cards in every patient's chart at the time of admission and making them easily accessible. Additionally, doctors were frequently reminded to report ADRs. Greater availability of yellow cards and verbal reminders about reporting ADRs resulted in an approximately five-fold increase in reports over the course of the three-month intervention. However, reporting rapidly declined when verbal reminders were removed, despite the cards continuing to be readily available, indicating that making cards available on their own does not significantly increase reporting.

In their intervention study, Kronenfeld et al. (2019) argued that although the intervention led to an initial increase in adverse drug reaction (ADR) reporting, one year of follow-up post-intervention revealed a significant decline in the ADR reporting rate. The contradiction in elucidating the time-effect on ADR reporting rate between our results and the current evidence could be emphasized on the basis that our study analyzed the effects of intervention at only one time point from the last follow-up, so the explicit longitudinal effects of different interventions cannot be directly elucidated from the current study. Furthermore, the different effects of various healthcare professional (HCP)-led or technology-driven interventions could not be directly compared due to the limited availability of sufficient studies characterizing the intrinsic influence of each specific type of intervention. The current study has several strengths. In addition to being the first to characterize the effects of interventions on adverse drug reaction (ADR) reporting in pediatric settings, we conducted a comprehensive literature search across major databases, including the most up-to-date evidence. Study selection, data extraction, and risk of bias assessment were independently performed by two reviewers to reduce errors and bias. We employed standard meta-analytic techniques and assessed heterogeneity, publication bias, and the quality of evidence following PRISMA guidelines (Liberati et al., 2009). However, there are

some limitations to consider. The included studies were mostly observational, with a high risk of bias due to a lack of blinding, controls, and randomization. Significant unexplained statistical heterogeneity was detected. Most evidence came from high-income countries, affecting the generalizability of our findings. The moderate overall quality of evidence limits certainty in effect estimates. Substantial heterogeneity reduces clarity on reasons for variability in results across settings. These factors should be considered when interpreting the findings from the current analysis.

The findings of this systematic review and meta-analysis carry significant implications for enhancing pharmacovigilance practices, especially in pediatric populations. Firstly, the integration of targeted health care professional (HCP)-led or technology-driven interventions into routine pharmacovigilance systems could substantially strengthen signal detection and drug safety surveillance. However, the elucidated substantial heterogeneity suggests that a one-size-fits-all approach may not be optimal. Tailoring initiatives to overcome context-specific barriers could improve effectiveness. For example, settings with limited resources may benefit most from simple enhancements like adverse drug reaction (ADR) reporting reminders, while advanced hospitals may derive greater impact from computerized systems. Additionally, combining several complementary interventions, such as education, improved reporting channels, and ongoing feedback, may have an additive effect compared to isolated interventions. Developing comprehensive pharmacovigilance programs addressing multiple known obstacles could maximize the detection, reporting, and monitoring of pediatric adverse drug events. Finally, the lack of data from low- and middle-income countries highlights an imbalance in pharmacovigilance resources and the evidence base globally. Urgent efforts are needed to expand capacity in under-resourced health systems, ensuring drug safety for pediatric populations worldwide. Several recommendations for enhancing ADR detection and reporting have been consistently proposed in the reviewed literature. Soyer et al. (2019) outlined three corrective actions that could significantly improve ADR reporting rates if appropriately implemented in hospital pharmacovigilance practices: 1) the introduction of a form explaining the addition and coding of an ADR to a patient's file; 2) a weekly exchange of a working file between medical records technicians and the pharmacovigilance team to facilitate review and reporting to regulatory authorities; and 3) the creation of a standardized pharmacist's note for patient files. However, our systematic review identified several remaining gaps in the literature

that warrant further investigation. Firstly, there is a shortage of high-quality randomized controlled trials evaluating specific interventions or conducting head-to-head comparisons of different strategies. The majority of evidence is derived from observational studies with inherent biases. Rigorously designed comparative effectiveness trials are needed. Secondly, details on the optimal design and implementation of interventions are lacking. Future research should assess contextual factors, program components, intensity, and cost-effectiveness to elucidate best practices for each intervention. Thirdly, studies tailoring approaches to overcome setting-specific barriers are also warranted. Fourthly, there is limited data on the sustainability and long-term impacts of the implemented interventions. Studies with extended follow-up are required to evaluate these outcomes. Relatedly, the generalizability of findings to low- and middle-income settings is restricted given the geographic limitations of included research.

Conclusion

In conclusion, this systematic review and meta-analysis revealed that interventions aimed at improving adverse drug reaction detection and reporting increased identification compared to standard practice in children. However, the reliability of our results is threatened by significant issues related to the risk of bias and heterogeneity. Further high-quality randomized studies are needed to better delineate the effectiveness of specific interventions in enhancing pharmacovigilance in pediatric populations.

References

Aagaard, L., Christensen, A., & Hansen, E. H. (2010). Information about adverse drug reactions reported in children: a qualitative review of empirical studies. British Journal of Clinical Pharmacology, 70(4), 481–491.

Andrade, P. H. S., Lobo, I. M. F., & da Silva, W. B. (2017). Risk factors for adverse drug reactions in pediatric inpatients: A cohort study. PloS One, 12(8), e0182327.

Baek, H. J., Cho, Y. S., Kim, K. S., Lee, J., Kang, H. R., & Suh, D. I. (2016). Multidisciplinary approach to improve spontaneous ADR reporting in the pediatric outpatient setting: a single-institute experience in Korea. Springerplus, 5, 1–8.

Balsamo, C., Del Bono, C., Pagano, G., Valastro, V., Ghizzi, C., & Lombardi, F. (2022). Pediatric Adverse Drug Reactions: An Observational Cohort Study After Health Care Workers' Training. The Journal of Pediatric Pharmacology and Therapeutics, 27(4), 324–329.

Cammack, B., Oschman, A., & Lewis, T. (2019). Improving recognition and reporting of adverse drug reactions in the NICU: a quality improvement project. Pediatric Quality & Safety, 4(5).

Carleton, B. C., Poole, R. L., Smith, M. A., Leeder, J. S., Ghannadan, R., Ross, C. J. D., … Hayden, M. R. (2009). Adverse drug reaction active surveillance: developing a national network in Canada's children's hospitals. Pharmacoepidemiology and Drug Safety, 18(8), 713–721.

Clarkson, A., Ingleby, E., Choonara, I., Bryan, P., & Arlett, P. (2001). A novel scheme for the reporting

of adverse drug reactions. Archives of Disease in Childhood, 84(4), 337–339. https://doi.org/10.1136/adc.84.4.337

Co, J. P. T., Johnson, S. A., Poon, E. G., Fiskio, J., Rao, S. R., Cleave, J. Van, … Ferris, T. G. (2010). Electronic health record decision support and quality of care for children with ADHD. Pediatrics, 126(2), 239–246.

Dittrich, A. T. M., Draaisma, J. M. T., van Puijenbroek, E. P., & Loo, D. M. W. M. te. (2020). Analysis of reporting adverse drug reactions in paediatric patients in a university hospital in the Netherlands. Pediatric Drugs, 22, 425–432.

Dreyer, N. A., Velentgas, P., Westrich, K., & Dubois, R. (2014). The GRACE checklist for rating the quality of observational studies of comparative effectiveness: a tale of hope and caution. Journal of Managed Care Pharmacy, 20(3), 301–308.

Fang, H., Lin, X., Zhang, J., Hong, Z., Sugiyama, K., Nozaki, T., … Asakawa, T. (2017). Multifaceted interventions for improving spontaneous reporting of adverse drug reactions in a general hospital in China. BMC Pharmacology and Toxicology, 18, 1–9.

Figueiras, A., Herdeiro, M. T., Polónia, J., & Gestal-Otero, J. J. (2006). An educational intervention to improve physician reporting of adverse drug reactions: a cluster-randomized controlled trial. Jama, 296(9), 1086–1093.

Goldman, J. L., Sullins, A., Sandritter, T., Leeder, J. S., & Lowry, J. (2013). Pediatric pharmacovigilance: enhancing adverse drug reaction reporting in a tertiary care children's hospital. Therapeutic Innovation & Regulatory Science, 47(5), 566–571.

Gonzalez-Gonzalez, C., Lopez-Gonzalez, E., Herdeiro, M. T., & Figueiras, A. (2013). Strategies to improve adverse drug reaction reporting: a critical and systematic review. Drug Safety, 36, 317–328.

Hazell, L., & Shakir, S. A. W. (2006). Under-reporting of adverse drug reactions. Drug Safety, 29(5), 385–396.

Hui, C., Vaillancourt, R., Bair, L., Wong, E., & King, J. W. (2016). Accuracy of adverse drug reaction documentation upon implementation of an ambulatory electronic health record system. Drugs-Real World Outcomes, 3, 231–238.

Impicciatore, P., Choonara, I., Clarkson, A., Provasi, D., Pandolfini, C., & Bonati, M. (2001). Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. British Journal of Clinical Pharmacology, 52(1), 77–83.

jin Kim, H., & Hwang, S. Y. (2022). Effect of Website-based Learning on Improved Monitoring of Adverse Drug Reactions by Clinical Nurses. Asian Nursing Research, 16(1), 45–51.

Kronenfeld, N., Gamsu, S., Keidar, R., Livneh, A., Berkovitch, M., Goldman, M., … Abu-Kishk, I. (2019). The role of an interventional program for improving pharmacovigilance at a pediatric facility. Frontiers in Pharmacology, 10, 1004.

Leitzen, S., Dubrall, D., Toni, I., Stingl, J., Christ, P., Köberle, U., … Sachs, B. (2023). Adverse Drug Reactions in Children: Comparison of Reports Collected in a Pharmacovigilance Project Versus Spontaneously Collected ADR Reports. Pediatric Drugs, 25(2), 203–215.

Li, R., Zaidi, S. T. R., Chen, T., & Castelino, R. (2020). Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: a systematic review. Pharmacoepidemiology and Drug Safety, 29(1), 1–8.

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., … Moher, D. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of Internal Medicine, 151(4),

W-65.

Lombardi, N., Crescioli, G., Bettiol, A., Tuccori, M., Capuano, A., Bonaiuti, R., … Vannacci, A. (2020). Italian emergency department visits and hospitalizations for outpatients' adverse drug events: 12-year active pharmacovigilance surveillance (The MEREAFaPS Study). Frontiers in Pharmacology, 11, 412.

Lopez-Gonzalez, E., Herdeiro, M. T., & Figueiras, A. (2009). Determinants of under-reporting of adverse drug reactions: a systematic review. Drug Safety, 32, 19–31.

Lopez-Gonzalez, E., Herdeiro, M. T., Piñeiro-Lamas, M., Figueiras, A., & Group, G. (2015). Effect of an educational intervention to improve adverse drug reaction reporting in physicians: a cluster randomized controlled trial. Drug Safety, 38, 189–196.

McGettigan, P., Golden, J., Conroy, R. M., Arthur, N., & Feely, J. (1997). Reporting of adverse drug reactions by hospital doctors and the response to intervention. British Journal of Clinical Pharmacology, 44(1), 98–100.

Mejía, G., Saiz-Rodríguez, M., Gómez de Olea, B., Ochoa, D., & Abad-Santos, F. (2020). Urgent hospital admissions caused by adverse drug reactions and medication errors—a population-based study in Spain. Frontiers in Pharmacology, 11, 734.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group*, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of Internal Medicine, 151(4), 264–269.

Musdar, T. A. (2019). Faktor yang mempengaruhi praktik pelaporan Adverse Drug Reactions (ADRs) oleh tenaga di beberapa rumah sakit wilayah kota Surabaya. Universitas Airlangga.

Nam, Y.-H., Nam, H.-J., Song, J.-E., & Lee, S.-K. (2015). A comparative analysis of adverse drug reactions: pre-and post regional pharmacovigilance center in a single tertiary hospital. World Allergy Organization Journal, 8, A60–A60.

Neubert, A., Dormann, H., Weiss, J., Criegee-Rieck, M., Ackermann, A., Levy, M., … Rascher, W. (2006). Are computerised monitoring systems of value to improve pharmacovigilance in paediatric patients? European Journal of Clinical Pharmacology, 62, 959–965.

Patel, P. B., Patel, T. K., Anturlikar, S., Khatun, S., Bhabhor, P., & Saurabh, M. K. (2017). Adverse drug reactions reporting by undergraduate medical students in a tertiary care teaching hospital of India: Content and quality analysis in comparison to physician reporting. Perspectives in Clinical Research, 8(3), 137.

Paudyal, V., Al-Hamid, A., Bowen, M., Hadi, M. A., Hasan, S. S., Jalal, Z., & Stewart, D. (2020). Interventions to improve spontaneous adverse drug reaction reporting by healthcare professionals and patients: systematic review and meta-analysis. Expert Opinion on Drug Safety, 19(9), 1173–1191.

Pirmohamed, M., James, S., Meakin, S., Green, C., Scott, A. K., Walley, T. J., … Breckenridge, A. M. (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. Bmj, 329(7456), 15–19.

Potlog Shchory, M., Goldstein, L. H., Arcavi, L., Shihmanter, R., Berkovitch, M., & Levy, A. (2020). Increasing adverse drug reaction reporting—How can we do better? PLoS One, 15(8), e0235591.

Pulford, A., & Malcolm, W. (2010). Knowledge and attitudes to reporting adverse drug reactions. British Journal of Nursing, 19(14), 899–904.

Reumerman, M., Tichelaar, J., Piersma, B., Richir, M. C., & Van Agtmael, M. A. (2018). Urgent need to modernize pharmacovigilance education in healthcare curricula: review of the literature. European Journal of Clinical Pharmacology, 74, 1235–1248.

Ríos, O. M., Gutiérrez, L. J., Talavera, J. O., Téllez-Rojo, M. M., López, V. O., Espinosa, J. G., & Hernández, O. M. (2016). A comprehensive intervention for adverse drug reactions identification and reporting in a pediatric emergency department. International Journal of Clinical Pharmacy, 38, 80–87.

Soyer, J., Necsoiu, D., Desjardins, I., Lebel, D., & Bussières, J.-F. (2019). Identification of discrepancies between adverse drug reactions coded by medical records technicians and those reported by the pharmacovigilance team in pediatrics: An intervention to improve identification, reporting, and coding. Archives de Pédiatrie, 26(7), 400–406.

Thiesen, S., Conroy, E. J., Bellis, J. R., Bracken, L. E., Mannix, H. L., Bird, K. A., … Peak, M. (2013). Incidence, characteristics and risk factors of adverse drug reactions in hospitalized children–a prospective observational cohort study of 6,601 admissions. BMC Medicine, 11(1), 1–10.

Tillman, E. M., Suppes, S. L., Feldman, K., & Goldman, J. L. (2021). Enhancing pediatric adverse drug reaction documentation in the electronic medical record. The Journal of Clinical Pharmacology, 61(2), 181–186.

Tripathy, R., Das, S., Das, P., Mohakud, N. K., & Das, M. (2021). Adverse drug reactions in the pediatric population: Findings from the adverse drug reaction monitoring center of a teaching hospital in Odisha (2015-2020). Cureus, 13(11).

Walsh, D., Lavan, A., Cushen, A.-M., & Williams, D. (2015). Adverse drug reactions as a cause of admission to a Dublin-based university teaching hospital. Irish Journal of Medical Science (1971-), 184, 441–447.