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ORIGINAL RESEARCH

Adverse Drug Reactions Related with Antibiotic Medicines in Malawi: A Retrospective Analysis of Prevalence and Associated Factors

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Objective: We aimed to assess the occurrence and characteristics of antibiotic-associated adverse drug reactions (ADRs) in Malawi.

Methods: We retrospectively reviewed 304 patient records from medical wards in three hospitals in Southern Malawi. A global trigger tool was applied for the detection of suspected ADRs, and we used the Naranjo scale, the World Health Organization classification and the Schumock and Thornton scale for causality, seriousness and preventability assessment respectively. ADRs were also further characterized according to anatomical systems. Statistical analysis was done in STATA 14.1. The Chi-square test was used to determine the association between categorical variables and logistic regression analysis was used to measure the strength of the association between various independent variables and the occurrence of ADRs.

Results: Suspected ADRs were detected in 24% (73/304) of patients, of which 1.4% were definite, 15.1% were probable and 83.6% were possible ADRs. Most of the sADRs were gastrointestinal events (42.5%), followed by: musculoskeletal (26.3%); cardiovascular (16.3%); central nervous system (13.8%; and urinary events (1.3%). About 27% of the sADRs were serious events such as convulsions. The geriatric age group (≥65 years) was more likely to experience sADRs as compared to the younger age group, with an adjusted odds ratio (aOR) of 4.53, 95% CI (2.21–9.28), P<0.001. Patients taking more than one antibiotic medicine had a higher risk of developing sADRs as compared to patients who were administered one type of antibiotic medicine, aOR 2.14, 95% CI (1.18–3.90), $p < 0.012$. A long hospital stay of >3days was associated with a higher risk of sADRs with aOR of 5.11, 95% CI (2.47–10.55), $p < 0.001$ than those who stayed ≤ 3 days in the hospital.

Conclusion: We found a higher prevalence of serious sADRs associated with antibiotic medicines than reported elsewhere. This may, among others, contribute to high patient mortality, poor treatment adherence, antibiotic resistance and increased cost of care.

Plain Language Summary:

What is already known and why we did the study?

- Most health care workers and patients are less likely to voluntarily report suspected adverse drug reactions in low- and middle-income countries such as Malawi.
- Studies have revealed a high usage of antibiotic medicines in Malawi, but there is limited data on the associated adverse drug reactions.

What did we do?

- We assessed the occurrence and characteristics of ADRs associated with antibiotics.

What are the new findings?

- We found a higher prevalence (24%) of adverse drug reactions associated with antibiotic therapy than reported elsewhere using the global trigger tool.
- About 27.4% of the events were serious ADRs such as convulsions, arrhythmia and hypotension.
- We observed a higher rate of convulsions which could be a potential safety signal.

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What do the new findings imply?

- The high prevalence of serious ADRs leads to complicated treatment strategies and contribute to patient mortality, poor treatment adherence and antibiotic resistance.
- ADR risk factors need to be considered when prescribing and monitoring patients on antibiotic therapy.

Keywords: adverse drug reactions, antibiotic medicines, pharmacovigilance, global trigger tool, Malawi

Background

Adverse drug reactions(ADRs) have a serious negative impact on patients and the healthcare system.[1] Globally, about 24% of elderly patients[2] and 8% of patients receiving primary health care in Europe and the United States of America experience at least one ADR.[3] About 5–8% % of ADRs are serious[4] and at least 1% of ADRs lead to patient death.[5] ADRs have also been reported to cause hospitalization or lead to prolonged hospitalization in almost 10% of patients.[6,7] Usually, ADRs are managed through switching of therapy, in some cases prescribing new medicines in order to counter the adverse effects, thus contributing to increased total cost of treatment.[8] The annual total cost of ADR treatment is estimated at $30 billion in the USA[9] and £2.2 billion in the UK.[10]

Antibiotics are among the most prescribed medicines in low- and middle-income countries (LMICs) with almost 50% of prescriptions containing at least one antibiotic medicine.[11,12] By 2030, the antibiotic consumption rate is estimated to increase by 200% if no policy change is effected in LMICs.[13] This is a major concern because as much as antibiotic medicines benefit the public especially in settings where the burden of infectious diseases is high, overuse of antibiotics potentially increases the incidence of associated risks such as ADRs and antibiotic resistance.[14,15] The majority of antibiotic-related ADRs are clinically significant and require additional medical attention.[16] Fatal or life-threatening ADRs such as jaundice, thrombocytopenia and difficulty in breathing have also been reported to be associated with antibiotic use.[17,18]

The rate of antibiotic prescribing is high in Malawi.[19] On the other hand, the high burden of antimicrobial resistance is also a concern. On average, 32% of common bacterial isolates have been found to be resistant to essential antibiotics such as cotrimoxazole, gentamicin and ciprofloxacin.[20] This may among other causes be attributed to inappropriate use of antibiotics including non-adherence to treatment.[21–23] The occurrence of ADRs is one of the factors associated with poor adherence to medicines as they affect the patients' quality of life and loss of trust in the health care professionals.[24,25] Efforts aimed at identifying and reducing ADRs require a strong Pharmacovigilance (PV) system in a country. PV policies at both the regulatory level and clinical practice need to be primarily informed by local medicine safety data. However, this is not usually the case especially in LMICs such as Malawi as there is a lack of evidence to determine the burden and determinants of ADRs. In this study, we assessed the occurrence and characterized the ADRs associated with antibiotic medicines in the southern Malawi.

Methodology

Study Design and Setting

A retrospective review of medical records was employed in medical wards of public hospitals between June 2022 and October 2022. Three districts (Zomba, Machinga and Nsanje) were randomly selected in southern region of Malawi using the RAND function in excel. Machinga and Nsanje District Hospitals represented the secondary level of care. For Zomba district, there is no secondary level hospital. The largest facility is a tertiary level hospital, the Zomba Central Hospital which acts as a referral health facility for the South-East zone of the country.

Study Population and Sample Size

Our study population were adult patients (≥18 years) who were administered one or more antibiotic medicines during their hospital stay. We targeted patients who were hospitalized in the medical wards as most adult patients with infectious diseases are hospitalized in these general medical wards. A total of 304 case management files were included in the study

of which 138 were from Zomba, 84 from Machinga and 82 from Nsanje. The large number from Zomba was as a result of the hospital being a referral health facility for the south-eastern region of Malawi with a bed capacity of 680, unlike Machinga and Nsanje whose bed capacity per facility is 300 patients.[26,27]

Data Collection

Data were abstracted from case management files of eligible patients using a structured questionnaire. Demographic and clinical data were collected. We applied the global trigger tool for the detection of adverse events (AEs). This tool was developed by the Institute for Healthcare Improvement in the United States of America to help optimize the retrospective detection of adverse events using inpatient hospital records. It applies the use of certain triggers or clues such as switching or ordering of new medicines, abrupt medication stops, abnormal vital signs or laboratory results, and changes in patient prognosis.[28] We used the WHO definition of an ADR;

A response to a drug that is noxious and unintended and occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of a disease or for modification of physiological function.

[29] Investigators who were experienced pharmacists, laboratory scientists and a medical doctor identified suspected adverse drug reactions (sADRs) by searching for triggers such as the administration of anti-emetic medicines, and any documented events that were experienced by patients after the administration of antibiotic medicines. Further evaluation of the sADRs was also done by the investigators, with one of the investigators, FC, being a senior leader in pharmacovigilance issues in Malawi.

All suspected ADRs (sADRs) were subjected to causality assessment using the Naranjo criteria.[30] The Naranjo criteria is an algorithm that uses weighted questions to categorize AEs as definite, probable, possible and unlikely or doubtful ADRs based on the gathered clinical information.[31] Suspected ADRs were further assessed for seriousness and preventability using the WHO classification[32] and the Schumock and Thornton scale[33] respectively.

Statistical Analysis

Data were entered and coded in Microsoft Excel and exported to STATA 14.1 for statistical analysis. The occurrence of sADRs among various patient characteristics was described in terms of frequencies and percentages while continuous variables such as length of hospital stay, and number of medicines administered were summarized in terms of means, medians, and interquartile ranges. The Chi-square test was used to determine the association between various categorical variables such as sex and the occurrence of sADRs. To further assess the strength of association between various independent variables and the occurrence of sADRs, we applied the logistic regression analysis. We used both univariate and multivariate analysis where odds ratios were adjusted by controlling for significant factors using reverse elimination in the regression model.[34,35] A P value of < 0.05 was considered statistically significant.

Results

Patients' Demographic Characteristics

Of the 304 patients included in the study, 138 (45.4%) were from Zomba Central Hospital, 84 (27.6%) from Machinga District Hospital, and 82 (27%) from Nsanje District Hospital. Among these patients, 48% (n=148) were female, while 52% (n=158) were male (Table 1). The participant's age range was 18–96 years old. Overall, the median age was 44.5 years (IQR 30–62 years) of which for female patients was 43 years (IQR 30–61 years) and for male patients was 45 years (IQR 30 −62 years). Fifty-three (17.4%) patients were HIV-positive, 51.6% were HIV-negative and 30.9% were with unknown HIV status. Among the 53 HIV-positive patients, 22.6% had other co-morbidities while 23.5% of the 251 patients who were HIV-negative or with unknown status had other co-morbidities. Common co-morbidities among patients were hypertension (15.1%), type II diabetes mellitus (5.9%) and asthma (2.3%). Diagnosis was based on clinical assessment in 43.2% of the patients while full blood count (FBC) was used to support diagnosis for 56.8% of the patients. No laboratory confirmation by either bacterial culture or anti-microbial sensitivity test was conducted in any of the patients in this study. The common diagnoses were sepsis (24.3%), pneumonia (19.7%), meningitis (4.9%), Cellulitis (3.6%) and peptic ulcers (2.9%).

Table 1 Demographic and Clinical Characteristics of Patients Whose Case Management Files Were Reviewed in the Study

Category	Sub-group or characteristic	Zomba Central Hospital, n (%) N=138	Machinga District Hospital, n (%) N=84	Nsanje District Hospital, n (%) N=82	Total (N =304)
Age	< 65	102 (42.3)	69 (28.6)	70 (29.1)	241
	≥ 65	36 (57.1)	15 (23.8)	12 (19.1)	63
Sex	Female	79 (54.1)	21 (14.4)	46 (31.5)	146
	Male	59 (37.3)	63 (39.9)	36 (22.8)	158
Co-morbidities (ICD code)	HIV (B24)	33 (62.3)	10 (18.9)	10 (18.9)	53
	Hypertension (I10)	38 (82.6)	4 (8.7)	4 (8.7)	46
	Diabetes Mellitus (E11.8)	12 (66.7)	5 (27.8)	1 (5.6)	18
	Asthma (J45.9)	6 (85.7)	1 (14.3)	0 (0)	7
	Others	10 (66.7)	3 (20)	2 (13.3)	15
Diagnosis (ICD code)	Sepsis (A41.9)	39 (52.7)	12 (16.2)	23 (31.1)	74
	Pneumonia (J18.9)	34 (56.7)	13 (21.7)	13 (21.7)	60
	Meningitis (G00.9)	9 (60.0)	4 (26.7)	2 (13.3)	15
	Cellulitis (L03.9)	3 (27.3)	4 (36.4)	4 (36.4)	11
	Peptic ulcers (K27.9)	5 (55.6)	2 (22.2)	2 (22.2)	9
	Others	48 (35.6)	49 (36.3)	38 (28.2)	135
Tests conducted	FBC	103 (59.9)	29 (16.9)	40 (23.3)	172
	Bacterial culture	0 (0)	0 (0)	0 (0)	0
	Antibiotic sensitivity	0 (0)	0 (0)	0 (0)	0
No. of antibiotics prescribed	1	104 (63.0)	33 (20.0)	28 (17.0)	165
	2	34 (29.8)	38 (33.3)	42 (36.8)	114
	3	0 (0)	13 (56.5)	10 (43.5)	23
	4	0 (0)	0 (0)	2 (100)	2
No. of concomitant medicines	0	2 (33.3)	1 (16.7)	3 (50.0)	6
	1	29 (32.6)	32 (36.0)	28 (31.5)	89
	2	28 (32.9)	28 (32.9)	29 (24.1)	85
	3	43 (56.6)	17 (22.4)	16 (21.1)	76
	4	36 (75.0)	6 (12.5)	6 (12.5)	48

Abbreviations: ICD, International Classification of diseases 2023 (https://icd.who.int/browse10/2019/en; accessed on 10/05/2023).

Occurrence of Suspected Adverse Drug Reactions

We detected suspected adverse drug reactions (sADRs) in 24% (73/304) of the patients. The prevalence of sADRs for Zomba Central Hospital was 23.9% while for Machinga and Nsanje District Hospitals was 25% and 23.2% respectively (Table 2). The median age for the patients with no sADRs was 42 years (IQR 30–60 years) while for the patients with sADRs, the median age was 48 years (IQR 36–70 years). The patient age group was significantly associated with occurrence of sADRs, $p < 0.001$. The

Table 2 Prevalence of Suspected Adverse Drug Reactions (sADRs) for Various Patient Characteristics

Variable	Characteristic	Cases With no sADRs n (%)	Cases With sADRs n (%)	P Value
Age	< 65	193 (80.1)	48 (19.9)	0.001*
	≥ 65	38 (60.3)	25 (39.7)	
Sex	Female	112 (76.7)	34 (23.3)	0.776
	Male	116 (74.8)	39 (24.7)	
HIV status	Negative	189 (76.2)	59 (23.8)	0.652
	Positive	39 (73.6)	14 (26.4)	
Co-morbidities	Non-hypertensive	191 (74.0)	67 (26.0)	0.059
	Hypertensive	40 (87.0)	6 (13.0)	
	Non-diabetic	218 (76.2)	68 (23.8)	0.7
	Diabetic	13 (72.2)	5 (27.8)	
	Non-asthmatic	224 (75.4)	73 (24.6)	0.132
	Asthmatic	7 (100)	0 (0)	
Number of antibiotics prescribed	1	133 (80.6)	32 (19.4)	0.04*
	>1	98 (70.5)	41 (29.5)	
Number of concomitant medicines	≤ 1	23 (92.0)	2 (8.0)	0.049*
	>1	207 (74.5)	71 (25.5)	
Length of stay (days)	≤ 3	106 (89.8)	12 (10.2)	<0.001*
	>3	125 (67.2)	61 (32.8)	
Hospital	Zomba Central	105 (76.1)	33 (23.9)	0.962
	Machinga District	63 (75.0)	21 (25.0)	
	Nsanje District	63 (76.8)	19 (23.2)	

Notes: Chi-square test was used to determine the association between various categorical variables and the occurrence of sADRs. *P value ≤ 0.05 was considered statistically significant.
Abbreviation: sADRs, suspected adverse drug reactions.

prevalence of sADRs was 23.3% among female and 24.7% among male patients. Among the HIV-negative patients, the prevalence of sADRs was 23.5% while for the HIV-positive patients, the prevalence was 26.4%. Suspected ADR prevalence for hypertensive and diabetic was 13% and 27.8% respectively while none of the asthmatic patients experienced an ADR. For the number of medicines prescribed to patients, the median number of antibiotics was one for patients with no sADRs while for patients with sADRs the median number of antibiotics prescribed was two. For the other concomitant medicines, the median number of medicines was two for both patients with and without sADRs. The median length of hospital stay (LoS) for patients without ADRs was 4 days (IQR 3–6 days) while for patients with ADRs, the median LoS was 6 days (IQR 4–9 days). Occurrence of sADRs was significantly associated with number of antibiotic medicines ($p < 0.049$) and patient LoS ($p < 0.001$).

Figure 1 illustrates sADRs according to anatomical system classifications. Most of the sADRs were gastrointestinal events (42.5%), followed by: musculoskeletal (26.3%); cardiovascular (16.3%); central nervous system (13.8%; and urinary events (1.3%).

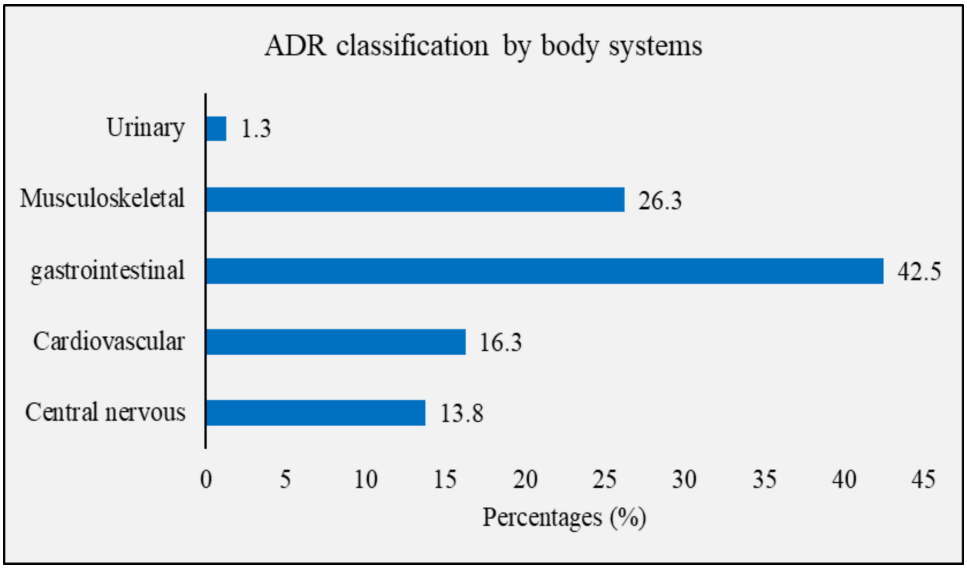

Figure 1 Occurrence of suspected adverse drug reactions (s(ADRs) by body systems. The sADRs were classified according to the anatomical system and presented in terms of percentages.

In this study, Ceftriaxone (47.6%) was the most prescribed antibiotic medicine followed by Metronidazole (22.9%), benzylpenicillin (13.2%), gentamicin (6.5%), Amoxicillin ± clavulanic acid (4.7%), ciprofloxacin (1.7%), flucloxacillin (1.1%), doxycycline (0.4%) and azithromycin (0.2%). By chemical classification, most of these antibiotics were beta-lactam (66.7%) and nitroimidazole antibiotics (22.9%) while only 10.4% of the antibiotics comprised of other classes. Occurrence of sADRs was proportional to the frequency of prescribing a particular antibiotic, $p < 0.001$. In total, there were 63 sADRs associated with ceftriaxone, 23 with metronidazole, 19 with benzylpenicillin, 15 with gentamicin and the rest of the sADRs were associated with amoxicillin ±clavulanic acid, azithromycin, ciprofloxacin, cotrimoxazole and flucloxacillin (Table 3). Common sADRs were abdominal pain (16 events) associated with amoxicillin, benzylpenicillin, ceftriaxone, co-trimoxazole, gentamicin and metronidazole; painful legs (7 events) associated with benzylpenicillin,

Table 3 Suspected Adverse Drug Reactions and Their Associated Antibiotic Medicines

Antibiotic Name	ATC Classification	Frequency of Prescriptions (%)	Frequency of sADRs Cases	Adverse Event Detected (Frequency)
Amoxicillin	J01CA04	20 (4.3)	4	Abdominal pain (1), body weakness (1) diarrhea (1), tachycardia (1)
Amoxicillin/ Clavulanic acid	J01CR02	2 (0.4)	1	Hypertension (1)
Azithromycin	J01FA10	1 (0.2)	0	
Benzylpenicillin	J01CE01	61 (13.2)	19	Abdominal pain (4), Hematuria (1), body weakness (1), diarrhea (1), joint pain (1), anxiety (1), dizziness (2), joint pain (1), painful legs (1), tachycardia (3), hypotension (1) vomiting (2)
Ceftriaxone injection	J01DD54	220 (47.6)	63	Abdominal pain (12), vomiting (1), irritability (1), back pain (2), body weakness (2), bradycardia (1), chest pain (2), swollen face (1), confusion (1), convulsions (5), dizziness (2), diarrhea (2), dysphagia (1), headache (1), hypertension (3), hypotension (2), joint pain (1), loss of appetite (1), numbness of legs (3), painful legs (6), tachycardia (5), vomiting (7)

(*Continued*)

Table 3 (Continued).

Antibiotic Name	ATC Classification	Frequency of Prescriptions (%)	Frequency of sADRs Cases	Adverse Event Detected (Frequency)
Ciprofloxacin	J01MA02	8 (1.7)	1	Hypertension (1)
Cotrimoxazole	J01EE01	7 (1.5)	3	Abdominal pain (1), chest pain (1), hypotension (1),
Doxycycline		2 (0.4)	0	
Flucloxacillin	J01CF05	5 (1.1)	3	Anxiety (1), painful legs (2)
Gentamicin	J01GB03	30 (6.5)	15	Abdominal pain (4), hematuria (1), irritability (1), body weakness (1), convulsions (1), dizziness (2), painful legs (1), tachycardia (3), hypotension (1),
Metronidazole	J01XD01	106 (22.9)	26	Abdominal pain (6), anxiety (1), back pain (1), body weakness (1), chest pain (1), convulsions (4), diarrhea (2), dysphagia (1), hypertension (1), painful legs (1), tachycardia (2), vomiting (5)

Abbreviations: ATC, Anatomical, Therapeutic and Chemical classification; sADRs, suspected Adverse Drug Reaction.

ceftriaxone, flucloxacillin, gentamicin and metronidazole; vomiting (8 events) associated with benzylpenicillin, ceftriaxone and metronidazole; tachycardia (7 events) associated with amoxicillin, benzylpenicillin, ceftriaxone, gentamicin and metronidazole; and convulsions (5 events) associated with ceftriaxone, gentamicin and metronidazole.

Causality, Seriousness, and Preventability of sADRs

Available clinical data was used to further assess the detected sADRs for causality, seriousness, and preventability. All AEs had a plausible temporal relationship with the culprit antibiotic medicine. Figure 2 provides details for the ADR classification. In terms of causality, 1.4% (n=1) of sADR were definite, 15.1% (n=11) were probable and 83.6% (n =71) were possible ADRs. Serious sADRs were 27.4% (n =20) while non-serious sADRs were 72.6% (n=53). These events were categorized as serious as they were either life threatening or prolonged hospitalization or both. Serious sADRs included convulsions (n = 5), bradycardia (n=1), tachycardia (n=7), hematuria (n=1), swollen face (n=1), hypertension (n=3) and hypotension (n=2). Among the sADRs, 26% (n=19) were preventable while 74% (n=54) were not preventable.

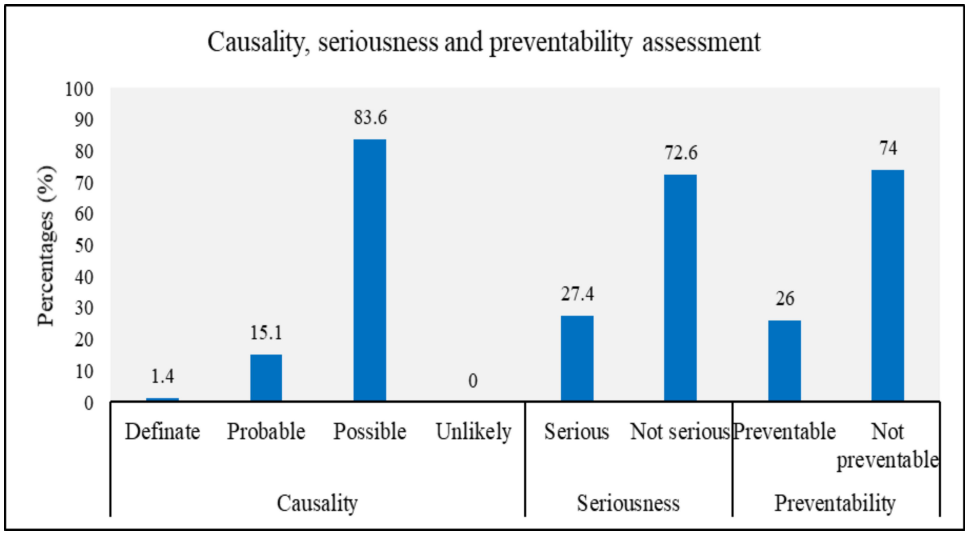

Figure 2 ADR Classification according to causality, seriousness, and preventability. The Naranjo scale, the World Health Organization classification and the Schumock and Thornton scale were applied to perform causality, seriousness and preventability assessments respectively.

Factors Associated with Occurrence of sADRs

A logistic regression analysis was conducted to determine the factors associated with occurrence of sADRs. For multivariate analysis, we adjusted the odd ratios by controlling for significant factors using reverse elimination in the regression model. Occurrence of sADRs was significantly associated with patient age, number of antibiotic medicines taken, and length of hospital stay (Table 4). The geriatric age group (≥65 years) was more likely to experience sADRs as compared to the younger age group, with adjusted odds ratio (aOR) of 4.53, 95% CI (2.21–9.28), p < 0.001. By hospital facilities, the results were significant for all the three facilities with aOR of 3.38, 95% CI (1.17–9.76), p< 0.024, aOR 12.97, 95% CI (2.29–73.4), p< 0.004, and aOR 6.95, 95% CI (1.43–33.76), p< 0.016, for Zomba, Machinga and Nsanje respectively. In terms of number of antibiotics administered, patients taking more than one antibiotic medicine had a higher risk of developing sADRs as compared to patients who were on one type of antibiotic medicine, aOR 2.14, 95% CI (1.18–3.90), p < 0.012. These results were not statistically significant when stratified by hospital facility. A hospital stay of > 3 days was also associated with a higher risk of sADRs, with aOR 5.11, 95% CI (2.47–10.55), p < 0.001 as compared to ≤ 3 days. By hospital facilities, the results were significant for all facilities with aOR 4.74, 95% CI (1.44–15.61), p< 0.010, aOR 19.09, 95% CI (2.37–15.77), p< 0.006, aOR 3.67, 95% CI (1.08–12.44), p< 0.037, for Zomba, Machinga and Nsanje respectively.

Discussion

We conducted this study in three districts of Malawi to assess the occurrence and characteristics of adverse drug reactions associated with antibiotic medicines. We found sADR prevalence of 24% among the study participants. A study done in Uganda found a 19% burden of antibiotic-associated ADRs among hospitalized patients. This study collected prospective

Table 4 Factors Associated with Occurrence of Adverse Drug Reactions

Variable	Characteristic	aOR	95% CI	P Value
Age	< 65	1		
	≥ 65	4.53	2.21–9.28	<0.001
Sex	Female	1		
	Male	1.07	0.63–1.82	0.800
HIV status	Non-reactive	1		
	Reactive	1.28	0.64–2.54	0.481
Co-morbidities	Non-hypertensive	1		
	Hypertensive	0.19	0.07–0.54	0.002
	Non-diabetic	1		
	Diabetic	1.29	0.44–3.78	0.647
Number of antibiotics prescribed	1	1		
	>1	2.14	1.18–3.9	0.012
Number of concomitant medicines	≤ 1			
	>1	2.82	1.39–5.74	0.004
Length of stay (days)	≤ 3			
	>3	5.11	2.47–10.55	<0.001

Notes: A multivariate logistics regression model was used to assess the strength of association between various independent variables and the occurrence of sADRs. A P value ≤0.05 was considered statistically significant.
Abbreviations: aOR, adjusted odds ratio, CIm, confidence interval.

data from both the medical and gynecological wards and was limited to only a tertiary level hospital.[17] In our study, we applied the global trigger tool which is reported to improve the detection rate of adverse events as compared to use of only clinical assessments which are done during routine patient care.[36] The global trigger tool has also been used in the detection of 221 ADRs among 1746 (12.7%) patients in a pediatric ward in China[37] and 62 ADRs out of 463 patients (13.4%) in the emergency department in India.[38]

We used the Naranjo criteria for causality assessment and found only one adverse event which was a definite ADR. This was a case of convulsions following administration of ceftriaxone. Patient records indicated that a similar incident had previously occurred in the patient. In addition, there was a positive de-challenge and re-challenge of the reaction, which is not normally done in clinical practice as observed in the rest of the cases. The majority of the sADRs were therefore classified as possible (83.6%) or probable ADRs (15.1%) according to the Naranjo score. The Naranjo criteria provides a simple and reproducible tool for ADR causality assessment.[39] However, the major challenge is that it is not possible to respond to all the necessary questions provided by the algorithm where limited patient information is available. This renders most of the potential ADRs rated with a low score.[40] As noted in our causality assessments, we found very few events which were characterized as definite or possible ADRs since there was limited information to completely rule out other possible causes of the adverse events. Since our patient records were paper based, we encountered challenges such as missing sections in the patient files which not only affects the accurate detection of ADRs but also the subsequent ADR assessments.

Among the detected sADRs, 27.4% were serious. These were central nervous and cardiovascular events such as convulsions, tachycardia, and hypotension. The events met the criteria for seriousness as they were either life threatening or prolonged hospitalization of patient.[32] Serious ADRs have worrisome clinical and economic consequences as they require critical patient care to prevent potential loss of life. A study conducted in South Africa found out that the cost of managing ADRs in patients on Tuberculosis (TB) treatment rendered the total cost 17 times higher than the actual cost of TB treatment.[41] In our study, the treatments for sADRs were not quantified as most of these sADRs were not recognized by health care professionals. We also noted a high prevalence of preventable sADRs which contributed to 26% of the cases. Preventability of an ADR is assessed based on the presence of a medication error or any action that would otherwise be avoidable such as administering the wrong dose or lack of monitoring of patients with a known ADR risk.[33] Lack of evidence-based diagnosis may contribute to a higher rate of wrong prescribing of antibiotics in Malawi which may increase the incidence of preventable ADRs. For instance, we observed that no bacterial culture or antimicrobial sensitivity tests were conducted in all patients in this study. FBC was the only test used to support the diagnosis of 56.8% (Table 1) of the patients despite the poor sensitivity and specificity for diagnosis of bacterial infections.[42–44] Furthermore, the choice of broad-spectrum antibiotics was noted to be very high which may increase the risk of antimicrobial resistance.[45] Lack of capacity to conduct bacterial culture and antimicrobial sensitivity tests limits the precise selection of the most appropriate narrow- spectrum antibiotic, hence clinicians opt for empirical therapy with broad-spectrum antibiotics.[46]

Occurrence of sADRs was significantly associated with geriatric age (≥65 years), number of antibiotic medicines and LoS. These are consistent risk factors for ADR.[47] Physiological changes such as renal and hepatic impairment are common in geriatric patients.[48] Usually, these conditions principally affect the elimination of medicines and therefore render geriatric age groups at risk of developing ADRs. Even though the geriatric group had a higher prevalence of sADRs in our study, available patient records did not reveal much information about the presence of age-related co-morbidities such as renal impairment.

Polypharmacy increases not only the drug exposure to patients, but also the potential for drug-drug interactions.[49] Common antibiotic combinations in this study were ceftriaxone and metronidazole (58 cases); benzylpenicillin and gentamicin (21 cases); benzylpenicillin and metronidazole (9 cases); and metronidazole and amoxicillin (8 cases). There is however limited information about known drug-drug interactions between these antibiotic combinations.[50] A long LoS is usually associated with a longer duration of treatment, hence increased risk of occurrence of ADRs.[45] On the other hand, a long LoS is also a consequence of occurrence of an ADR as the affected patients require additional treatment and monitoring.[51,52] We lacked evidence to make this determination as the days on which sADRs manifested were not recorded in our study.

PV systems seek to identify safety signals.[53] These can be previously unknown ADRs or changes in certain aspects of already known ADRs such as presentation or frequency of occurrence that require further investigations.[54] The majority of the sADRs detected in this study have been previously documented to be associated with antibiotic medicines. To our knowledge, limited information is available for events such as painful legs and joints, tachycardia, and hypotension (Table 3). Convulsions could also be a potential signal as they are observed to occur at a higher frequency in Malawi than expected (<1/1000).[55,56]

Study Strengths and Limitations

Limitations of this study include measurement bias due to poor documentation or missing information in patient records which might have affected the accuracy of detection and assessment of sADRs. Extremely poor records which were missing crucial data such as medication charts and patient demographics were, however, excluded from the study. Study findings were based on retrospective data. This may underestimate the prevalence of ADRs as we did not directly interview the patients to further explore their personal experiences after taking the medicines. Some of these medicine-related problems may not be documented by clinicians and nurses.[57] Furthermore, there was a limitation of sample size per health facility. Suspected ADRs in this study may not have been detected or reported to the national PV centre by healthcare providers or patients. This is mostly due to the lack of PV awareness and skills among healthcare workers.[58] Furthermore, we did not interview possible informants where more information was required for the assessment of sADRs. Based on the available patient data, we precisely assessed the sADRs in terms of causality using the Naranjo criteria. This algorithm has been used in several other studies and reported to be easy to use and reproducible.[39]

Conclusion

We used the global trigger tool to determine the prevalence of sADRs using retrospective data from patient files. We found a higher prevalence of sADRs associated with antibiotic medicines than reported elsewhere. Furthermore, the number of serious events was high which is a concern regarding the achievement of optimal antibiotic treatment outcomes. This may, among others, contribute to high patient mortality, poor treatment adherence, complicated treatment strategies, antibiotic resistance and increased cost of care.

Abbreviations

ADR, Adverse drug Reactions; sADR, suspected Adverse drug Reactions; ATC, Anatomical Therapeutic Chemical Classification; PV, Pharmacovigilance; WHO, World Health Organization; LMICs, low- and middle-income countries; IQR, Interquartile Range; FBC, Full Blood Count; LoS, Length of Hospital Stay; aOR, adjusted Odds Ratio; CI, Confidence Interval.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Approval and Consent to Participate

Approval was granted by the Institution Review Board of Kamuzu University of Health Sciences-Malawi (College of Medicine Research and Ethics Committee (COMREC) under study number P.10/21/3447). In addition, permission was sought from the hospital director or directorates of health and social services in Zomba, Machinga and Nsanje before data collection. All informed consents were obtained from individual patients or their legal guardian after thorough discussion with them before data collection. The study was approved in line with the principles of the declaration of Helsinki.

Consent to Publication

All the hospitals have provided the permission to publish as long as there is no data that might link to specific patients.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflict of (competing) interests.

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