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REPORTED ADVERSE DRUG REACTIONS IN PUBLIC HEALTH FACILITIES IN SABAH: A CROSS-SECTIONAL STUDY

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ABSTRACT

Adverse drug reactions (ADRs) are among the major causes of death in many countries. ADR reporting is crucial to pharmacovigilance as it confers constant update on the safety of medicinal products. This study aimed to describe major causative therapeutic groups and common clinical manifestations of ADRs reported in public health facilities in Sabah. Data submitted to Malaysia Adverse Drug Reactions Advisory Committee (MADRAC) by public health facilities in Sabah from January to June 2022 were retrospectively reviewed. A total of 1,410 ADRs were included for analysis. Out of these, majority (80.2%, n = 1,131) were related to adults, while children constituted a notable proportion (12.7%, n = 180). More females (63%, n = 888) were involved than males. The West Coast Division reported the most ADRs (43.9%, n = 619) while Kudat Division reported the least number of ADRs (9.2%, n = 130). Anti-infectives for systemic use (48.5%, n = 684), in particular, penicillins (18.3%, n = 258), direct acting antivirals (9.6%, n = 136) and viral vaccines (6.5%, n = 91), were the most common contributors. Other common causative therapeutic groups were anti-inflammatory and anti-rheumatic products (10.9%, n = 153) and analgesics (6.9%, n = 97). Nirmatrelvir/Ritonavir (8.5%, n = 120) emerged as the most implicated drug, with a mean latency period of 14 hours, followed by amoxicillin (5.7%, n = 81) with a mean latency period of 27 hours. Skin and subcutaneous tissue disorders were the most common ADRs (45.7%, n = 644), with rash (n = 246), pruritus (n = 123), and swelling/oedema (n = 107) constituting the most common clinical manifestations. Severe cutaneous adverse reactions (SCARs) accounted for a minute proportion (0.64%, n = 9) of the analysed ADRs, wherein allopurinol (n = 3) was the most implicated causative drug. The minimal number (1.1%, n = 15) of reported drug rechallenges reflects inadequate implementation of allergy delabeling in Sabah.

***Keywords*:** Adverse drug reactions, Major causative drugs, Common clinical manifestations, Drug rechallenge, Sabah

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INTRODUCTION

Adverse drug reactions (ADRs) can be defined as responses to drugs which are noxious and unintended, and which occur at doses normally used in men for prophylaxis, diagnosis, or treatment of diseases (National Pharmaceutical Regulatory Agency 2021). ADRs have always had a significant impact in clinical practice as they provide safety information relating to the use of a medicinal product, and in many cases, warrant specific treatment, alteration of dosage regimen or withdrawal of the product. According to the U.S. Food and Drug Administration Adverse Events Reporting System, there were over 2 million ADRs reported in 2024, 1 million of which were classified as serious, with nearly 150,000 deaths reported alongside (U.S. Food and Drug Administration 2025). In Japan, ADRs accounted for 5% of hospitalisations between 2018 to 2021, with cardiovascular agents reported as the most common contributors (Komagamine 2024). A prospective study conducted in a large tertiary hospital in Singapore in 2015 found that ADRs accounted for 8.1% of hospital admissions, wherein cardiovascular agents were the most common ADR-inducing drug categories and gastrointestinal manifestations were the most reported ADR phenotypes (Chan *et al.* 2016). Meanwhile, a review based upon a literature search of ADRs in Indonesia from 2011 to 2021 concluded insulins, cardiovascular agents and anti-inflammatories as the drugs with the highest incidences of ADRs (Maharani and Yugatama 2023).

Malaysia has seen a surge in the number of ADR reports received by National Pharmaceutical Regulatory Agency from 2015 to 2024, recording a total of 34,035 reports in 2024 (Pharmacovigilance Section 2025). ADRs reported from 2000 to 2013 for infants and children below 2 years old in Malaysia had been evaluated, wherein penicillins and other B-lactam antibacterials emerged as the most common contributors, with most of the events manifesting as skin reactions (Rosli *et al.* 2017). Hepatic ADRs reported in Malaysia from 2000 to 2017 were also analysed. The findings concluded antituberculosis drugs as the most common causative agents (Lee *et al.* 2020). Meanwhile in Sabah, a retrospective study analysing pharmacy cutaneous ADR database from 2014 to 2016 was conducted in three tertiary hospitals. The study concluded urticaria and angioedema as the most common cutaneous manifestations, with antibiotics being the major causative agents accounting for more than half of the reported ADRs (Gan *et al.* 2018).

Although studies have been conducted on reported ADRs in Malaysia, they were limited to analysing specific clinical manifestations or were involving specific populations only. Sabah has vastly distinct ethnic distributions from the other states of Malaysia, with at least 33 indigenous groups constituting 89% of its population (Sabah State Government 2023; Department of Statistics Malaysia 2023). The main capital, Kota Kinabalu, is categorised as an ageing district (population aged 65 years and over reached 7.0%) in 2023 (Department of Statistics Malaysia 2023). Often, the reaction phenotypes of adverse drug events and their causative agents vary among different populations, wherein regional differences in prescribing practice and genetic markers may play a role (Demoly *et al.* 2014). The general pattern of ADRs experienced by the general population of Sabah thereby remains a knowledge gap due to the lack of studies conducted in local settings.

By analysing the ADR data reported in all public health facilities in Sabah from January to June 2022, this study aimed to identify the major causative drugs and the clinical phenotypes of ADRs induced in Sabah population. Latency period of ADRs caused by highly implicated drugs as well as the prevalence of severe cutaneous adverse reactions (SCARs) were analysed. Factors related to age and gender were evaluated. This study also aimed to provide insights on the implementation of drug rechallenges as well as the pattern of ADR reporting in Sabah. By characterising the reported ADRs, this study aims to contribute to pharmacovigilance and to support medical decision process in Sabah.

METHODOLOGY

Study Design

This retrospective cross-sectional study was carried out at Hospital Wanita dan Kanak-Kanak Sabah (HWKKS). Sabah Adverse Drug Reactions Report 2022 was retrieved via HWKKS's Drug Information Service (DIS) department.

Sabah Adverse Drug Reaction Report 2022

All 1,752 ADR data contained within were reported by either pharmacists or physicians in public health facilities in Sabah from 1 January 2022 to 30 June 2022. Reported ADRs were assessed for validity by DIS Department in respective facilities prior to electronic or manual submission to National Centre for Adverse Drug Reactions Monitoring, the secretariat to MADRAC. Assessment of all submitted data was then carried out by MADRAC prior to entry into Malaysian database. This was followed by presentation and causality grading in MADRAC meeting and subsequent relay of data to the central WHO Global ICSR (Individual Case Safety Report) database, which is maintained by the Uppsala Monitoring Centre, the WHO Collaborating Centre in Sweden. Extracted data were eventually compiled by MADRAC into Sabah Adverse Drug Reactions Report 2022 and forwarded to respective public health facilities for documentation purposes.

The indexed data consists of case report number, patient's age, gender and ethnic, ADR terminology, time to onset of reaction, outcome of reaction, suspected causative active ingredient and the product's name if available, dose and frequency of the suspected drug, route of administration, action taken, execution of dechallenge or rechallenge, relatedness, qualification of reporter and institution from which the ADR was reported.

Only ADRs with relatedness assessed as certain, probable and possible were analysed. ADRs attributable to unregistered products as well as ADRs with incomplete details relating to patient's age, gender or time to onset of reaction were excluded from the study.

Study Objectives

Common causative therapeutic groups

The active ingredients of suspected causative drugs were categorised using World Health Organisation - Anatomical Therapeutic Chemical (ATC) Classification System, of which the first, second, and third levels were used to identify pharmacological subgroups. Latency period of ADRs, defined as time from first exposure to a drug to the time the reaction occurs, was analysed for the most implicated causative drugs. Associated ADRs were further categorised into immediate reactions (occurring ≤ 6 hours of drug exposure) or delayed reactions (occurring > 6 hours of drug exposure) (Khan *et al.* 2022).

Common clinical manifestations

All reported ADR terminologies were classified using Medical Dictionary for Regulatory Activities (MedDRA), of which the highest level (System Organ Class) was used to identify the anatomical or physiological systems involved and hence the clinical phenotypes manifested in the reported adverse events.

Incidence of SCARs

SCARs is an umbrella term for acute generalised exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and generalised bullous fixed drug eruptions (GBFDE) (American Academy of Allergy, Asthma & Immunology 2024). Both incidence as well as latency period of reported SCARs were analysed.

Incidence of ADRs in different age categories and gender

Eligible ADR data were subdivided into four age categories based on the definition of age group terminology outlined in the Fourth Edition of Basic Skills in Interpreting Laboratory Data, namely infants (> 28 days to 12 months of age), children (1 to 12 years of age), adolescent (13 to 17 years of age) and adult (≥ 18 years of age) (Lee 2009). The occurrences of ADRs in each age category, as well as in each gender, male and female, were analysed in this study.

Incidence of drug rechallenge

Rechallenge is defined as the administration of a further dose(s) of a drug to a person who had previously taken a dose(s) of the same drug and in whom an adverse reaction, which might be attributable to that drug, had subsequently occurred (Stephens 1985). In view of 2022 drug allergy practice parameter updates which place emphasis on drug challenge as the reference standard for determining drug tolerance as well as the advocation for proactive delabeling of penicillin allergy, the incidence of drug rechallenges carried out in Sabah's public health facilities in response to ADRs was also assessed (Khan *et al.* 2022).

Number of ADRs reported by each administrative division of Sabah

Sabah consists of five administrative divisions, namely Kudat Division, West Coast Division, Interior Division, Sandakan Division and Tawau Division. Our study further categorised public health facilities in Sabah into hospital and clinic settings.

Proportion of reported ADRs with incomplete data

ADRs with missing information pertaining to age, gender or time to onset of reaction were classified as incomplete.

Ethical Approval

No consent was obtained prior to analysis as all patients were already anonymised upon entry into National Pharmaceutical Regulatory Agency (NPRA) database. This research was registered with the National Medical Research Registry (NMRR), and it was approved by the Malaysian Medical Research and Ethics Committee (NMRR-24-00702-TFZ).

Statistical Analysis

Data analysis was carried out using Microsoft Excel and Statistical Package for the Social Sciences (SPSS) version 27. Data normality was checked using skewness, histogram and Q-Q plot. Descriptive analysis was used to represent the sorted data. Categorical data such as ADRs according to age categories, pharmacological groups, clinical phenotypes, SCARs, drug challenges, number reported by each facility and proportion of incomplete reports were described as frequencies and percentages. Numerical data such as age of study population and time to onset of reaction of ADRs were expressed as mean.

RESULTS

A total of 1,752 ADRs were reported to MADRAC by all public health facilities in Sabah from 1 January 2022 to 30 June 2022. After exclusion criteria, only 1,410 ADRs remained for analysis (see Figure 1).

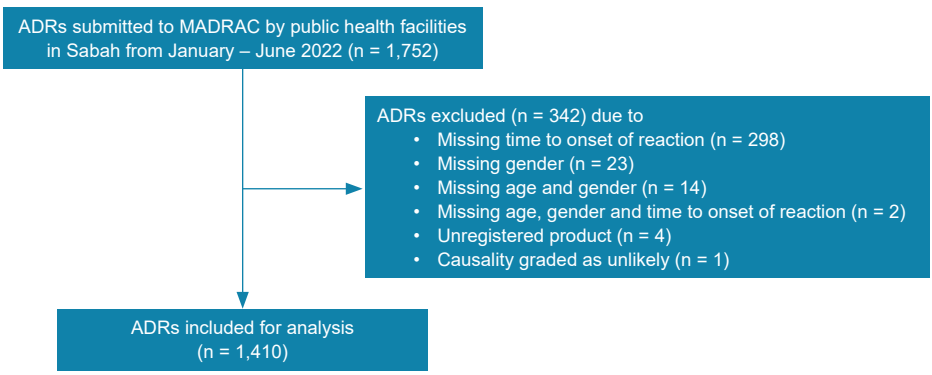

Figure 1: A total of 1,410 ADRs were included for study analysis.

Common Causative Therapeutic Groups

As illustrated by Table 1, anti-infectives for systemic use contributed to nearly half (48.5%, n = 684) of the analysed ADRs. Among anti-infectives for systemic use, antibacterials (29.0%, n = 409), notably penicillins (18.3%, n = 258) and other beta-lactam antibacterials (5.5%, n = 78), were the most common contributors, with 50.1% of the elicited ADRs being immediate reactions (see Table 2). Systemic antivirals (9.6%, n = 136) and vaccines (8.0%, n = 113) also constituted a considerable proportion of the reported anti-infectives. Other common causative pharmacological groups were those used for musculoskeletal system (13.8%, n = 195), in particular anti-inflammatory and anti-rheumatic products (10.9%, n = 153); as well as those used for nervous system (11.7%, n = 165), notably analgesics (6.9%, n = 97).

Table 1: Suspected causative drugs (categorised into respective anatomical or pharmacological groups in accordance to the first level of WHO-ATC classification system) in different age categories.

ATC LEVEL 1	Infants	Children	Adolescent	Adult	Incidence	%
Anti-infectives for systemic use	21	129	29	505	684	48.5
Musculo-skeletal system	0	3	14	178	195	13.8
Nervous system	4	25	16	120	165	11.7
Blood and blood forming organs	1	5	0	100	106	7.5
Cardiovascular system	0	0	0	98	98	7.0
Alimentary tract and metabolism	0	7	2	57	66	4.7
Antineoplastic and immunomodulating agents	0	0	3	20	23	1.6
Respiratory system	1	6	5	6	18	1.3
Various	0	3	0	14	17	1.2
Sensory organs	2	2	0	12	16	1.1
Systemic hormonal preparations, excl. sex hormones and insulins	0	0	1	8	9	0.6
Dermatologicals	0	0	0	8	8	0.6
Genito urinary system and sex hormones	0	0	0	5	5	0.4
Total	29	180	70	1131	1410	100.0

Table 2: Pharmacological groups which emerged as common contributors to analysed ADRs.

Pharmacological group	Incidence	Immediate	Delayed
1. Anti-infectives for systemic use	**684**	**330**	**354**
1A. Antibacterials for systemic use	409	205	204
• Beta-lactam antibacterials, penicillins	258	134	124
• Other beta-lactam antibacterials	78	43	35
• Other antibacterials	30	12	18
• Macrolides, lincosamides and streptogramins	18	10	8
• Sulfonamides and trimethoprim	10	4	6
• Tetracyclines	6	2	4
• Quinolone antibacterials	6	0	6
• Aminoglycoside antibacterials	3	0	3
1B. Antivirals for systemic use	136	68	68
• Direct acting antivirals	136	68	68
1C. Vaccines	113	52	61
• Viral vaccines	91	48	43
• Bacterial vaccines	18	4	14
• Bacterial and viral vaccines, combined	4	0	4
1D. Antimycobacterials	22	5	17
• Drugs for treatment of tuberculosis	20	5	15
• Drugs for treatment of lepra	2	0	2
1E. Antimycotics for systemic use	2	0	2
• Antimycotics for systemic use	2	0	2
1F. Immune sera and immunoglobulins	2	0	2
• Immunoglobulins	2	0	2
2. Musculo-skeletal system	**195**	**147**	**48**
2A. Antiinflammatory and antirheumatic products	153	131	22
• Antiinflammatory and antirheumatic products, non-steroids	153	131	22
2B. Antigout preparations	32	8	24
• Antigout preparations	32	8	24
2C. Muscle relaxants	9	7	2
• Muscle relaxants, centrally acting agents	5	3	2
• Muscle relaxants, peripherally acting agents	4	4	0
2D. Other drugs for disorders of the musculo-skeletal system	1	1	0
• Other drugs for disorders of the musculo-skeletal system	1	1	0

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Table 2: (*Continued*)

Pharmacological group	Incidence	Immediate	Delayed
3. Nervous system	**165**	**105**	**60**
3A. Analgesics	97	78	19
• Other analgesics and antipyretics	66	51	15
• Opioids	31	27	4
3B. Psycholeptics	21	9	12
• Antipsychotics	15	3	12
• Hypnotics and sedatives	5	5	0
• Anxiolytics	1	1	0
3C. Antiepileptics	19	1	18
• Antiepileptics	19	1	18
3D. Psychoanaleptics	16	5	11
• Antidepressants	15	5	10
• Psychostimulants, agents used for ADHD and nootropics	1	0	1
3E. Anesthetics	12	12	0
• Anesthetics, general	10	10	0
• Anesthetics, local	2	2	0

Nirmatrelvir/ritonavir emerged the most reported drug (8.5%, n = 120) for all 1,410 analysed ADRs, with a mean latency period of 14 hours. As illustrated in Table 3, about half (51.7%, n = 62) of the reactions reported for nirmatrelvir/ritonavir occurred within 6 hours of administration. Nervous system disorders (46.7%, n = 56), notably dysgeusia (n = 42), dizziness (n = 6) and headache (n = 4), were commonly associated with nirmatrelvir/ritonavir (see Table 4). Other common causative drugs were amoxicillin (5.7%, n = 81), COVID-19 vaccines (5.5%, n = 78), diclofenac (5.5%, n = 78), amoxicillin/clavulanate (5.3%, n = 75) and ibuprofen (3.9%, n = 55). Of the listed drugs, ibuprofen had the shortest mean latency period of 4 hours (see Table 3). Skin and subcutaneous tissue disorders were the most commonly reported ADRs for amoxicillin, COVID-19 vaccines, amoxicillin/clavulanate and ibuprofen whereas eye disorders were the most notable ADRs for Diclofenac (see Table 4).

Common Clinical Manifestations

Table 5 depicts the clinical phenotypes portrayed by different age categories in the reported ADRs. Skin and subcutaneous tissue disorders were the most common clinical manifestations (45.67%, n = 644), with rash (n = 246), pruritus (n = 123), swelling/oedema (n = 107) and urticaria (n = 97) constituting majority of the reactions. Other commonly reported ADRs were nervous system disorders (11.4%, n = 160), notably dizziness (n = 39) and headache (n = 28), and eye disorders (10.9%, n = 153), wherein periorbital oedema (n = 75) and orbital oedema (n = 40) emerged as the most reported eye conditions.

Table 3: Drugs with the most number of reported ADRs.

Active ingredient	Incidence	%	Immediate	Delayed	Mean time (Hours)
Nirmatrelvir/ritonavir	120	8.5	62	58	14
Amoxicillin	81	5.7	31	50	27
COVID-19 vaccine	78	5.5	39	39	36
Diclofenac	78	5.5	68	10	10
Amoxicillin/clavulanate	75	5.3	40	35	24
Ibuprofen	55	3.9	45	10	4
Paracetamol	46	3.3	32	14	10
Perindopril	38	2.7	10	28	192
Allopurinol	32	2.3	8	24	240
Cloxacillin	32	2.3	17	15	19

Table 4: Clinical manifestations of ADRs reported for common causative drugs.

Clinical phenotype	Nirmatrelvir/ ritonavir	Amoxicillin	COVID-19 vaccines	Diclofenac	Amoxicillin/ clavulanate	Ibuprofen
Blood and lymphatic system disorders			1			
Ear and labyrinth disorders			1		1	
Eye disorders		4	2	32	2	25
Cardiac disorders			2			
Gastrointestinal disorders	40	4			7	
General disorders and administration site conditions	2		10			
Immune system disorders				2		
Investigations	2		10	2		
Metabolism and nutrition disorders	2					
Musculoskeletal and connective tissue disorders			2			
Nervous system disorders	56	2	19	4		1
Psychiatric disorders	4					
Renal and urinary disorders	1					
Reproductive system and breast disorders	1					
Respiratory, thoracic and mediastinal disorders	2		7	13	3	2
Skin and subcutaneous tissue disorders	9	71	24	25	61	27
Vascular disorders	1				1	
Incidence	120	81	78	78	75	55

Table 5: Clinical phenotypes (classified by MedDRA – System Organ Class) manifested by different age categories in the reported ADRs.

System organ class	Infant	Children	Adolescent	Adult	Incidence	%
Skin and subcutaneous tissue disorders	22	121	38	463	644	45.7
Nervous system disorders	0	4	3	153	160	11.4
Eye disorders	2	14	10	127	153	10.9
Respiratory, thoracic and mediastinal disorders	0	9	4	122	135	9.6
Gastrointestinal disorders	2	10	7	99	118	8.4
General disorders and administration site conditions	1	16	4	51	72	5.1
Investigations	0	1	0	40	41	2.9
Vascular disorders	1	0	0	17	18	1.3
Musculoskeletal and connective tissue disorders	0	2	1	13	16	1.1
Cardiac disorders	1	1	0	10	12	0.9
Psychiatric disorders	0	1	2	6	9	0.6
Blood and lymphatic system disorders	0	0	1	7	8	0.6
Immune system disorders	0	0	0	7	7	0.5
Renal and urinary disorders	0	0	0	6	6	0.4
Ear and labyrinth disorders	0	1	0	5	6	0.4
Metabolism and nutrition disorders	0	0	0	3	3	0.2
Hepatobiliary disorders	0	0	0	1	1	0.1
Reproductive system and breast disroders	0	0	0	1	1	0.1
Total	29	180	70	1,131	1,410	100.0

Incidence of SCARs

SCARs, all of which occurred in adults and were delayed reactions, constituted 0.6% (n = 9) of the analysed ADRs (see Table 6). DRESS was the commonest (n = 4) with a mean latency period of 43 days. Drugs which contributed to DRESS included allopurinol (n = 2), phenytoin (n = 1) and vancomycin (n = 1). Other reported SCARs were SJS (n = 3) and TEN (n = 2), with a mean latency period of 19 days and 16 days respectively. As shown in Table 6, allopurinol was the most implicated drug (33.3%, n = 3) for the reported SCARs.

Table 6: Reported severe cutaneous adverse reactions.

Severe cutaneous adverse reactions	Incidence	Latency	Avg time to onset
Drug reaction with eosinophilia and systemic symptoms	4		43 days
• Allopurinol	2	Delayed	63 days
• Phenytoin	1	Delayed	23 days
• Vancomycin	1	Delayed	21 days
Steven-johnson syndrome	3		19 days
• Allopurinol	1	Delayed	30 days
• Sulfasalazine	1	Delayed	16 days
• Carbamazepine	1	Delayed	10 days
Toxic epidermal necrolysis	2		16 days
• Griseofulvin	1	Delayed	16 days
• Cephalexin	1	Delayed	16 days
Incidence of SCARs	9 (0.64%)		

Incidence of ADRs in Different Age Categories and Gender

The age of the studied population ranged from 1 month to 89 years old, with a mean age of 36.7 ± 20.6 years. The highest number of ADRs were reported in adults (≥ 18 years of age) (80.2%, n = 1,131), followed by children (1 to 12 years of age) (12.8%, n = 180) as shown in Table 1. Among adults, the middle-aged group (40 to 49 years of age) experienced the most ADRs (23.2%, n = 262), followed by young adults aged 20 to 29 years (19.7%, n = 223) and 30 to 39 years (19.5%, n = 220) (see Figure 2). Of all 1,410 included ADRs, 37% (n = 522) involved males and 63% (n = 888) involved females.

Incidence of Drug Rechallenge

Rechallenge was only carried out in 1.1% (n = 15) of the analysed ADRs. Of the 15 rechallenges, 9 were carried out in response to immediate reactions. Two of the drug rechallenges involved infants. Suspected causative drugs that have been rechallenged include atorvastatin, chloramphenicol and anti-tuberculocis drugs such as isoniazid and pyrazinamide. No penicillin rechallenge was reported. Eye disorders, gastrointestinal

disorders and skin and subcutaneous tissue disorders were among the clinical manifestations portrayed by subjects in which drug challenges were called for. No SCARs were involved in the rechallenge cases.

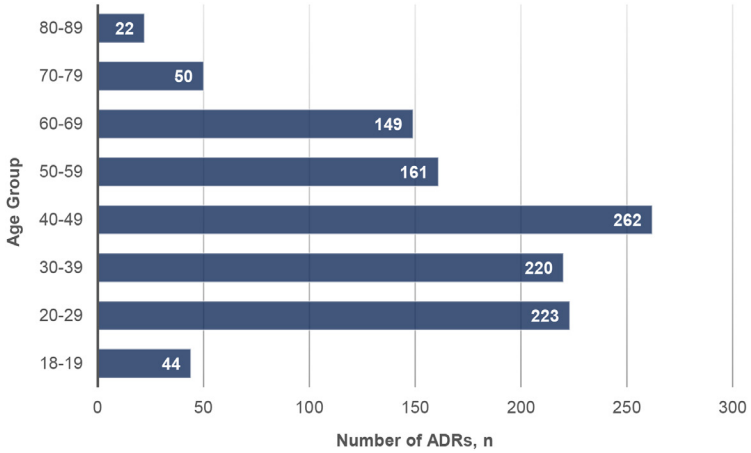

Figure 2: Incidence of ADRs in adults (≥ 18 years) across different age groups.

Number of ADRs Reported by Each Administrative Division of Sabah

Facilities in the West Coast division contributed to the most number of ADRs (43.9%, n = 619), whereas facilities in the Kudat division reported the least number of ADRs (9.2%, n = 130) (see Table 7). Majority of the ADRs were reported by hospitals (70.8%, n = 998). Hospital Queen Elizabeth reported the most number of ADRs (14.1%, n = 199), followed by HWKKS (8.9%, n = 126) and Hospital Queen Elizabeth II (5.6%, n = 79). Pharmacists were the reporters for majority (86.6%, n = 1,221) of the ADRs, with the remaining attributable to physicians.

Table 7: Number of ADRs reported by public health facilities in Sabah from January – June 2022. Of all 58 facilities analysed, only five institutions who reported the most number of ADRs are listed.

Setting	**Incidence**	**%**
Hospital	998	70.8
Clinic	412	29.2
Division	**Incidence**	**%**
West Coast division	619	43.9
Sandakan division	179	12.7
Tawau division	243	17.2
Interior division	239	17.0
Kudat division	130	9.2

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Table 7: (*Continued*)

Institution	Incidence	%
Hospital Queen Elizabeth	199	14.1
Hospital Wanita dan Kanak-Kanak Sabah	126	8.9
Hospital Queen Elizabeth II	79	5.6
Klinik Kesihatan Tandek	76	5.4
Klinik Kesihatan Sandakan	68	4.8

Proportion of Reported ADRs with Incomplete Data

Of all 1,752 data, it was found that 19.2% (n = 337) of the submitted data had missing information on onset of reaction, age and/or gender as shown in Figure 1. The aforementioned ADRs were excluded from the study.

DISCUSSION

Our study reported anti-infectives for systemic use, notably antibacterials, as the most common causative therapeutic groups for the reported ADRs across all age categories. Similar findings were observed by local studies (Rosli *et al.* 2016; Rosli *et al.* 2017; Abu and Shafie 2018). Antimicrobials are the most commonly prescribed drugs worldwide, with a 65% increment in global consumption from 2000 to 2015 (Agrawal, Singh and Joshi 2021). The extensive use of antibacterials in Sabah might have culminated in the increased risk of ADRs attributable to this particular therapeutic group, a phenomenon in line with studies conducted in foreign settings (Sharma *et al.* 2021; Jiang *et al.* 2022). Of all antibacterials, the appreciable risk of ADRs shown by beta-lactams in our study was in parallel to the finding observed in a nationwide analysis on infant ADRs in Malaysia (Rosli *et al.* 2017). Antivirals for systemic use and vaccines were the other common contributing therapeutic groups to the ADRs analysed in this study. Such observation might be attributable to the increased use of COVID-19 antivirals and vaccines during the pandemic. Previous ADR studies conducted in Malaysia and India had respectively reported antivirals as one of the common causative therapeutic groups (Rosli *et al.* 2017; Agrawal, Singh and Joshi 2021). In fact, vaccine-induced ADRs were relatively common in Malaysia wherein they comprised more than half of the ADR reports submitted to NPRA between 2000 to 2013 for subjects aged from birth to 17 years old (Rosli *et al.* 2016). Vaccines were also repeatedly reported for causing ADR admissions in a large tertiary paediatric hospital in United Kingdom (Gallagher *et al.* 2012). Other common causative drug classes in our study were non-steroidal anti-inflammatory and anti-rheumatic products as well as analgesics, an observation not dissimilar to those found in local and foreign studies conducted in the past (Rosli *et al*. 2016; Gallagher *et al.* 2012; Elkalmi *et al.* 2021).

Nirmatrelvir/ritonavir, amoxicillin and COVID-19 vaccines were the most implicated agents of all reported causative drugs. Nirmatrelvir/ritonavir is indicated for the treatment of COVID-19 in adults who are at increased risks for progression to severe disease and who do not require supplemental oxygen (Choo 2022). The drug was approved for use in Malaysia under Conditional Marketing Authorisation in 2022 wherein further safety evidence was awaited and healthcare professionals were mandated to report all suspected ADRs (Pfizer Malaysia 2022). The high incidence of nirmatrelvir/ritonavir-related ADRs

in our study might be related to the drug's extensive use in Sabah during COVID-19 pandemic. NPRA received 1,714 suspected ADRs associated with nirmatrelvir/ritonavir as of August 2022, with bitter taste, diarrhoea, dysgeusia, vomiting and nausea being the most reported manifestations (Choo 2022). This is parallel with our study which reported nervous system and gastrointestinal disorders as the most commonly portrayed phenotypes with nirmatrelvir/ritonavir. Amoxicillin, a widely prescribed antibiotic in Malaysia, had been repeatedly implicated for causing ADRs in the past. As of June 2018, NPRA had received a total of 7,343 amoxicillin-associated adverse events, with pruritus, maculopapular rash and urticaria being the most frequent manifestations, an observation not dissimilar to our finding (Jauze 2018). Adverse events following immunisation (AEFIs) for COVID-19 vaccines had been extensively reported in Malaysia during the pandemic, as testified by summary report by NPRA as of April 2023 which showed 13,480 minor AEFI responses for every 1,000,000 doses of vaccines administered (National Pharmaceutical Regulatory Agency 2023). Summary of COVID-19 vaccines Yellow Card Reporting in United Kingdom showed that majority of the reports received related to injection site reactions and generalised symptoms such as 'flu-like' illness, both of which were common manifestations seen in our study alongside skin and nervous system disorders (Medicines and Healthcare products Regulatory Agency 2023).

Timely detection and intervention of ADRs is crucial to effectively reducing negative health impacts on patients as well as possible societal costs resulting from additional treatments and wastage of unoptimised medicines. The relatively short mean latency period (< 1 day) of nirmatrelvir/ritonavir-associated ADRs, wherein half of the reactions occurred within 6 hours, warrants caution within the first 24 hours of nirmatrelvir/ritonavir ingestion. For amoxicillin and COVID-19 vaccines, our observations suggested close monitoring within 48 hours of administration. Studies analysing time to onset of COVID-19 vaccines-induced adverse events were scarce. Two recent studies reported a median time to onset of 14 to 24 hours and 12 to 13 hours, respectively (Raethke *et al.* 2024; Ciccimarra *et al.* 2024). Non-steroidal anti-inflammatory drugs (NSAIDs), namely diclofenac and ibuprofen, which portrayed the shortest mean latency period out of all commonly implicated drugs, with majority of the adverse events being immediate reactions, reflected the need to exercise extra vigilance within the first 6 hours of drug administration. Our finding is in parallel to that published in Seven Steps to the Diagnosis of NSAIDs Hypersensitivity, which stated 3 hours as the usual latency period for NSAIDs-exacerbated respiratory diseases and 6 hours as the usual latency period for NSAIDs-exacerbated cutaneous diseases (Kowalski and Makowska 2015).

Skin and subcutaneous tissue disorders were found to be the most common ADRs across all age categories in our study. Nervous system, eye, respiratory and gastrointestinal disorders, while not as frequent as skin disorders, were other common clinical phenotypes observed in our study population. This finding conforms with many other local studies. Skin appendage disorders, especially rash, urticaria and pruritus, were reported as the most common ADRs in children under 2 years of age in Malaysia from 2000 to 2013 (Rosli *et al.* 2017). Another retrospective analysis of all ADRs reported to NPRA in 2015 concluded urticaria, rash and itching as the most common reported clinical manifestations (Abu and Shafie 2018). As to studies conducted in foreign settings, a similar finding was found by a 7-year surveillance study in India wherein skin and subcutaneous tissue disorders accounted for the most ADRs (Sharma *et al.* 2021). ADRs reported in China from 2011 to 2020, however, showed gastrointestinal disorders as the most common ADRs (Jiang *et al.* 2022). In England, a systematic review on ADRs in children reported gastrointestinal disorders, namely nausea, vomiting and diarrhoea, as well as skin rash as

the most common associated clinical phenotypes (Smyth *et al.* 2012). The discrepancy in manifested ADRs between local and foreign settings might be attributable to the different drug formularies as well as prescribing practice adopted in different countries.

All reported SCARs in our study occurred in adults. The contributing drugs, namely allopurinol, phenytoin, carbamazepine and cephalexin are not dissimilar to those found in a 5 year retrospective study on SCARs in Malacca (Tee *et al.* 2022). Allopurinol, the most implicated offending drug in our study, has long been known for inducing SCARs. There was an estimated incidence of 2.5 SCARs per 1,000 new allopurinol users in Malaysia (Ng *et al.* 2022). Of the 9 SCARs found in our study, DRESS and SJS were the commonest manifestations, a finding consistent with a 3 year study conducted by in Sabah (Gan *et al.* 2018). The prolonged latency period of all SCARs reported in our study was consistent with the observations from the other studies. A median time to onset of 3 weeks had been reported for allopurinol-induced SCARs (Copaescu and Trubiano 2022). In fact, a median time to onset of up to 5 weeks for SJS and up to 8 weeks for DRESS had been reported (Hali *et al.* 2023). Educating patients to be alert to any signs of SCARs which develop after prolonged use of potentially offending drugs thereby remains crucial to ensure timely detection.

The higher number of reported ADRs for adults compared to other age categories in our study might be attributable to the fact that our studied population has a mean age of 36.7 ± 20.6 years, which reflected a higher involvement of the adult population. This finding is similar to a study conducted on cutaneous ADRs in Sabah wherein the study population had a similar mean age of 36.0 ± 21.2 years and showed a higher number of cases in adult than paediatric patients (Gan *et al.* 2018). Paediatric population accounted for 19.8% of the reported ADRs in our study, a finding which resonates with earlier studies that showed an appreciable risk of ADRs for paediatric patients (Rosli *et al.* 2017; Gallagher *et al.* 2012; Clavenna and Bonati 2009). The relatively low percentage of cases in infants (2.1%) compared to other age categories in our study might be due to under-reporting of ADRs in the population, which is not uncommon as infants could not directly communicate the side effects they experience (Behera *et al.* 2022; Wilkinson 2021).

Our study showed a higher percentage of women experiencing ADRs than men. This is in accord with a global analysis on ADRs reported between 1967 to 2018 which showed that reports concerning female (60.1%) outnumbered those concerning male (39.9%) (Watson *et al*. 2019). Sex-related differences in ADRs have been evaluated by various studies. A systematic review concluded that gender differences in the context of fat mass, extracellular water volume, metabolising enzymes, hormones and microorganisms did impact on drugs' pharmacokinetics and pharmacodynamics properties and hence the likelihood of experiencing ADRs (Shan *et al.* 2023). Earlier studies showed that women were 1.5-1.7 times more prone to ADRs than men (Martin *et al.* 1998). In 2013, the U.S. Food and Drug Administration (FDA) required manufacturers to lower the recommended doses of zolpidem for women following evidence of higher risk of next-morning impairment in this gender subgroup due to the reduced metabolic clearance (U.S. Food and Drug Administration 2018). Nevertheless, women also tend to report more ADRs than men, thereby subjecting the gender differences to possible reporting bias (Hendriksen *et al.* 2021).

Previous ADR studies conducted locally had not analysed incidence of drug rechallenges in response to ADRs. According to Drug Allergy 2022 Practice Parameter Update, drug rechallenges are considered the reference standard for ascertaining tolerance to a specific drug (Khan *et al.* 2022). However, the remarkably low rate of drug rechallenges in our analysed reports reflects that further initiative could be put forth in Sabah practice while determining drug allergies to minimise incorrect drug allergy labels. In fact, the 2022 update

placed a new emphasis on the importance of reevaluating patients labelled with penicillin allergy to ascertain the validity of the allergy due to the detrimental effects associated with misdiagnosed penicillin allergy. Patients with a history of penicillin allergy are more likely to be treated with suboptimal antibiotics, culminating in increased costs as well as potential negative health impacts (Khan *et al.* 2022). Nevertheless, no penicillin rechallenges had been reported in our study despite the relatively high incidence of amoxicillin-associated ADRs. This disaligns with the call for proactive penicillin allergy delabeling outlined in the 2022 update, an observation worth reflecting upon.

Our study showed that Kudat division reported the least number of ADRs compared to the other zones of Sabah. An earlier study concluded that only 48% of the rural communities in Kudat and Pitas areas of Sabah utilised healthcare services (Oo Tha *et al.* 2020). Restricted geographic access to healthcare facilities in the aforementioned areas might have led to reduced patient visits which might explain the lowest percentage of reported ADRs from the Kudat division.

The notable proportion of incomplete ADR reports identified in this study, of which 19.2% were missing important details pertaining to time to onset of reaction, subject's age or gender, revealed that further effort could still be put forth to improve the completeness and quality of ADR reports by public health facilities in Sabah. There is a relative lack of research on the quality of ADR reports in Malaysia. A small-scale retrospective assessment of ADR reports was conducted in a local Clinical Training Centre. The study found that about half of the analysed reports were missing important information pertaining to the suspected drugs or to the onset of reaction, and concluded the need to improve the quality of ADR reports in the setting (Elkalmi *et al.* 2021). In Western India, a study attributed the incompleteness of ADR reports by medical practitioners to the country's low doctor-to-patient ratio wherein priority was given to patient care in place of ADR forms filling (Mahajan *et al*. 2018). All extracted ADR reports in our study were submitted by either pharmacists or physicians in public health facilities in Sabah, a state with well-perceived low doctor- and pharmacist-to-population ratios (Nordin 2024). Restricted manpower might have resulted in insufficient time to produce quality ADR reports. Insufficient information from patients, which had been reported as a barrier to ADR reporting in Malaysia, could also explain the missing fields in the extracted reports (Zin *et al.* 2019; Hadi, Helwani and Long 2013). Various studies concluded that there was a lack of knowledge or awareness on ADR reporting amongst healthcare personnel in Malaysia (Agarwal, Daher and Mohd Ismail 2013; Aziz, Siang and Badarudin 2007). Such findings might explain the incomplete ADR reports in our study which might be attributable to casual attitude as well as limited professional knowledge of reporters.

This is the first ADR study involving all public health facilities in Sabah. The large number of facilities (n = 63) involved allows for reasonably detailed description of the ADRs experienced in the local setting. Instead of selectively reviewing a specific population or a targeted ADR phenotype, we studied ADRs occurring in all age categories and included all reported clinical manifestations. This allows us to better capture the ADR patterns experienced by the general population of Sabah and thus allows for a more precise estimation of the burden induced by ADRs in the local setting. In addition, our study analysed the latency period of ADRs induced by common contributing drugs as well as that of reported SCARs, an observation not commonly reported in local studies. Such findings could aid in cautionary use of relevant drugs and thus timely detection of ADRs. This is also the first study reviewing the implementation of drug rechallenges in Sabah. Studies analysing the incidence of drug rechallenges following the occurrences of ADRs are especially lacking in both local and global contexts, despite the emphasis placed by 2022 Drug Allergy Practice Parameter Updates on employing drug rechallenge as a reference standard for determining

drug tolerance. Our study provides an insight into measures adopted by Sabah public health sector in ascertaining ADRs, allowing any gaps within the practice to be identified and studied upon in future research.

This study has several limitations. First, the present study was conducted by retrospectively reviewing ADR data submitted to MADRAC. No patient interaction was involved during data collection hence the results might not be as accurate as those reported by prospective studies. Second, ethnicity was not specified in the submitted ADR data thus occurrences of ADRs across different ethnics remains an unexplored gap in this study. Third, seriousness of ADRs apart from cutaneous reactions was not studied due to unavailable data. Likewise, outcomes of adverse drug events and mortality rate data were not analysed since some of the data were not readily available and no follow-up on patients was conducted in this study. Lastly, while this study did have a large sample size extracted data from Sabah Adverse Drug Reactions Report 2022, 19.2% of the data which had missing information on crucial details were excluded from analysis. Exclusion of these data was bound to impact on the precise estimation of ADR incidence across the general population of Sabah. This, alongside the long-known under-reporting of ADRs in local setting as observed by various studies, resulted in an incomplete presentation of the general ADR pattern in Sabah (Chen *et al.* 2023; Agarwal, Daher and Mohd Ismail 2013; Aziz, Siang and Badarudin 2007). Future research could be done to address the aforementioned unexplored contexts. Nevertheless, raising awareness among local healthcare professionals on the importance of quality ADR reporting should remain an utmost priority to ensure reliable contribution to pharmacovigilance.

CONCLUSION

A large proportion of ADRs reported in public health facilities in Sabah were skin and subcutaneous tissue disorders. SCARs constituted only a minor percentage of the analysed ADRs. Majority of ADRs were attributable to systemic anti-infectives. Nirmatrelvir/ritonavir was the most implicated causative drug. Adults reported the most ADRs, with female involved in more ADRs than male. Kudat division reported the least number of ADRs. Study also reveals inadequate implementation of drug rechallenges as well as the need to further improve the quality of ADR reports in Sabah.

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