Received: 16 September 2020 | Revised: 7 October 2020 | Accepted: 12 October 2020

DOI: 10.1111/jcpt.13306

ORIGINAL ARTICLE

Journal of Clinical Pharmacy and Therapeutics WILEY

Adverse Drug Reactions Spontaneously Reported at a Tertiary Care Hospital and Preventable Measures Implemented

Laila Carolina Abu Esba BSc, MSc, PharmD[1,2,3] | **Ghada Al Mardawi BSc, SSC-PhP**[2,4] | **Mohammed I. AlJasser MBBS, FRCPC**[2,5,6] | **Badr Aljohani PhD**[2,5,7,8] | **Amjed Abu Alburak BSN, MSc**[2,5,9]

[1]Pharmaceutical Care Department, King Abdulaziz Medical City- Ministry of National Guard, Health Affairs, Riyadh, Saudi Arabia

[2]King Abdullah International Medical Research Center, Riyadh, Saudi Arabia

[3]College of Pharmacy, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[4]Department of Quality Improvement, King Abdulaziz Medical City, Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia

[5]College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

[6]Division of Dermatology, Ministry of National Guard Health Affairs, Riyadh, Saudi Arabia

[7]William Harvey Research Institute, Queen Mary University of London, London, UK

[8]Ministry of National Guard Health Affairs (MNGHA), Riyadh, Saudi Arabia

[9]Nursing Medication Safety Program, King Abdulaziz Medical City, Riyadh, Saudi Arabia

Correspondence
Laila Carolina Abu Esba BSc, MSc, PharmD, King Abdulaziz Medical City - Ministry of National Guard, Health Affairs, Joint Appointment Lecturer of Pharmacy Practice, King Saud Bin Abdulaziz University for Health Sciences, King Abdullah International Medical Research Centre, PO Box 22490, Riyadh 11426, Saudi Arabia.
Email: abuesbala@ngha.med.sa

Abstract

What is known: Limitations of clinical trials in determining all safety concerns related to a drug are well recognized. Monitoring spontaneous adverse drug reaction (ADR) reports remains an easy and relatively inexpensive method for overseeing that a drug remains a safe and effective option for patients.

Objective: To characterize and describe ADR reports at one of the largest healthcare institutions in the region and share the measures implemented by the team.

Methods: We conducted a retrospective analysis of all ADRs submitted by healthcare providers in a tertiary healthcare system in Saudi Arabia between January 2016 and December 2019. The main outcome measures included reporting rate, patient characteristics, suspected drugs involved, seriousness and reporting specialities.

Results and discussion: Throughout this study, 1156 ADR reports were submitted. The top reported ADR was immune system disorders (87.8%). The most represented class were antimicrobials (56.8%), followed by analgesics (11.4%) and diagnostic agents (5.1%). The ADRs were deemed definitely avoidable in 11.4% (132/1156) of the cases, and 24.2% (280/1156) were deemed possibly avoidable. Reporting ADRs has steadily increased over the years at our institution, but there continues to be a lack of reporting by physicians. Almost one-third of the reported ADRs were considered to be avoidable or possibly avoidable, which is a driver to continue pharmacovigilance activates on an institutional level and provide specific and tailored preventative measures guided by the specific types of ADRs reported.

What is new and conclusion: This is the first study to report trends of ADRs spontaneously reported at one of the largest healthcare institutions in the Middle East. It shows similar trends to what has been reported by other institutions, with mainly immediate immunological ADRs being the top reported ADRs, which could be explained by the immediate onset which simplifies the temporal association. Every institution should support and maintain an active ADR team, with responsibilities of evaluating incidents, monitoring trends and most importantly identifying opportunities to

improve medication and patient safety. We share here our workflow and hope it serves as a guide for other institutions.

KEYWORDS
ADR team, adverse drug reaction, pharmacovigilance, spontaneous ADR reporting

1 | WHAT IS KNOWN AND OBJECTIVE

Adverse drug reaction (ADR) is defined as "any response to a drug, which is noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis, or therapy or for modification of physiologic function".[1] ADRs are a concern in the pharmacotherapeutic approach in treating a disease and a burden that may alter the benefit-risk balance. This benefit-risk assessment on the basis of which drug regulatory authorities approve drugs is done at a time of point where not all risks related to a drug are identified. This is due to the inherent limitations of initial regulatory required clinical trials in detecting all safety concerns.

Limitations of a clinical trial setting in determining all safety concerns related to a drug are well recognized by statistical facts where rare incidents are impossible to be picked up in the frame of the limited sample size. Most clinical trial designs have strict inclusion criteria that may exclude patients with comorbidities, specific population (e.g.pregnant) or patients using other drugs; and therefore fail to capture all risks and ADRs that may render the drug unsafe.[2]

When it comes to the generalizability of clinical trial findings, it becomes explicitly more concerning for developing countries in which patient populations of a specific genetic background are not included in main drug approval trials.[3] These countries extrapolate safety and efficacy data from trials on patients with a different genetic background, healthcare setting, culture and disease prevalence.

Monitoring spontaneous ADR reports remains an easy, convenient and relatively inexpensive method for overseeing that a drug therapy remains a safe and effective option for patients. Many countries have published their spontaneous ADR reported data, as a means of informing the medical society of ADR prevalence and rates in real practice,[4-10] and other studies have explored the economic burden and consequences of ADRs on the healthcare system.[11]

The objective of this study is to characterize and describe ADR reports at one of the largest healthcare institutions in the region, with respect to reporting rate, patient characteristics, suspected drugs involved, seriousness and reporting specialities. We also share in this paper measures implemented as direct actions related to the ADRs being reported at our institution.

Ethics Approval: The study protocol was reviewed and approved by the Institutional Research Ethics Board (Study number RC20/427/R). Individual patient consent was not required for this type of study.

Impact on Practice Statement

A few papers describe the features of institutional reported ADRs, most studies are from national pharmacovigilance centres which usually lack specific details related to the ADR incidence and types. Our paper describes the ADRs reported at one of the largest healthcare systems in our region with details of drugs involved and insight on preventable measures that can be implemented on an institutional level.

2 | METHODS

Setting: The Ministry of National Guard Health Affairs (MNGHA) is a tertiary healthcare system established in 1983; it has facilities in the Central, Eastern and Western regions of Saudi Arabia. It is one of the largest healthcare institutions in Saudi Arabia; this study describes ADRs reported in its central region Riyadh. The central region has two medical sites: King Abdulaziz Medical City (established 1982) and King Abdullah Specialist Children's Hospital (established 2015); together they provide a total bed capacity of 2100 beds. During 2017, there were 51,508 admissions, 492,955 outpatient visits, 194,831 emergency department visits, 18,790 operations, and 8391 deliveries.[12]

We conducted a retrospective analysis of all ADRs submitted by healthcare providers at NGHA from January 2016 to December 2019, through our internal electronic reporting system SRS.

All reports were included for analysis and the following information was extracted for each ADR report:

- the unique report number
- year reported
- age and sex of the patient,
- suspected drug/s,
- the system organ class related to the ADR
- in-patient or outpatient setting,
- medical services where the ADR occurred,
- the description of the reaction,
- profession of the reporter,
- score of causality associations (Naranjo probability score),
- severity of outcome and preventability

2.1 | Classification

Drug classes: drugs were classified according to the categories for therapeutic groups based on the categorization used by American Association of Poison Control Centers (AAPCC)[13]

Organ Affected: The *System organ class* (SOC) related to the ADR was coded with The Medical Dictionary for Regulatory Activities (MedDRA) [14]

ADR outcome: they were classified utilizing Hartwig's severity assessment scale, which is divided into seven levels (Table 1).

Causality Assessment: assessed utilizing the Naranjo scoring tool, score legend below: Definite ADR (>=9), Probable ADR (5–8), Possible ADR (1–4), Doubtful ADR (<=0).[15]

2.2 | Statistical analysis

All of the data was extracted from the Safety Reporting System (SRS) and downloaded in an Excel spreadsheet. Descriptive statistics were used to summarize data. Patient characteristics, drugs implicated, and system affected, all were presented in numbers and percentages for qualitative variables.

The annual number of reports of ADRs were determined from 2016 through 2019. Frequencies were determined according to each outcome category or drug. The proportion of ADR reports by age group was estimated based on the total number of ADR reports and compared against the proportion of drug use attributable to each age group. All analyses were conducted using SAS software package 9.4 (SAS Institute, Cary, NC).

The comparison of ADRs according to the characteristics of the patients was carried out in a univariate analysis with a chi-square test, and the significance threshold having been set at 0.05.

About our ADR team: Each region has its own designated ADR team; the ADR team in the central region is responsible for ADRs reported at King Abdulaziz Medical City the main hospital and King Abdullah Specialized Children Hospital.

Our ADR team is multidisciplinary and includes members of the following disciplines: clinical pharmacists, medication safety officer, medication safety auditors, physician (dermatologist), nurse, and a specialist in bioequivalence and counterfeit drugs.

Workflow: Any MNGHA healthcare provider can report ADRs; through our internal electronic safety reporting system (SRS), under a specific ADR field. The SRS is easily accessed through the hospital's intranet portal. The medication safety auditors initially assess every ADR report for duplication, completeness and overall validity. Reports are then sent to the clinical pharmacist covering the ward where the ADR incident occurred for a further detailed assessment, for wards not covered by a clinical pharmacist and ADRs that occur in the outpatient setting the ADR team conducts the assessment. Every ADR goes through a thorough evaluation process by a clinical pharmacist.

The Individual ADR Report Evaluation Process Includes:

TABLE 1 Hartwig's severity assessment scale[17]

Level 1	Level 2	Level 3	Level 4	Level 5	Level 6	Level 7
An ADR occurred but required no change in treatment with the suspected drug.	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay	The ADR required that treatment with the suspected drug be held, discontinued, or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS)	Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission	Any level 4 ADR which requires intensive medical care	The adverse reaction caused permanent harm to the patient	The adverse reaction either directly or indirectly led to the death of the patient

- Causality Assessment: the probability that the drug caused the adverse effect; assessed utilizing the Naranjo scoring tool[15]
- Preventability: an assessment of whether the event is preventable by any means, for example monitoring or dose adjustment. Based on the Liverpool ADR avoidability assessment tool [16]
- Severity of the Outcome: the severity of the outcome of the ADR is categorized utilizing the Hartwig's severity assessment scale[17]
- Electronic Health Record (EHR) Documentation of the ADR: A recommendation on whether the ADR should be documented in the patient's electronic record, as this will result in a system alert should another prescriber order the drug in the future for the patient.
- Comments: Finally, the clinical pharmacist may add any comment they have related to the ADR, for example future challenging with the drug or tolerated alternatives

The evaluation form is built in an Excel sheet with drop-down menus to ease the clinical pharmacist's assessment. The ADR team may make further recommendations for individual reports. All ADR reports with the evaluations are kept in the SRS database and utilized to generate reports and monitor trends.

Quarterly ADR Hospital Report (aggregated data assessment): on a quarterly basis the ADR team creates reports from the SRS database, monitors for specific trends and makes further recommendations on how to mitigate harm. Recommendations are discussed at the hospital's medication safety committee and pharmacy & therapeutics committee.

Sharing ADR reports with the national pharmacovigilance centre: All ADRs are compiled and sent to the Saudi Food and Drug Authority pharmacovigilance centre, contributing locally and internationally to the global knowledge about the safety of drugs.

TABLE 2 Demographic data

Characteristic	Value N (%)
Total number of ADRs	1156
Male	494 (42.7%)
Female	662 (57.3%)
Paediatrics ≤ 18	318 (27.5%)
Adults (19–64 years)	628 (54.3%)
Elderly > 65	210 (18.2%)

3 | RESULTS

Over the period of this study, 1156 ADR reports were submitted through the SRS between 2016 and 2019. Of these, 20.8% (240 reports) in 2016, 19.2% (222 reports) in 2017, 26.7% (309 reports) in 2018, and 33.3% (385) were submitted in 2019.

3.1 | Demographic characteristics

The median age of the patients was 35 years (IQR 16–58). Ranging from <1 month to 104 years. The adult group comprised the largest

TABLE 3 Classification *System organ class* (SOC), classification in order of frequency and age distribution of patients

System organ class (SOC)	Paediatrics = 18	Adults (19-64)	Elderly > 65	Total
Immune system disorders	87.8% (280)	83.7% (525)	83.3% (175)	84.8% (980)
Product issues	3.5% (11)	3.4% (21)	1% (2)	2.9% (34)
Hepatobiliary disorders	0% (0)	4% (25)	2.4% (5)	2.6% (30)
Renal and urinary disorders	0.6% (2)	1.8% (11)	3.3% (7)	1.7% (20)
Blood and lymphatic systems disorders	0% (0)	1.8% (11)	3.3% (7)	1.6% (18)
Gastrointestinal disorders	0.6% (2)	1.9% (12)	1.4% (3)	1.5% (17)
Nervous system disorder	0.3% (1)	1.9% (12)	1.4% (3)	1.4% (16)
Skin and subcutaneous tissue disorders	3.8% (12)	0.2% (1)	0% (0)	1.1% (13)
Vascular disorders	1.9% (6)	0% (0)	0% (0)	0.5% (6)
Cardiac disorders	0.9% (3)	0.3% (2)	1.4% (3)	0.7% (8)
Endocrine disorders	0% (0)	0.2% (1)	1.4% (3)	0.4% (4)
Musculoskeletal and connective tissue disorders	0% (0)	0.3% (2)	1% (2)	0.4% (4)
Respiratory thoracic and mediastinal disorders	0.3% (1)	0.3% (2)	0% (0)	0.3% (3)
Psychiatric disorders	0.3% (1)	0.2% (1)	0% (0)	0.2% (2)
Pregnancy–puerperium and perinatal conditions	0% (0)	0.2% (1)	0% (0)	0.1% (1)

portion of reported ADRs (54.3%), followed by paediatrics (27.5%), and elderly patients > 65 years (18.2%). The male: female ratio was 3:4. (Table 2).

Classification *System organ class* (SOC): Table 3 lists ADRs by type of SOC affected, out of the 27 MedDRA system organ classes related to an ADR only 15 classes were involved, and the top reported ADR was immune system disorders accounting for 87.8% of all reports. The least frequently reported were pregnancy conditions, psychiatric and respiratory disorders.

3.2 | Causative drugs

Table 4 illustrates the frequency of ADRs by drug class suspected to be involved, which included 27 drug classes and 200 specific drugs/herbs (see top 10 drugs, Figure 1), the most represented class were antimicrobial drugs (56.8%), followed by analgesics (11.4%) and diagnostic agents (5.1%). More than half of the classes had less than 10 reports. Figure 1 shows the top 10 drugs involved, where ceftriaxone was the top drug, followed by other antibiotics but also includes morphine, contrast dye and acetaminophen.

3.3 | Association of drug class with SOC

Altogether, 84.8% of the ADRs were immunologically mediated reactions, and 15.2% were non-immunologically mediated reactions. Among the commonly implicated medication classes, analgesics [OR (95% CI) 17.25 (6.79, 43.82) p value < 0.001] was more frequently associated with immunologically mediated reactions, followed by diagnostic agents and antimicrobials, see Table 5.

3.4 | ADRs by severity

Overall, the majority of ADRs resulted in level 3 severity of outcome 1024 (88.6%) (Table 6). Table 1 supplementary describes the ADRs with severity 6 and 7, and Table 2 supplementary shows the top drug classes implicated with ADRs level 4–5.

TABLE 4 Frequencies of ADRs By drug class, in order of frequency and age distribution of patients

Drug class	Paediatrics = 18	Adults (19-64)	Elderly > 65	Total
Antimicrobials	54.2% (173)	51.0% (320)	78.1% (164)	56.8% (657)
Analgesics	9.4% (30)	14.2% (89)	6.2% (13)	11.4% (132)
Diagnostic agent	3.5% (11)	6.2% (39)	4.3% (9)	5.1% (59)
Gastrointestinal preparations	4.7% (15)	4.5% (28)	1.9% (4)	4.1% (47)
Serums-toxoids-vaccines	6% (19)	2.6% (16)	0.5% (1)	3.1% (36)
Cardiovascular Drugs	4.1% (13)	2.6% (16)	2.4% (5)	2.9% (34)
Anticonvulsants	2.2% (7)	2.6% (16)	0.5% (1)	2.1% (24)
Antineoplastics	3.1% (10)	2.2% (14)	0% (0)	2.1% (24)
Hormones-hormone antagonists	1.6% (5)	2.9% (18)	0.5% (1)	2.1% (24)
Immunomodulating Agents	1.3% (4)	2.1% (13)	0% (0)	1.5% (17)
Anesthetics	1.3% (4)	1.6% (10)	0% (0)	1.2% (14)
Electrolytes-minerals	1.3% (4)	0.8% (5)	1% (2)	1% (11)
Sedatives-hypnotics-antipsychotic	0.31% (1)	1.28% (8)	0.5% (1)	0.9% (10)
Muscle relaxants	0% (0)	1.4% (9)	0% (0)	0.8% (9)
Antihistamines	0% (0)	1.1% (7)	0.5% (1)	0.7% (8)
Topical preparation	1.9% (6)	0.2% (1)	0.5% (1)	0.7% (8)
Anticholinergic drugs	1.6% (5)	0.2% (1)	0% (0)	0.5% (6)
Diuretics	0.6% (2)	0.3% (2)	1% (2)	0.5% (6)
Anticoagulants	0.3% (1)	0.6% (4)	0% (0)	0.4% (5)
Miscellaneous drugs	0.3% (1)	0.2% (1)	1.4% (3)	0.4% (5)
Dietary supplements and herbals	0% (0)	0.5% (3)	0.5% (1)	0.4% (4)
Eye-ear-nose-throat preparation	0.6% (2)	0.3% (2)	0% (0)	0.4% (4)
Total Parenteral Nutrition	0.6% (2)	0.2% (1)	0.5% (1)	0.4% (4)
Antidepressants	0% (0)	0.5% (3)	0% (0)	0.3% (3)
Asthma therapies	0.6% (2)	0.2% (1)	0% (0)	0.3% (3)
Cold-cough preparations	0.3% (1)	0% (0)	0% (0)	0.1% (1)
Stimulants	0.3% (1)	0% (0)	0% (0)	0.1% (1)

3.5 | Causality assessment

Causality was determined as "Definite" in 33 (2.9%), "probable" in 707 (61.2%), "Possible" in 384 (33.2%), and "Doubtful" in 32 (2.7%) using Naranjo scale.

3.6 | ADR avoidability assessment

The ADRs were deemed definitely avoidable in 11.4% (132/1156) of the cases, 24.2% (280/1156) were deemed possibly avoidable, and 64.4% (744/1156) were deemed not avoidable.

3.7 | ADRs by reporting profession

Most of the reporters were nurses (87.6%), followed by pharmacists (11.8%), and very few reporters were physicians (0.6%) (Table 7). The most frequently reported ADRs by nurses were immunological ADRs while ADR reported by pharmacists were mostly rare and non-immunological types of ADRs.

4 | DISCUSSION

Reporting ADRs has steadily increased over the years at our institution, with an increase in the involvement of different providers. This could be explained by an increase in awareness through institutional campaigns and educational activities. However, as described in the literature, underreporting is the main challenge in pharmacovigilance activities, and methods such as campaigns, incentives, and even legislative changes have minimal effect on reporting.[18-20] Our team's goal was, despite the limited number of reports, to focus on measures that could be taken to prevent harm based on those few reports we received.

Although studies have shown a higher incidence of ADRs in elderly and paediatric patients,[21-23] the highest number of reports in our study was in adults. This could be explained by the higher percentage of drugs being prescribed to adults, as the paediatric population accounted for 26% of all prescribed drugs, and elderly patients accounted for ~23% during 2019. The higher rate of ADRs reported in females can also be explained by the higher rate of drugs being prescribed for females especially in the adult age group.

The main system organ classes involved were immunological-related ADRs (84.8%), manifested in reactions ranging from severe anaphylaxis to mild rashes. These types of ADRs are expected to be the highest reported due to the nature of immediate onset and ease of temporal association with the administered drug, compared to ADRs that are delayed or rarely known to be caused by a drug.

Analgesics, diagnostic agents, and antimicrobials were the most associated drugs with immunological-related ADRs. Of analgesics, morphine was the highest reported, accounting for 43% of the reports in this class. Antimicrobials accounted for the highest total number of immunological-related ADRs, with ceftriaxone being the top reported drug followed by piperacillin/tazobactam and vancomycin, these drugs are also the top prescribed antibiotics at our institution as per consumption records.

As for severe immunological reactions over the period of this study, there was one reported case of Stevens-Johnson syndrome associated with phenytoin, and one reported case of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) associated with vancomycin use.

ADRs related to product issues were the following top reported ADRs, issues were mainly related to ADRs occurring after a generic switch or a switch to a biosimilar. These types of reports were highly investigated, case by case, and further reported to the SFDA with an official request to investigate the products and lots involved. Reports were also shared with the manufacturing companies. In addition, we communicated with other local hospital ADR teams to make them aware of our observations and explore if they had any similar reports. An investigation into a series of ADRs related to two drugs led us to recall specific lots and finally switching to a different manufacturer.

Hepatobiliary ADRs were the third most reported ADRs, and the top reported ADRs by pharmacists, manifested mainly by an increase in liver enzymes, jaundice, or cholestasis. Several of these ADRs were related to unidentifiable herbal products. After an increase in the number of these types of ADRs, we decided to incorporate the Council

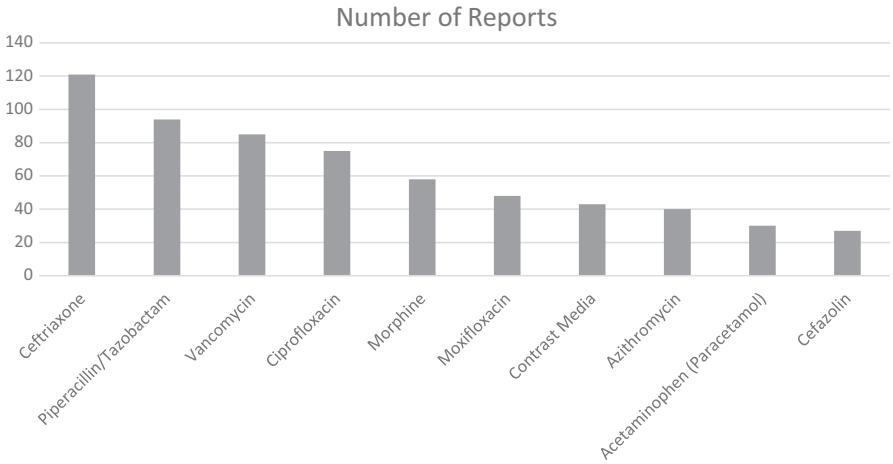

FIGURE 1 Top 10 Drugs implicated in ADR Reports, 2016–2019

TABLE 5 Associated drug class with immunologically mediated reactions compared to other ADR

Drug class (Ref - Other drugs)	OR (95% CI)	*p* value
Analgesics	17.25 (6.79, 43.82)	<0.001
Antimicrobials	8.43 (5.68, 12.5)	<0.001
Diagnostic agent	12.68 (3.85, 41.74)	0.018
Gastrointestinal preparations	2.51 (1.19, 5.31)	0.2
Serums-toxoids-vaccines	0.68 (0.34, 1.38)	<0.001

for International Organizations of Medical Sciences/Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) for assessing hepatotoxicity ADRs. This method has been shown to be more reliable than other scales in the evaluation of drug-induced liver injury (DILI), the scale can easily be filled in online to give a probability score.[24]

Rare and difficult to associate classes such as malignancy or reproductive system related ADRs were not reported during this study period, these types of ADRs are difficult to associate with a specific drug, and usually requires a specialized practitioner aware of both the drug's potential to cause something like malignancy and a long-term follow-up of the same patient. Physicians had a minimal contribution to reporting ADRs so this was expected. As for causality assessment, almost 60% of the ADRs were deemed possible and rarely deemed definitive or doubtful. One limitation of interpreting the data presented in our study is that multiple clinical pharmacists were involved in individual ADR report assessments, nevertheless, the Naranjo scale consists of ten objective questions that are simple and straightforward. Besides, the conclusion on causality will depend on a score that falls within a range which minimizes discrepancies between evaluators.

With respect to the severity of ADR outcomes, 88.6% as per Hartwig's classification required that the treatment with the suspected drug be changed and/or treatment be given, but resulted in no increase in the length of stay. The economic burden of treating ADRs is beyond the scope of this paper, however, the cost of administering drugs such as antihistamines, corticosteroids, epinephrine, and the cost of changing to a less favourable drug, indicates that the burden is substantial.

For ADRs with a higher significant clinical outcome and economic impact: 1.6% resulted in hospital admission, 1.4% required intensive medical care and 0.3% of the reported ADRs caused permanent harm. There was one ADR during the period of this study that resulted in death. The suspected drug was lidocaine administered as a local anesthetic during a dental procedure. The patient suffered a severe anaphylaxis reaction that resulted in cardiac arrest. The patient was asthmatic and had underlying cardiac disease, which are known risk factors for fatal anaphylaxis outcomes.[25,26]

Almost one-third of the reported ADRs assessed in this study period were considered to be avoidable or possibly avoidable. This is in line with findings reported in other studies[22-29] and is a driver to continue pharmacovigilance activates on an institutional level and provide specific and tailored preventative measures guided by the specific types of ADRs reported.

Examples of avoidable ADRs: prescribing a drug with a known cross-allergy to a patient's documented allergy, renal injury resulting from inadequate monitoring or an uncommon drug interaction, or exposing a patient with a high risk for an ADR when the benefit is

TABLE 6 ADRs by Severity

ADR Level	Per cent (Frequency)
Level 2 (required that treatment with the suspected drug be held, discontinued or otherwise changed. No antidote or other treatment requirement was required. No increase in length of stay)	8.0 (93)
Level 3 (required that treatment with the suspected drug be held, discontinued or otherwise changed. AND/OR An Antidote or other treatment was required. No increase in length of stay (LOS))	88.6 (1024)
Level 4 (Any level 3 ADR which increases length of stay by at least 1 day. OR The ADR was the reason for the admission)	1.6 (19)
Level 5 (Any level 4 ADR which requires intensive medical care)	1.4 (16)
Level 6 (The adverse reaction caused permanent harm to the patient)	0.3 (3)
Level 7 (The adverse reaction either directly or indirectly led to the death of the patient)	0.1 (1)

TABLE 7 Characteristics of healthcare professionals reporting ADRs in the SRS between 2016 and 2019

	2016 [N = 240 (20.8%)]	2017 [N = 222 (19.2%)]	2018 [N = 309 (26.7%)]	2019 [N = 385 (33.3%)]	Total
Nurse	237 (98.8%)	209 (94.14%)	278 (89.97%)	289 (75.1%)	1013 (87.6%)
Pharmacist	3 (1.3%)	13 (5.9%)	31 (10.1%)	89 (23.1%)	136 (11.8%)
Physician	0 (0%)	0 (0%)	0 (0%)	7 (1.8%)	7 (0.6%)

TABLE 8 Initiatives, Recommendation and Actions taken by the ADR team based on received reports

Category	Initiatives, Recommendation and/or Actions
Drug Guidelines/Safety Alerts and Material developed and shared on the Hospital's Intranet	Guidance on the teratogenic risk profile of antiepileptic drugs Antiepileptic cross-allergy algorithm Beta-lactam side chain similarity cross-allergy guide. List of drugs commonly associated with drug-induced thrombocytopenia List of drugs most commonly associated with liver-toxicity List of medications with high sodium content Patient educational material regarding the safety of herbal products Butylscopolamine to be avoided in patients with cardiac disease Metoclopramide and avoiding its use with fluoxetine Risk of seizure with imipenem
Activities to Improve Reporting	An educational awareness campaign to encourage all healthcare providers to report ADRs. Awards and incentives to top reporters and those that supported the ADR team. Created a clear link to the ADR electronic reporting system on the hospital's home page. Designed an ADR brochure for HCPs on why and how to report. Designed an ADR logo used in all email communications.
ADR General Activities	Quarterly educational report shared with all HCP on the hospital's intranet Daily follow-up on patients that have a reported ADR, which were not documented in the EHR under the ADR-specific field. Adopted the (CIOMS/RUCAM) scale for evaluating hepatobiliary ADRs. Started to report total number of ADR reports in the hospital per 1000 patients' bed days. Official communication with manufacturer when an ADR was linked to a specific manufacturer. SFDA quality reports filled and sent in cases of suspected lack of efficacy. Met CBAHI/JCI standards on ADRs Integrating the SFDA Risk Minimization Measures in the EHS. Collaboration with the antimicrobial stewardship to assess the use of antibiotics post-misoprostol therapy in patients that develop fever and develop tools to minimize unnecessary antibiotic use. Added a field in the ADR electronic reporting form to identify if the reported ADR was related to a biosimilar product
Formulary Changes	Added tropicamide 0.5% minims to formulary (after a premature baby developed bradycardia, cyanosis and de-saturated while using the 1%) Recalled lots of vancomycin from a specific manufacturer Recalled lots of tacrolimus from a specific manufacturer
EHS System Changes	Multiple enhancements to the allergy documentation field in the EHS Established a task force with the EHS team to create a hard stop function in the system when a patient with a history of severe drug allergy, for example SJS and TEN has been prescribed the offending drug. Initiated a project for uploading a photo of the patient's allergic reaction in the EHS with a consent form Penicillin Decision Kit to be implemented Standardized infusion time for vancomycin and recommended avoiding administering in a (Y site) with other drugs to avoid red-man syndrome.[30,31] Created a dashboard to extract documented ADRs in MNGHA patient's EHRs[32] (data not included in this study).
Shared Rare Case Reports	Tingling sensation with colistin Autoimmune haemolytic anaemia with alemtuzumab Quetiapine and neuroleptic malignant syndrome Linezolid and hyponatremia Piperacillin/tazobactam-induced thrombocytopenia Ketamine and psychosis Linezolid and thrombocytopenia Vanishing bile duct syndrome with celecoxib Severe pancytopenia with piperacillin/tazobactam

Abbreviations: CBAHI, The Saudi Central Board for Accreditation of Healthcare Institutes; DILI, drug-induced liver injury; EHR, Electronic Healthcare Record; EHS, Electronic Healthcare System; HCP, Healthcare Provider; JCI, Joint Commission International; SFDA, Saudi Food & Drug Authority; TEN, Toxic Epidermal Necrolysis.

clearly outweighed (e.g. metoclopramide for nausea in a patient on fluoxetine resulting in extrapyramidal symptoms).

Top reporting providers at our institution are nurses, this explains why the most commonly ADRs being reported are allergic-type reactions, which are generally monitored and identified by nurses during the medication administration phase. Pharmacists were the second top reporters and relatively reported more rare ADRs that would require more experience in drugs to identify it as a culprit. Physicians on the other hand had almost negligible ADR reports.

Lack of reporting by physicians was discussed and investigated by the team and attributed to an organizational culture that nurses were responsible for reporting ADRs. Some physicians also coined their concern with the technical difficulty of reporting and suggested that reporting would be more feasible if it were available directly through the EHS.

The ultimate goal of having an active institutional ADR team is to improve medication safety and prevent harm. Despite the limitations of a spontaneous ADR reporting system, it serves as a valuable tool to monitor internal trends and provide signals on medication safety issues that could be addressed through internal policies and initiatives. Table 8 summarizes the initiatives, recommendations, and/or actions taken by our team during the period of this study.

5 | WHAT IS NEW AND CONCLUSION

This is the first study to report trends of ADRs spontaneously reported at one of the largest healthcare institutions in the region. It shows similar trends to what has been reported by other institutions, with mainly immediate immunological ADRs being the top reported ADRs, which could be explained by the immediate onset which eases temporal association. Every institution should support and maintain an active ADR team, with responsibilities of evaluating incidents, monitoring trends, and most importantly identifying opportunities to improve medication and patient safety.

CONFLICT OF INTEREST

No funding was received for this study. All authors certify that they have no conflicts of interest or competing interests to the content of this study. The data sets during and/or analysed during the current study available from the corresponding author on reasonable request.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Laila Abu Esba. The first draft of the manuscript was written by Laila Abu Esba, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

ORCID

Laila Carolina Abu Esba https://orcid.org/0000-0003-2459-1485
Ghada Al Mardawi https://orcid.org/0000-0002-3820-0863
Mohammed I. AlJasser https://orcid.org/0000-0003-1759-1057
Badr Aljohani https://orcid.org/0000-0002-2548-8474

REFERENCES

1. World Health Organization (WHO). *Requirements for adverse drug reaction reporting*. Geneva: WHO; 1975.
2. Naranjo CA, Busto U, Sellers EM. Difficulties in assessing adverse drug reactions in clinical trials. *Prog Neuropsychopharmacol Biol Psychiatry*. 1982;6(4–6):651-657. https://doi.org/10.1016/s0278-5846(82)80162-0
3. Stuart EA, Bradshaw CP, Leaf PJ. Assessing the generalizability of randomized trial results to target populations. *Prev Sci*. 2015;16(3):475-485. https://doi.org/10.1007/s11121-014-0513-z
4. Marques J, Ribeiro-Vaz I, Pereira AC, Polónia J. A survey of spontaneous reporting of adverse drug reactions in 10 years of activity in a pharmacovigilance centre in Portugal. *Int J Pharm Pract*. 2014;22(4):275-282. https://doi.org/10.1111/ijpp.12078
5. Shin YS, Lee Y-W, Choi YH, et al. Spontaneous reporting of adverse drug events by Korean regional pharmacovigilance centers. *Pharmacoepidemiol Drug Saf*. 2009;18(10):910-915. https://doi.org/10.1002/pds.1796
6. Leporini C, Marrazzo G, Mumoli L, et al. Adverse drug reactions reporting in Calabria (Southern Italy) in the four-year period 2011–2014: impact of a regional pharmacovigilance project in light of the new European Legislation. *Expert Opin Drug Saf*. 2017;16(5):515-522. https://doi.org/10.1080/14740338.2017.1316486
7. Kua KP, Jamil MFB, Liew MH, Si JY, Lee SWH. A retrospective analysis of reporting of adverse drug reactions over 4 years in a primary care health clinic in Malaysia. *Pharmacoepidemiol Drug Saf*. 2019;28(12):1560-1561. https://doi.org/10.1002/pds.4913
8. Hawcutt DB, Mainie P, Riordan A, Smyth RL, Pirmohamed M. Reported paediatric adverse drug reactions in the UK 2000–2009. *Br J Clin Pharmacol*. 2012;73(3):437-446. https://doi.org/10.1111/j.1365-2125.2011.04113.x
9. Wallerstedt SM, Brunlöf G, Sundström A. Rates of spontaneous reports of adverse drug reactions for drugs reported in children: a cross-sectional study with data from the Swedish adverse drug reaction database and the Swedish Prescribed Drug Register. *Drug Saf*. 2011;34(8):669-682. https://doi.org/10.2165/11591730-000000000-00000
10. Thiessard F, Roux E, Miremont-Salam G, et al. Trends in spontaneous adverse drug reaction reports to the French pharmacovigilance system (1986–2001). *Drug Saf*. 2005;28(8):731-740. https://doi.org/10.2165/00002018-200528080-00007
11. Formica D, Sultana J, Cutroneo PM, et al. The economic burden of preventable adverse drug reactions: a systematic review of observational studies. *Expert Opin Drug Saf*. 2018;17(7):681-695. https://doi.org/10.1080/14740338.2018.1491547
12. Kingdom of Saudi Arabia Ministry of National Guard Health Affairs. Organization Profile. https://ngha.med.sa/English/AboutNGHA/Pages/profile.aspx. Accessed January 15, 2020
13. Mowry JB, Spyker DA, Cantilena LR, et al. 2013 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 31st annual report. *Clin Toxicol (Phila)*. 2014;52(10):1032-1283. https://doi.org/10.3109/15563650.2014.987397
14. MedDRA MSSO.Introductory Guide for Standardised MedDRA Queries (SMQs) Version 21.0. https://www.meddra.org/sites/default/files/guidance/file/smq_intguide_21_0_english.pdf. Accessed May 6, 2020
15. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239-245. https://doi.org/10.1038/clpt.1981.154
16. Bracken LE, Nunn AJ, Kirkham JJ, et al. Development of the liverpool adverse drug reaction avoidability assessment tool. *PLoS One*. 2017;12(1):e0169393.
17. Hartwig S, Siegel J, Schneider PJ. Preventability and severity assessment in reporting adverse drug reactions. *Am J Hosp Pharm*. 1992;49(9):2229-2232.

18. Karlsson SA, Jacobsson I, Boman MD, et al. The impact of a changed legislation on reporting of adverse drug reactions in Sweden, with focus on nurses' reporting. *Eur J Clin Pharmacol*. 2015;71(5):631-636. https://doi.org/10.1007/s00228-015-1839-6
19. Hazell L, Shakir SA. Under-reporting of adverse drug reactions : a systematic review. *Drug Saf*. 2006;29(5):385-396. https://doi.org/10.2165/00002018-200629050-00003
20. Li R, Zaidi STR, Chen T, Castelino R. Effectiveness of interventions to improve adverse drug reaction reporting by healthcare professionals over the last decade: a systematic review. *Pharmacoepidemiol Drug Saf*. 2020;29:1-8. https://doi.org/10.1002/pds.4906
21. Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. *Pharm World Sci*. 2002;24(2):46-54. https://doi.org/10.1023/a:1015570104121
22. Pirmohamed M, James S, Meakin S, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ*. 2004;329(7456):15-19. https://doi.org/10.1136/bmj.329.7456.15
23. Aagaard L, Christensen A, Hansen EH. Information about adverse drug reactions reported in children: a qualitative review of empirical studies. *Br J Clin Pharmacol*. 2010;70(4):481-491. https://doi.org/10.1111/j.1365-2125.2010.03682.x
24. Danan G, Benichou C. CIOMS/RUCAM Scale. Roussel Uclaf Causality Assessment Method. http://farmacologiaclinica.info/scales/CIOMS-RUCAM/#cform. Accessed January 15, 2020
25. Pumphrey RS. Fatal anaphylaxis in the UK, 1992–2001. *Novartis Found Symp*. 2004;257:116-285.
26. Greenberger PA, Rotskoff BD, Lifschultz B. Fatal anaphylaxis: postmortem findings and associated comorbid diseases. *Ann Allergy Asthma Immunol*. 2007;98(3):252-257. https://doi.org/10.1016/S1081-1206(10)60714-4
27. Lövborg H, Eriksson LR, Jönsson AK, Bradley T, Hägg S. A prospective analysis of the preventability of adverse drug reactions reported in Sweden. *Eur J Clin Pharmacol*. 2012;68(8):1183-1189. https://doi.org/10.1007/s00228-012-1237-2
28. Hakkarainen KM, Hedna K, Petzold M, Hägg S. Percentage of patients with preventable adverse drug reactions and preventability of adverse drug reactions–a meta-analysis. *PLoS One*. 2012;7(3):e33236. https://doi.org/10.1371/journal.pone.0033236
29. Temple ME, Robinson RF, Miller JC, Hayes JR, Nahata MC. Frequency and preventability of adverse drug reactions in paediatric patients. *Drug Saf*. 2004;27(11):819-829. https://doi.org/10.2165/00002018-200427110-00005
30. Bauters T, Claus B, Schelstraete P, Robays H, Benoit Y, Dhooge C. Vancomycin-induced red man syndrome in pediatric oncology: still an issue? *Int J Clin Pharm*. 2012;34(13–16):2.
31. Sivagnanam S, Deleu D. Red man syndrome. *Crit Care*. 2003;7(2):119-120. https://doi.org/10.1186/cc1871
32. Esba LCA. Complementing ADR data by utilizing electronic health records: experience form a tertiary care hospital in Saudi Arabia. *J Pharmacovigil*. 2019;7:1.

How to cite this article: Abu Esba LC, Al Mardawi G, AlJasser MI, Aljohani B, Abu Alburak A. Adverse Drug Reactions Spontaneously Reported at a Tertiary Care Hospital and Preventable Measures Implemented. *J Clin Pharm Ther*. 2021;46:460–469. https://doi.org/10.1111/jcpt.13306