Adverse drug reactions to Ivermectin and Albendazole following mass drug administrations

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ABSTRACT

Background: The concept of Pharmacovigilance gain worldwide attention following the thalidomide incident of the 1960 s

Objectives: This study aimed at assessing the adverse drug reactions to ivermectin and albendazole recorded in the database of the National Pharmacovigilance Center for all Lymphatic Filariasis campaigns conducted in the country and to determine challenges to reporting of adverse drug reactions during such campaigns in Sierra Leone.

Methods: This study was a mixed descriptive study design that involved the retrospective review of data collected during mass administration of ivermectin and albendazole for lymphatic filariasis between 1st January 2007 and 31st May 2023. A semi-structured questionnaire was administered to staff of District Health Management teams in order to identify possible challenges to the reporting of adverse drug reactions.

Results: Out of the 1135 adverse drug reactions entered into the WHO database, 1.23 % (14) were considered to be serious reactions. The most common adverse reaction recorded was pruritus (9.78%). 93 (93 %) out of the 100 respondents are aware that there is drug safety monitoring programme in Sierra Leone. Eighty (80 %) of the respondents indicated that lack of training on the detection of adverse drug reactions was the major challenge to the reporting of adverse drug reactions.

Conclusion: The study showed that ivermectin and albendazole have a good safety profile. Lack of training on the detection of adverse drug reactions was the major challenge to the reporting of adverse drug reactions.

Keywords: Adverse Drug Reactions, Ivermectin, Albendazole, Mass Drug Administration, Lymphatic filariasis, District Health Management.

Effets indésirables des médicaments à l'ivermectine et à l'albendazole suite à des administrations massives de médicaments

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RESUME

Contexte: Le concept de pharmacovigilance a gagné en popularité dans le monde entier suite à l'incident de la thalidomide des années 1960.

Objectifs: Cette étude vise à évaluer les effets indésirables des médicaments à l'ivermectine et à l'albendazole enregistrés dans la base de données du Centre national de pharmacovigilance pour toutes les campagnes de lutte contre la filariose lymphatique menées dans le pays et à déterminer les défis liés à la déclaration des effets indésirables des médicaments au cours de ces campagnes en Sierra Leone.

Méthodes: Cette étude était une étude descriptive mixte qui comprenait l'examen rétrospectif des données recueillies lors de l'administration massive d'ivermectine et d'albendazole pour le traitement de la filariose lymphatique entre le 1er janvier 2007 et le 31 mai 2023. Un questionnaire semi-structuré a été administré au personnel des équipes de gestion de la santé du district afin d'identifier les éventuels défis liés à la déclaration des effets indésirables des médicaments.

Résultats: Sur les 1135 effets indésirables des médicaments enregistrés dans la base de données de l'OMS, 1,23 % (14) ont été considérés comme des réactions graves. L'effet indésirable le plus fréquemment enregistré était le prurit (9,78 %). 93 (93 %) des 100 répondants savent qu'il existe un programme de surveillance de la sécurité des médicaments en Sierra Leone. Quatre-vingts (80 %) des répondants ont indiqué que le manque de formation sur la détection des effets indésirables des médicaments était le principal défi à la déclaration des effets indésirables des médicaments.

Conclusion: L'étude a montré que l'ivermectine et l'albendazole présentent un bon profil de sécurité. Le manque de formation sur la détection des effets indésirables des médicaments a constitué le principal obstacle à leur déclaration.

Mots clés: effets indésirables des médicaments, ivermectine, albendazole, administration massive de médicaments, filariose lymphatique, gestion de la santé au niveau du district.

INTRODUCTION

The concept of Pharmacovigilance or drug safety monitoring gained worldwide attention following the thalidomide incident of the 1960 s. Thalidomide was a drug given to pregnant women to prevent "morning sickness". The babies born to some of these women were badly deformed and it took a while before the link between the deformed babies and the drug was made. Once this link was established, the drug was banned and drug regulatory authorities and agencies around the world became aware of the fact that seemingly safe drugs could have potentially serious adverse effects.[1]

This led the World Health Organization (WHO) to call for the close monitoring of adverse effects of all drugs. By the continuous monitoring of all drugs, it is possible to detect drugs causing unwanted adverse drug reactions and to control them. This can only be done effectively if the healthcare professionals and the general public report all suspected adverse drug reactions (ADRs).[2]

The drug safety monitoring programme (PVG) in Sierra Leone was set up with funds initially provided by the global fund project with contributions from the health sector support project, EU/Malaria project and the government of Sierra Leone when the country was about to change its treatment policy for malaria from chloroquine as the first line to artesunate and amodiaquine for the treatment of uncomplicated malaria in 2005.[3]

This system was however adapted to monitor the safety profile of all drugs used in the healthcare delivery system within the country. This programme is hosted by the PVG and Clinical Trials Department (PVG/CTD) of the Pharmacy Board of Sierra Leone (PBSL) which serves as the National Pharmacovigilance Centre.

The PVG/CTD works with a sixteen-man drug safety and clinical trial committee comprising experts in various fields relating to drug safety. The PBSL has appointed PVG focal persons in all tertiary and secondary hospitals in the country. The PVG programme was launched in 2006. Sierra Leone attained full membership status of the WHO Drug Safety Monitoring Programme in October, 2008 and became the 87th Member.[4]

Mass drug administration (MDA) campaigns, such as those aimed at treating lymphatic filariasis, are crucial public health interventions. However such interventions have the potential to harm patients and as such it important to establish a robust PVG program capable of offering support and essential guidance for such interventions.

The neglected tropical disease programme (NTDP) in Sierra Leone is one of the public health programmes in the Ministry of Health and Sanitation and is responsible for the coordination of all activities relating to the eradication of all neglected tropical diseases that are a health burden to the general populace. The programme was born out of the National Onchocerciasis Programme which was upgraded to NTDP in 2006 in consultation with the WHO when Sierra Leone was about to embark on an integrated management of onchocerciasis, Lymphatic Filariasis (LF), schistosomiasis, soil transmitted helminthes and trachoma.[5]

LF also known as elephantiasis is a neglected tropical disease that causes a chronic, debilitating disease that affects people in tropical and subtropical areas of Asia, Africa, the Western Pacific and some areas of the Americas caused by the parasites Wuchereria bancrofti, Brugia malayi and B. timori, transmitted by culex, anopheles and other mosquitoes.[6]

LF is prevalent in poor communities and is the second leading cause of permanent disability second to leprosy. An estimated 90 % of all LF cases worldwide and all cases in Africa are infections with the parasite Wuchereria. bancrofti. The main vectors in West Africa are the anopheles mosquitoes.[7]

In year 2000 the WHO launched the Global Programme to Eliminate lymphatic filariasis (GPELF) with the strategies to interrupt transmission, alleviate suffering and manage morbidity in affected individuals.[7]

WHO recommends three regimens for the treatment of LF-ivermectin+ diethylcarbamazepine +albendazole, diethylcarbamazipine+Albendazole and Ivermectin+Albendazole.[8]

These have been proven to be effective with a reduction in morbidity and the incidence of ADRs.[9, 10, 11, 12, 13]

Documented ADRs to Ivermectin and Albendazole when combined during MDA for the treatment of LF are fever, malaise, body pain, itching, rash, swelling of the limbs, nausea, vomiting, diarrhoea, headache and dizziness. Severe ADRs include mild liver elevation, hepatotoxicity, bone marrow depression, hypotension, tachycardia,

encephalopathy and severe allergy.[14,15,16]

Sierra Leone started the MDA of ivermectin and albendazole for the treatment of LF in 2007 and since then, several rounds have been conducted with Several studies conducted and findings published with regards to the programmatic aspects of the MDA, but none with respect to the drug safety component.[17,18,7,19]

Since its inception in 2006 the PVG program in Sierra Leone has faced the challenge of under reporting of ADRs. From literature review common causes of under reporting are lack of awareness, attitudinal barriers such as diffidence, work load, resource constraints such as lack of reporting tools, weak PVG systems, complex reporting systems, lack of training on the detection of adverse drug reactions, lack of motivation and poor timing or design during MDAs.[20,21,22]

This study aimed at assessing the characteristics of ADRs to ivermectin and albendazole recorded at the data base of the National PVG Center for all the LF campaigns conducted in the country during the study period. The study also aims at exploring the experiences and challenges of the NTDP, stakeholders, community health volunteers, PVG focal persons and District Surveillance Officers towards detecting and reporting of ADRs in Sierra Leone.

The specific objectives of this study are: (1) To identify the common ADRs to ivermectin and albendazole administered during MDA for the treatment of lymphatic filariasis and to compare these with what is observed in the WHO Global database for drug safety monitoring. (2) To classify the ADRs to ivermectin and albendazole observed in terms of seriousness (3) To classify the ADRs to ivermectin and albendazole observed in terms of system organ class. (4) To conduct causality assessment for all serious ADRs observed. (5) To determine the challenges to reporting ADRs to ivermectin and albendazole MDA.

MATERIALS AND METHOD

Study design

This study was a mixed descriptive study design. The first part of the study involved the retrospective review of data collected passively during MDA of ivermectin and albendazole for the treatment of LF between the 1st of January 2007 and the 31st of May 2023.

The second part of the study involved the administration of a semi-structured questionnaire in order to identify possible challenges to the reporting of ADRs by staff of District Health Management Teams (DHMTs) including NTDP focal points, PVG focal points and District Surveillance Officers.

Study setting general setting

Sierra Leone is situated on the coast of West Africa with a population of about 8 million of which at least 1 million live in the capital city of Freetown.[23] The country has an area of 71,740 km^2 and is divided into five administrative regions: the Northern region, North-western region, Eastern region, Southern region, and the Western area. The five areas are subdivided into 16 districts and DHMTs.

Specific settings

The specific settings included:

(1) The National Pharmacovigilance Centre housed by the PBSL for the retrospective review. The center collects ADRs from healthcare providers, general public as well as the various public health programmers in the country. ADR reports are mainly through a paper based system but can also be electronic (open data kit for data collection).
(2) The DHMTs offices in each of the Districts

Study population and periods

This study population included:

(1) All individual case safety reports to ivermectin and albendazole available in the PVG database (vigiflow) between 1st of January 2007 and 31st of May 2023.
(2) Staff of the DHMTs offices in the Districts

Data source, collection and validation

Retrospective review

All data variables were extracted from the vigiflow database to include all individual case safety report data that were cross-validated as part of the routine PVG procedures prior to entry into vigiflow. The variables included identifiers, gender, and age, types of reported ADRs, seriousness and patient outcomes.

Questionnaire administration section

A structured questionnaire was developed after review of similar studies conducted in Africa and other parts of the

world. The questionnaire contained questions bordering on challenges, experiences, detection and reporting ADRs during MDAs. Two districts in each of five provinces of the country were selected at random.

Twenty (20) questionnaires were administered to staff of the DHMTs in each District selected.

This method of sampling was used base on the ease of accessibility as well as the expertise gained over of the years by staff of the DHMTs as they have played the lead or coordinating role in MDAs in their respective Districts.

The individual case safety reports on the MDA of ivermectin and albendazole were exported to a Microsoft excel sheet and analysed using the most recent SPSS Version.

ADRs were categorized using the Medical Dictionary for Regulatory activities (MedDRA) classification and presented in the System Organ Classification.

Patient outcomes were stratified by recovered and not recovered. Frequencies and proportions were used to report the distribution of adverse drug reactions types and patient outcomes.

Causality assessment was done using the WHO Causality Algorithm for serious cases and categorized into certain, probable, possible, unlikely and unclassifiable. For the qualitative study each questionnaire was coded and the data analysed using frequency and proportions.

Ethical considerations

The data for this study was predominantly obtained from data already entered into the national pharmacovigilance database (Vigiflow). Permission therefore, was sought from the Registrar of the PBSL for access to the PVG database. Consent was sought from all of those who took part in the interview process.

RESULTS

Retrospective review section

The ADR classification, outcome and organ class affected are shown in Table 1 while the casualty assessment result is shown in Table 2.

Table: 1 Result of ADR classification, outcome and system organ class affected by ADRs to ivermectin and albendazole.

No	Variable	Results	N	%
1	Classification of ADR	Serious	14	1.23
		Non serious	1121	98.77
2	ADR reported	Pruritus	111	9.78
		Headache	106	9.34
		Diarrhoea	104	9.16
		Dizziness	52	4.58
		Vomiting	47	4.14
		Urticaria	34	2.99
3	System organ class affected	Gastrointestinal	349	30.75
		Skin and subcutaneous	158	13.92
		Nervous system disorder	121	10.75
		Neurological signs and symptoms	72	6.34
		Nervous system disorder and gastrointestinal disorder	35	3.08
4	Outcome of ADR	Not recovered	11	0.97
		Recovered	1124	99.03

As shown in Table 1 above, 1135 ADR reports to ivermectin and albendazole for LF campaigns were recorded of which 14 (1.23 %) were classified as serious. Pruritus (9.78 %) was the most common ADR reported. Gastrointestinal disorders (30.75 %) were the most system organ disorder recorded.

Some individual case safety reports had two or more ADRs with the incidence of experiencing one, two, > three types of ADRs being 70.4 %, 17.6 %, and 12 % respectively (see Fig. 1).

Also some individual case safety reports had two or more system organ class involvement. The incidence of one, two, > three system organ classes involvement were 78.9 %, 13.9 % and 7.2 % respectively(see fig.2 below). The 14 serious adverse drug reactions were subjected to causality using the WHO criteria as shown in Table 2.

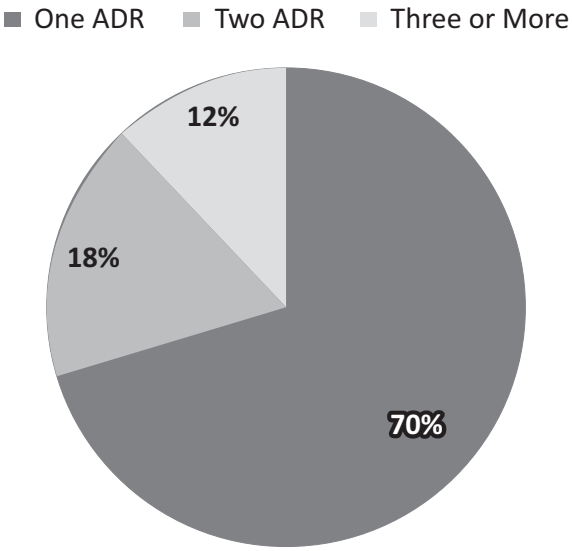

Fig 1: Percent % Score of adverse drug reaction experienced

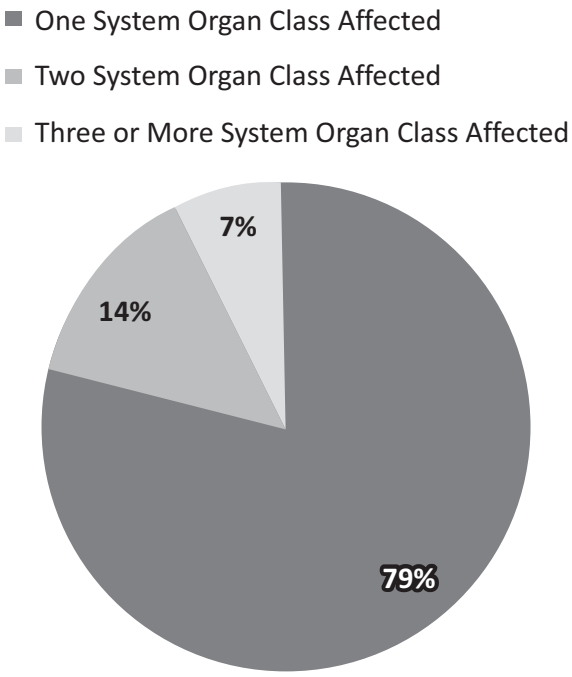

Fig 2: Percent % System Organ Class Affected

Table 2: Result of causality assessment of serious ADR to ivermectin and albendazole

Identification	MedDRA Term	Outcome	SOC	Classification	Causality
SL-PBSL-2011-00132	Impotence/ sexual Dysfunction	Recovered	Reproductive system disorders	Serious	Probable
SL-PBSL-2014-0027	Unconscious ness	Recovered	Neurological signs and symptoms	Serious	Probable
SL-PBSL-2015-00001	Dystonia Bloody Diarrhoea	Recovered	Nervous system and Gastrointestin al signs and symptoms	Serious	Probable
SL-PBSL-2018-00191	Shock	Recovered	Ear and Labyrinth disorder	Serious	Probable
SL-PBSL-2018-00210	Orthostatic Collapse and Nervousness	Recovered	Neurological signs and symptoms	Serious	Probable
SL-PBSL-2018-00274	Tachycardia and Vomiting	Recovered	Gastrointestin al and cardiac system disorders	Serious	Probable
SL_PBSL_ 300002765	Generalized tonic Clonic and seizures Haemorrhagia	Recovered	Nervous system and disorders Bleeding disorders	Serious	Probable

Table 2: Result of causality assessment of serious ADRs to ivermectin and albendazole cont.

Identification	MedDRA Term	Outcome	SOC	Classification	Causality
SL-PBSL-2013-0017	Abdominal discomfort/ Headache/ vomiting/ Diarrhoea	Recovered	Gastrointestinal and nervous system disorder	Serious	Probable
SL-PBSL-2013-0018	Headache/ Abdominal discomfort/ itching and vomiting	Recovered	Nervous system, gastrointestinal and skin and connective tissue disorder	Serious	Probable
SL-PBSL-2013-0019	Headache, dizziness vomiting and oedema	Recovered	Nervous Gastrointestinal, neurological and generalized system disorder	Serious	Probable
Sl-PBSL-2013-00120	Headache dizziness and vomiting	Recovered	Nervous Gastrointestinal and neurological system disorder	Serious	Probable
SL-PBSL-2018-00216	Vomiting, and Imbalance	Recovered	Gastrointestinal and orthostatic	Serious	Probable
SL-PBSL-2012-0038	Palpitation	recovered	Cardiac disorder	Serious	Probable
SL-PBSL - 2028-00111	Palpitation	recovered	Cardiac disorder	Serious	Probable

Questionnaire administration section

Sex and cadre of respondents

A total of 100 questionnaires which were administered were received from the respondents comprising of 59 % males and 41 % females (table 3). 11 % of respondents were Doctors, 16 % were Pharmacists, 14 % were Pharmacy Technicians, 12 %, 32 %, 4 %, 5 %,1 %, 1% and 4 % were Community Health Officers, Nurses, Community Health Assistants, District logistics officers, District Surveillance Assistants, Monitoring and Evaluation officer sand Store Keepers respectively.

Table 3: Results for sex and cadre of respondents

No	Variable	Results	No	%
1	Sex	Male	59	59
		Female	41	41
2	Cadre	Doctor	11	11
		Pharmacist	16	16
		Pharmacy Technician	14	14
		CHO	12	12
		Nurse	32	32
		CHA	4	4
		DLO	5	5
		DSA	1	1
		M&E	1	1
		Storekeeper	4	4

As shown in Table 3 above 93 % of respondents are aware that there is a drug safety monitoring programme in Sierra Leone. 60 % of the respondents indicated that they have taken part in the MDA for LF with 32 % serving as mass drug distributors.

Table 4: Results for Awareness of drug safety monitoring programme, implementing agency, participation and role in MDA, awareness of reporting channels and filling out of ADR report.

No	Variable	Results	No	%
1.	Respondents awareness of the drug safety monitoring programme	Yes	93	93
		No	7	7
2.	Respondents view on the implementing agency for drug safety	Pharmacy Board of Sierra Leone	87	87
		Directorate of disease prevention and control	4	4
		Hellen Keller	2	2
		Neglected Tropical Disease Programme	1	1
		Not aware	6	6
3.	Participation in mass drug administration	Yes	60	60
		No	40	40
4.	Role of respondents in mass drug administration	No role	40	40
		Mass Drug Distributor	32	32
		Safety Officer	10	10
		Clinical Officer	9	9
		Programme Officer	2	2
		Surveillance Officer	5	5
		Other Please State	2	2
5.	Proportion of respondents that have filled out an adverse drug reaction	Yes	64	64
		No	36	36
6.	Awareness of the reporting channels	Yes	73	73
		No	27	27

As shown in Table 4, 64 % of the respondents have fill out an ADR report form before with 73 % knowing the reporting channels for ADR reports.

Table 5: Results for where ADR reports are sent

No	Variable	Results	N	%
	AD Rreports are sent directly to	Not aware as to where to send reports	18	18
		Pharmacy Board of Sierra Leone	42	42
		PVG focal point District health management team	38	38
		Healthcare Provider	2	2
		NTDP	0	0

As shown in Table 5, majority (42 %) of respondents indicated that ADRs are sent directly to the PBSL during MDAs.

Table 6 shows that the most (80 %) common challenge to the reporting of ADRs was lack of training on the detection of ADRS. Also. another major challenge (53 %) was lack of reporting tools.

Table 6: Results for challenges to reporting ADRs

Variable	Results	N	%
Challenges to reporting adverse drug reactions	Lack of training on the detection of adverse drug reactions	80	80
	Lack of reporting tools	53	53
	Workload at station of deployment	47	47
	Lack of interest	13	13
	Lack of incentives	45	45
	Reporting channel not clear	36	36
	Failure to identify focal persons in the District health management	32	32
	Lack of feedback on cases reported	42	42
	Lack of sensitization or awareness on adverse drug reaction reporting	48	48
	Failure of healthcare providers to report adverse drug reactions	45	45
	Other please specify	2	2

DISCUSSIONS

Retrospective review section

Nature of adverse drug reactions and system organ class involvement

The results of this study showed that majority of the documented ADRs were considered non serious which is consistent with a study conducted in Tanzania.[15]

It was observed that pruritus was the most common ADR which was followed by headache and diarrhoea. However, this was found to be at variance with a study conducted in Tanzania in which the most common ADR was headache.[15]

The incidence of experiencing one, two, ≥ three types of AEs were 70.4 %, 17.6 %, and 12 %, respectively. This was found to be at odds with Fimbo (2022).[15]

The most common ADR to ivermectin and albendazole recorded in this study was pruritus followed by headache and diarrhoea in decreasing order as shown in table 1 above whilst in the WHO Global data base (Vigibase) the most common ADR was headache followed by pruritus and muscle pain in decreasing order.[24]

The system organ class involvement most recorded was gastrointestinal disorders. This is consistent with the effect of ivermectin and albendazole on the gastrointestinal tract and the central nervous system.

Questionnaire administration section

Sex and cadre of respondents

Majority of the respondents were nurses, this is consistent with the fact that the bulk of the health workers in Sierra Leone consists mainly of nurses.[25]

Awareness as to the drug safety monitoring programme in Sierra Leone and implementing agency

With regards to awareness of the drug safety monitoring programme, a vast majority of respondents were aware that there is a drug safety monitoring programme in Sierra Leone. This was found to be lower than that of a study conducted in India.[26] This was comparable to Rikhotso.[27]

In terms of the implementing agency for pharmacovigilance in Sierra Leone majority of the respondents were able to state rightly that the PBSL is the implementing agency for the drug safety monitoring programme in Sierra Leone. The overall implication of the above is that there is a high awareness amongst healthcare providers as to the drug safety monitoring programme in Sierra Leone. However, this was found to be higher than two studies conducted in India.[28, 29]

Taking part in MDA for LF and the role played

More than half of the respondents indicated that they have taken part in the mass drug administration for lymphatic filariasis. This is consistent with the fact that more than half the respondents have a working experience of 8 years and above. Among the respondents that have taken part in the mass drug administration for lymphatic filariasis,[32] were mass drug distributors whilst the others were Safety Officers, Clinical officers, Programme Officers and Surveillance Officers. This is consistent with the fact that in most mass campaigns in Sierra Leone the bulk of staff deployed as mass drug distributors are Nurses and Community Health Officers. These staffs are also engaged in the training of non-medical staff.[25]

Filling out an ADR report form and being aware of the reporting channels

From this study the ADR reporting rate was above average. This was found to be higher than that reported by Gupta.[27] and Nagumo.[21] The reporting rate was however found to be comparable to Rikhotso.[27]

Regarding the reporting channels for ADRs, 73 % indicated that they are aware as to the reporting channels. This was found to be higher than Kunene and Teo.[30] However this implies that there is still need for continuous training and further awareness raising with regards PVG especially amongst health care providers.

In terms of where ADRs are sent after filling, there was almost an even split between the PBSL and DHMTs focal points and was found to be consistent with the reporting channels for adverse drug reaction reports during mass campaigns.

Challenges to adverse drug reaction reporting

From this study the most common factor for not reporting ADRs was the lack of training on the detection of ADRs. This was followed by lack of ADR reporting tools, workload at station of deployment, lack of interest and lack of incentives in that order. The lack of training and lack of reporting tools as challenges to reporting adverse drug reactions observed in this study compares closely to that

of a study conducted in South Africa where it stated that 36.6 % have not seen an ADR report form in their facility.[27]

The percentages in terms of lack of incentives, lack of interest and lack of training were observed to be lower than Gupta.[26] Dharmadhikari.[29] and Bepari.[31]

CONCLUSION

From the results of this study, it can be concluded that ivermectin and albendazole have a relative good safety profile as the vast majority of ADRs documented were non serious and gastrointestinal in nature. The major challenge major challenge to the reporting of ADRs was lack of training on the detection of ADRs with awareness amongst healthcare providers as to the drug safety programme in Sierra Leone very high.

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