COLLEGE OF MEDICINE

Antibiotic medicine-related problems: pharmaceutical quality, availability, adherence to treatment guidelines and associated adverse drug reactions in Southern Malawi

By

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DECLARATION

I **Francis Kachidza Chiumia,** declare that the work presented in this thesis (including raw data, analysis, and figures) is original and has not been submitted before to the University of Malawi or any other university for the purpose of obtaining a doctoral degree or any other academic qualification by myself or any other person. The thesis includes research papers which are already published or submitted for publication in open access journals, and the corresponding author, other co-authors of the papers and I (primary author) remain the copyright holders as stated in the copyright section of the publications and journal information.

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DEDICATION

I dedicate this PhD thesis to my son, Francis Upovu Chiumia Jr. I pray that God should give him the grace to excel even higher in academics, and that he should become a better scientist. Most importantly, I pray that he should grow with great wisdom and kindness towards humanity.

ABSTRACT

Globally, there are concerns of increasing incidence of antimicrobial resistance (AMR). However, there is limited literature on antibiotic medicine-related problems that may exacerbate the risk of AMR. The aim of this research was to assess the pharmaceutical quality, availability and use of antibiotic medicines and the associated adverse drug reactions in Southern Malawi. We tested the quality of 293 medicine samples from Zomba, Machinga and Nsanje districts and retrospectively reviewed 304 patient files to evaluate the clinical outcomes. Data on medicine availability was collected from stock cards. The prevalence of substandard medicines among antibiotics was 25.4% and were associated with local manufacturing and plastic primary packaging, $p<0.01$. Over six months, the antibiotic stock outs were 12.5%, 64.3% and 85.7% for Zomba, Machinga and Nsanje respectively. Adherence to treatment guidelines was lower for antibiotics that were stocked out than those that were not stocked out, $p< 0.002$. About 75% of prescribed antibiotics were from the watch class. The ADR prevalence was 24% of which 27% were serious events. The ADR occurrence was associated with age, polypharmacy and length of hospital stay, $p<0.005$. Patients who received antibiotics with optimal content of the active pharmaceutical ingredient (API) had higher rates of both ADR occurrence and patient recovery as compared to the patients who received antibiotics with lower than the required API content. However, the differences were not statistically significant. In summary, the study revealed that high prevalence of SF antibiotic medicines, overuse of watch antibiotics, poor adherence to standard treatment guidelines and occurrence of ADRs are serious problems affecting antibiotic therapy. These problems need to be tackled as part of antimicrobial stewardship and pharmacovigilance strategies in Malawi.

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ABBREVIATIONS

ACSoMP	Advisory Committee on Safety of Medicinal Products
ADR	Adverse Drug Reactions
AE	Adverse Events
AEFI	Adverse Events Following Immunization
API	Active Pharmaceutical Ingredient
CDC	Centre for Disease Prevention and Control
EML	Essential Medicines List
GPHF	Global Pharma Health Fund
HIA	Health International Action
HICs	High-Income Countries
HPLC	High Performance Liquid Chromatography
LMICs	Low- Middle- Income Countries
LOD	Limit of Detection
LOQ	Limit of Quantification
ME	Medication Errors
MEML	Malawi Essential Medicine List
MRH	Medicine-related Harm
MSTG	Malawi Standard Treatment Guidelines
NCCMERP	National coordination council for medication error reporting and prevention
OTC	Over the Counter

PV	Pharmacovigilance
QECH	Queen Elizabeth Central Hospital
sADRs	Suspected Adverse Drug Reactions
STG	Standard Treatment Guideline
TLC	Thin Layer Chromatography
UMC	Uppsala Monitoring Centre
UV/Vis	Ultraviolet Visible
WHO	World Health Organization

LIST OF PAPERS

This thesis is based on the papers listed below. Permission was sought from copyright holders for re-printing of the published papers.

Publications

i. Chiumia FK, Nyirongo HM, Kampira E, Muula AS, Khuluza F. Burden of and factors associated with poor quality antibiotic, antimalarial, antihypertensive and antidiabetic medicines in Malawi. PLoS One [Internet]. 2022;17(12):e0279637. Available from: http://dx.doi.org/10.1371/journal.pone.0279637

ii. Chiumia FK, Muula AS, Chimimba F, Nyirongo M, Kampira E, Khuluza F. Effect of antibiotic medicines availability on adherence to standard treatment guidelines among hospitalized adult patients in southern Malawi. PLoS One [Internet]. 2023;1–16. Available from: http://dx.doi.org/10.1371/journal.pone.0293562

iii. Chiumia FK, Chimimba F, Nyirongo HM, Kampira EL, Muula AS, Khuluza F. Adverse Drug Reactions Related with Antibiotic Medicines in Malawi: A Retrospective Analysis of Prevalence and Associated Factors. *Drug Healthc Patient Saf*. 2024;(July):89-101. doi:10.2147/DHPS.S468966

Manuscript under peer review

i. Substandard and falsified antibiotics and their clinical outcomes among hospitalized patients in southern Malawi: A pilot study

CHAPTER ONE: INTRODUCTION

1.0 Chapter overview

This chapter introduces the scope of this study and summarizes the reviewed literature. The available international and local pharmacovigilance structures including the Program for International Drug Monitoring (PIDM) and the operations of the National Pharmacovigilance Centre (NPC) are also explained in the chapter. The chapter explores the global burden of medicine related safety issues such as adverse drug reactions, loss of efficacy, substandard and falsified medicines, and antimicrobial resistance. We also highlight the historical background, basic principles and current practices and regulatory frameworks for pharmacovigilance, which is key to the timely detection, assessment and prevention of medicine related problems and other patient safety issues.

1.1 Background of the study

Medicine-related harm (MRH) is a global health concern [1]. About 10% of patients in high income countries (HICs) experience MRH [2]. Medicine safety data in Low-middle income countries (LMICs) including Malawi is limited. However, several factors such as inadequate resources, poor health care practices and inefficient health systems suggest a higher burden of MRH in LMICs than HICs [3–6]. In response to the increasing incidences of MRH, the World Health Organization (WHO) has been working with member states to develop evidence-based strategies that can mitigate various challenges to achieving safe and efficacious medication and ensuring quality of medicines [7]. Medicine related problems include, among others, adverse drug reactions (ADRs), medication errors, medicine abuse, loss of efficacy, antimicrobial resistance, and product quality defects.

Complementary to other initiatives, the WHO launched 'Medication Without Harm' as a third global patient safety challenge in 2017. This involved a high-level ministerial engagement to table national and global plans for improving the safety of medicines. The goal was to mitigate the burden of MRH by at least 50% by 2022 [8]. In order to achieve this, it requires high level coordination by WHO and commitment of member states through stakeholders such as medicine regulatory authorities, the academia, health facilities and other professional bodies in strengthening national pharmacovigilance systems [1,9].

1.1.1 Pharmacovigilance

WHO defines pharmacovigilance (PV) as the 'science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other possible drug-related problems' [10]. PV aims at early detection of medicine-related problems, sharing the information globally, and establishing risk minimization strategies. The concept of PV was started in the early 1960's due to Thalidomide Tragedy. Thalidomide is now marketed as an immunomodulator for the treatment of various forms of cancer including multiple myeloma [11]. Previously, the medicine was commonly used as a non-barbiturate sedative and an anti-emetic [12]. The use of the medicine for morning sickness during pregnancy was first associated with phocomelia by an Australian physician, Dr Mc Bride who observed increased incidences of babies born with deformed limbs and multiple bone deformities among women who were exposed to the medicine [13]. The events were also confirmed by independent observations in other different countries including Germany. More than 10,000 new-born babies in more than 40 countries were affected by Thalidomide leading to withdrawal of the medicines from the market in 1961 [14,15].

1.1.2 WHO Program for International Drug Monitoring

Following the Thalidomide tragedy, WHO established a program for international drug monitoring (PIDM) in 1968 [16]. This is a system for collaborating global monitoring and reporting adverse drug reactions (ADRs) and adverse events following immunization (AEFI). The centre was established in Geneva, Switzerland and later moved to Uppsala in Sweden, now officially referred to as the Uppsala Monitoring Centre (UMC). Member countries collect Individual Case Safety Reports (ICSRs) through National Pharmacovigilance Centres (NPC). These reports are commissioned into the WHO-UMC database which is referred to as Vigibase®. The reports are analyzed and shared among all other member states for action [17,18]. WHO also plays an advisory role on implementation of risk minimization plans though the Advisory Committee on Safety of Medicinal Products (ACSoMP) [19].

Over the past decades, the scope of PV has been extended from focusing only on adverse drug reactions to other medicine related problems such as product quality defects, inappropriate use of medicines, medication errors and antimicrobial resistance [20].

1.1.3 WHO Global Surveillance and Monitoring System for Substandard and Falsified Medical Products

Quality of pharmaceutical products is another major concern. Poor quality medicines are associated with higher risk of ADRs and other problems such as lack of efficacy [21]. The WHO coordinates monitoring of defective medical products through the Global Surveillance and Monitoring System (GSMS) [22]. This was established in 2012 as a separate arm and had 126 member states as of 2017. Through the initiative, WHO trained more than 500 personnel under various Regional or National Medicine Regulatory

Authorities on conducting post marketing surveillance of medicine quality. The trained personnel work as WHO focal persons who receive reports within the country or region, conduct preliminary investigations and report cases of poor quality products to the GSMS [23]. More than 1500 reports of suspected substandard and falsified medicines had been reported to the GSMS between 2013 and 2017, of which 42% were from African, 21% European, 21% America, 8% Western Pacific, 6% Mediterranean, and 2% South East Asian region [24].

1.1.4 Pharmacovigilance challenges in Africa

Pharmacovigilance principally relies on good safety data collection systems. This requires strong collaborations among countries or regions, and partnership among various professionals and public health programs [25]. Although significant progress has been made over the past decades globally, African countries are lagging in terms of monitoring of medicine safety [26]. Since 1968, when founding members namely: Canada, Australia, Germany, Ireland, Czechoslovakia, Netherlands, New Zealand, United States of America (USA) and United Kingdom (UK) formed the PIDM, African countries started joining the program in 1992; 24 years later [17]. The first African countries to join PIDM were Morocco and South Africa, followed by Tunisia and Tanzania in 1993.

In most LMICs including Malawi, PV systems are not fully functional due to poor regulatory frame work, lack of qualified staff in PV, failure to allocate adequate funding for PV, and lack of integration of essential public health programs with PV [27]. In addition, ADR reporting rate is very low in most of African countries. For instance, by 2015 Africa contributed to only <1% of the total 12 million ICSRs which were submitted to the

Vigibase® [17]. Furthermore, none of the African countries met the WHO requirement of reporting at least 200 reports per million population[28].

Malawi joined the programme as an associate member in 2016 as the 135th country out of the current 155 member states of the PIDM and later became a full member in 2019 [29]. Over the years, the PV centre have been conducting trainings and awareness campaigns on pharmacovigilance principles and practices including the detection and reporting of suspected ADRs and medicinal product quality defects [29]. Further, safety reporting forms were designed and made accessible to health care workers and the public. These PV strategies aim at improving the number of safety reports received at the national PV centre so that preventative measures are taken in a timely manner [27].

1.2 Problem statement

There is a high burden of antibiotic resistance in Malawi [30–32], but data on antibiotic medicine-related problems is limited.

Previous studies reported presence of substandard and falsified medicines including antibiotics in Malawi between 2014 and 2017 [33–37] with a median prevalence of 24.6% (range 12.5-88.4%). The variability in the previous findings would be due to the highly dynamic pharmaceutical market which responds to a number of factors such as disease burden, standard treatment guidelines, regulatory policies and enforcement [38]. The Pharmacy and Medicines Regulatory Authority (PMRA) established the NPC and became a full member of the Program for International Drug Monitoring (PIDM) in 2019. There is a need to evaluate if PV programs are helping to reduce the burden of SF medicines in Malawi. Furthermore, no study has assessed the clinical outcomes associated with the use of SF medicines among patients.

Appropriate use of antibiotics improves patient outcomes and reduces the risk of antibiotic resistance. LMICs face several challenges that hinder the implementation of antimicrobial stewardship strategies. These include: lack of knowledge among health practitioners, limited resources to enable proper diagnosis and high prevalence of substandard antibiotic medicines [39–41]. In addition, the unstable supply of essential medicines in LMICs influence inappropriate selection of antibiotic medicines [42]. Studies done in Malawi have revealed unstable supply of essential medicines including antibiotics [43,44]. However, the impact of availability of antibiotics on prescribing pattern in Malawi also remains unknown.

Knowledge on the quality of antibiotic medicines, factors that affect inappropriate use of medicines and the associated clinical outcomes are critical in coming up with strategies for improving delivery of patient care and curbing antibiotic resistance.

1.3 Justification

1.3.1 Rationale for focusing on antibiotic medicines

1.3.1.1 High burden of bacterial infections

Bacterial infections are amongst the leading causes of mortality globally [45]. Nearly 13% of deaths around the world are attributed to bacterial infections [46]. The burden of bacterial diseases is disproportionally higher in low-middle income countries including Malawi [47]. This is attributable to poor living conditions which are characterized by: malnutrition, indecent housing, lack of clean portable water, poor hygiene and sanitation, and lack of health education and quality health services [48]. In 2019, a bacterial infection-related mortality rate of 230 deaths per 100,000 population was reported in Sub-Saharan

Africa. This was significantly higher than high-income countries which reported a 0.2 fold lower mortality rate of 52.2 death per 100,000 population [46].

1.3.1.2 Presumed demand for antibiotic medicines

The high prevalence of infectious diseases in LMICs has led to overuse and misuse of antibiotics [49–53]. Studies have reported that antibiotic medicines are prescribed to more than 60% of patients who visit a health care facility in LMICs [54–57]. Klein et. al analyzed the global antibiotic consumption between 2000 and 2015 and found that there was a significant correlation between the consumption of antibiotics and country's gross domestic product (GDP) per capita. During the study period, antibiotic consumption rate in LMICs increased by more than 100%, while high income countries(HICs), reported only a 6% increase in antibiotic medicine consumption [58]. Further, it is estimated that antibiotic consumption would increase further by 200% (From 43 billion defined daily doses (DDDs) to 168 DDDs) by 2030, if no intervention will be applied [58]. Among the most used antibiotics in LMICs are penicillins, cephalosporins, quinolones, Nitroimidazoles and macrolides [58,59].

1.3.2. Comparison of antibiotics with other medicine classes

Studies have shown that due to the differences in disease burden and lifestyles, the burden of SF medicines is higher for medicines used for the treatment of infectious disease especially antibiotics and antimalarials in LMICs, while in high-incomes countries the major concern is for medicines which are used for treatment of non-communicable diseases [60,61]. However, Malawi also faces an increasing burden of non-communicable diseases such hypertension and diabetes [62,63]. Thus, to comprehensively understand the problem,

it is also important to compare the quality of antibiotic medicines with the other medicine classes.

1.3.4 Concerns of antibiotic resistance

There are concerns of increasing incidences of antibiotic resistance due to the haphazard use of antibiotic medicines [64,65]. In 2019, it was estimated that about five million deaths were associated with antibiotic resistance globally. Death associated with antibiotic resistance was highest in sub-Saharan Africa, with 98.9 deaths per 100,000 while in high-income countries the rate was 55.7 deaths per 100,000 [66]. The high burden of antibiotic resistance in low-middle income countries (LMICs) is attributed to both high and inappropriate use of antibiotics [67]. With increased exposure to antibiotic medicines, bacteria tend to reduce the effectiveness of the medicines through molecular mechanisms such as bio-inactivation of the active compounds, alteration of the target molecules, reducing the permeability to the medicines and blockade of the metabolic pathways [68]. In LMICs, AMR is further perpetuated by the weak regulations and antimicrobial stewardship, self-medication by the public, lack of compliance to prescribed antibiotic treatments, poor quality of antibiotic medicines, and inappropriate antibiotic use [69].

1.4 Study aims and objectives

1.4.1 Broad Objective

To assess the quality, availability and use of antibiotic medicines and the associated clinical outcomes in Southern Malawi

1.4.2 Specific Objectives

I. To assess the factors associated with substandard and falsified antibiotics and other selected medicine classes (antimalarials, antihypertensives and antidiabetics)

II. To evaluate the effect of antibiotic medicine availability on adherence to standard treatment guidelines

III. To characterize adverse drug reactions related with antibiotic therapy

IV. To determine the association between the substandard and falsified antibiotic medicines and clinical outcomes

CHAPTER TWO: LITERATURE REVIEW

2.0 Chapter overview

This chapter focuses on the pharmacovigilance methods and how they are applied in various studies to evaluate medicine-related problems (MRPs). It covers various MRPs including adverse drug reactions (ADRs), substandard and falsified (SF) medicines and medication errors.

2.1 Pharmacovigilance Methods

2.1.1 Passive pharmacovigilance methods

Spontaneous reporting is the most widely used method for collection of safety data in real life situations. Health care workers, patients or members of the public associates an observed adverse event with a medicinal product and voluntarily reports to the regulatory authorities [70]. National Pharmacovigilance Centres (NPCs) use data from spontaneous reports to generate safety signals. In PV, a signal refers to new information from one or multiple sources which suggests a causal association between a treatment and an adverse effect [71].

A spontaneous report is an unsolicited communication from an individual (such as a healthcare worker or patient) to a company or a regulatory authority that describes a suspected adverse drug reaction or any other medicinal product-related problem [72]. Despite the low costs associated with spontaneous reporting, under-reporting is one of the major problems [73]. This is due to a number of factors including lack of knowledge, complacency, fear of litigation and heavy workload among health care providers [74].

2.1.2 Active pharmacovigilance methods

Active surveillance methods are initiated to complement spontaneous reporting. These methods aim at achieving a higher number of safety reports in a more organized fashion or to confirm a hypothesis that was generated through spontaneous reporting. Active surveillance is done through several ways such as sentinel site surveillance, targeted reporting, intensified reporting, linkage of hospital records, cohort event monitoring and epidemiological research methods [75].

2.1.3 Application of trigger tools in active surveillance

Detection of adverse drug reactions is a challenging [76]. Most ADRs present in a similar manner to disease signs and symptoms. In addition, health care workers may struggle to associate a medicine to an ADR with long time to onset [74,77]. Trigger tools are used in clinical settings for rapid screening of patient case management files to enhance detection of adverse events. They comprise of a list of pre-defined clues that indicate a possible harm in a patient such as de-challenge, ordering of new medicines and dose titration [78].

In 2000, the Institute for Healthcare Improvement (IHI) through a group of academic and clinical experts began to develop lists of triggers which were tailored to specific clinical sites and fields. Later these were combined to form the IHI global trigger tool which can be largely used at hospital level and for research purposes [79]. The global trigger tool comprises of a comprehensive list of clues such as switching or abrupt stop of medication, prescribing of new medicines such as antidotes, dose titration and lack of efficacy [80].

2.2 Adverse drug reactions

The WHO defines an adverse drug reaction (ADR) as ‘a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis,

or therapy of diseases or for modification of physiological function' [81]. This definition is limiting as it excludes harm caused by a medicine due to medication errors, medicine misuse or abuse and occupational exposure. However, the WHO definition is suitable for characterizing events that occur when the product or medicinal agent is used within the terms of the marketing authorization [82]. In 2000, Edwards and Aronson expanded the ADR definition to an 'appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration, and warrants prevention or specific treatment, alteration of dosage regimen, or withdrawal of the product [83].

ADRs have serious negative impact on the patient and health care system[84]. Globally, about 24% of older adult patients [85] and 8% of patients receiving primary health care in Europe and United States of America experience at least one ADR [86]. About 5-8% % of ADRs are serious [87] and at least 1% of ADRs lead to patient death [88]. ADRs have also been reported to cause hospitalization or lead to prolonged hospitalization in almost 10% of patients [89,90]. Usually, ADRs are managed through switching of therapy, and in some cases prescribing new medicines in order to counter the adverse effects. This contributes to increased total cost of treatment [83]. The total cost of ADR treatment is estimated at $30 billion in the USA [91] and £2.2 billion in the UK [92].

2.2.1 Classification of adverse reactions

ADRs are characterized based on the nature, mechanism of action, severity, and preventability. Rawlins and Thomson categorized ADRs into two major classes: Augmented and Bizarre ADRs.

2.2.1.1 Augmented ADRs (Type A)

Type A ADRs are most prevalent and account for >80% of ADRs [93]. They are predictable based on the pharmacological properties of the medicine. Usually, they present as exaggerated known effects or secondary effects of the medicine [94]. For example, the occurrence of bleeding following warfarin administration is pharmacological plausible and dose related [95].

2.2.1.2 Bizarre ADRs (Type B)

Type B are rare ADRs and are not easily predictable as they do not have a direct relationship with the pharmacological properties of a medicine [96]. Mechanisms of type B ADRs are either immunological or idiosyncratic. Most of them are complex to manage, present with life threatening symptoms and are associated with high mortality [97,98]. Examples include Steven Johnson's Syndrome (SJS) or Toxic Epidermal Necrolysis (TEN) following administration of allopurinol [97].

2.3 Medicine quality

Substandard and falsified (SF) medicines are global public health concerns [99]. Substandard medical products are also referred to as 'out of specification' products [24]. These are "authorized medical products that fail to meet either their quality standards or specifications or both" [100]. This is caused by limitations during manufacturing processes or post-production degradation, for instance due to subjection to poor handling and storage [101]. On the other hand, falsified medical products are "medical products that deliberately or fraudulently misrepresent their identity, composition or source" [100]. Undesirable characteristics of SF medicines such as inadequate content of active pharmaceutical

ingredient (API), may lead to harmful effects such as lack of response to treatment, adverse drug events, mortality, and antimicrobial resistance [102].

In 2017, WHO estimated that the prevalence of SF medicines was 10.5% [24]. The burden of SF medicines is high for African countries with a prevalence of 18.9%. For Asian countries, the prevalence is about 10.2%, while for other countries (especially HICs), the prevalence is as low as below 1% [60].

2.3.1 Techniques for detecting SF medicines

Various techniques are used to evaluate the quality of medicines. Official tests are designed to evaluate medicine specifications as defined in official pharmaceutical literature such as the Pharmacopeia. Such tests include quantification of active pharmaceutical ingredients (API), evaluation of weight variation and dissolution test.

2.3.1.1 Screening techniques

Not all quality parameters require sophisticated laboratory equipment for testing. Fast and affordable but effective methods are available for screening purposes.

2.3.1.2 Visual Inspection

Assessment of physical characteristics for dosage forms is widely used as part of in-process controls, evaluation of finished products and during post-marketing surveillance. Any formulation defects such as presence of breakages, cracks or abrasions, non-uniformity of color or shape, and presence of microbial or particulate contaminants may indicate significant quality problems. Dosage form units are visually inspected for such defects including integrity of packaging and labelling, organoleptic properties such as smell and flavour to detect quality problems [103].

2.3.1.3 Thin layer chromatography (TLC)

TLC is an analytical technique that separates non-volatile compounds based on the differential affinities towards a stationery and mobile phase [104]. Liquid extraction is first applied to extract the API from pharmaceutical formulations. The solutions containing the API are spotted on a solid stationary phase such as silica or alumina gel matrix plate (also referred to as chromatoplates). Spotted plates are placed in a development chamber containing appropriate solvent or solvent mixture (mobile phase). The mobile phase elutes the compounds spotted in the chromatoplate depending on their relative affinity [105]. The retention factor (Rf value) of the sample spot is compared to the standard to confirm the identity of the API. The Rf value is calculated using the formula:

$$Rf\ value = \frac{Distance\ travelled\ by\ compound}{Distance\ travelled\ by\ solvent\ front}$$

In principle, the distance travelled by the principal spot confirms the identity of the compound if it is equal to distance travelled by the standard. On the other hand, the size and intensity of the spot indicates the relative content of API in the formulation. Generally, ultraviolet (UV) active compounds are visible under UV light (usually 254nm and 366nm). For non-UV active compounds, various staining techniques such as iodine and ninhydrin staining are used to visualize the spots [106]. **Figure 1** below illustrates the principle of TLC and the detection of sample spots under UV light and iodine staining.

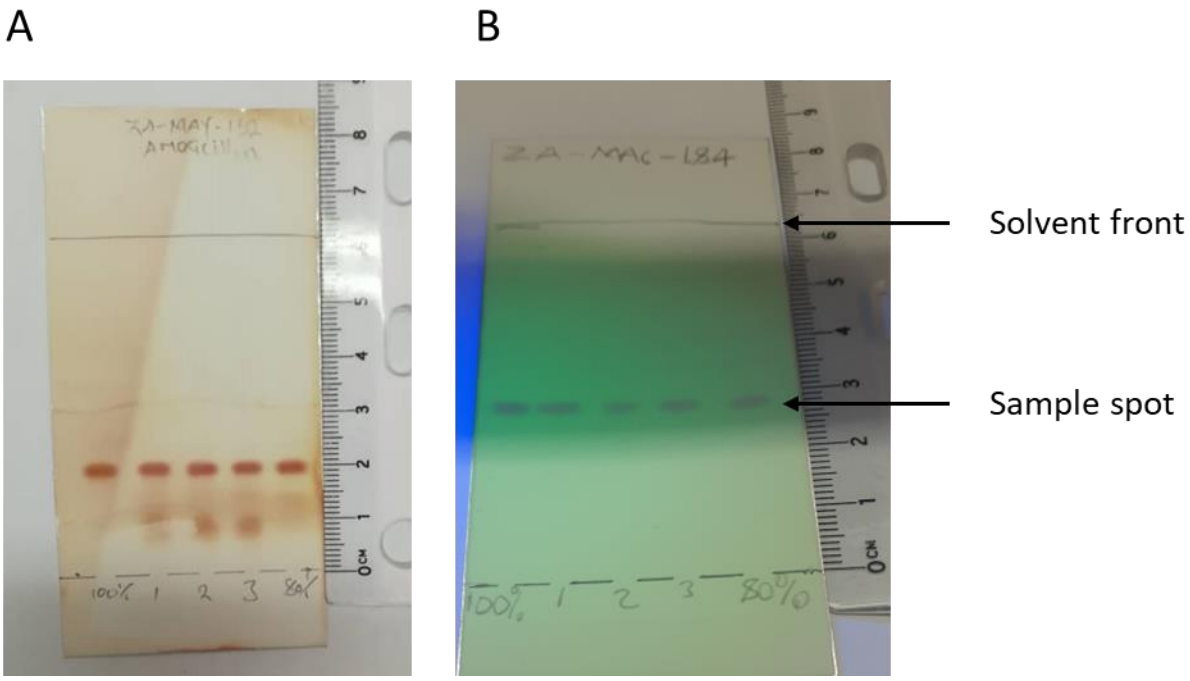

Figure 1 Principle of Thin Layer Chromatography (TLC)

A. TLC visualization using iodine staining. A sample drug is spotted in triplicate (labelled 1, 2 and 3) between a 100% concentration standard(left) and 80% concentration standard (right). The retention factor value (rf value) is used for detection, while the size of the spots represents an estimated concentration of the active ingredient. **B**. TLC visualization under ultraviolet light.

2.3.1.4 Disintegration time test

The bioavailability of a medicine is dependent on the disintegration and subsequent dissolution of the formulation [107]. Disintegration time test is a screening method used to predict the ability of the formulation to demonstrate adequate dissolution [108]. To perform disintegration test, dosage units are placed in baskets containing perforated floaters. The baskets are raised and lowered into a chamber containing water or simulated gastric fluid at 37^{o}C. The time taken for the dosage unit to completely break down is recorded [109].

2.3.1.5 Confirmatory test methods

Pharmacopeial methods are gold standards for evaluating quality of medicines [110]. Thus, medicines suspected to be of poor quality upon screening are supposed to be confirmed by official pharmacopeial methods to ensure reliability of the results.

2.3.1.6 High performance liquid chromatography (HPLC)

HPLC is a highly sophisticated chromatographic technique widely applied in analytical chemistry [111]. Its principle is based on separation of compounds in a column containing tightly packed polymeric solid phase using a mobile phase that is pumped through the column at very high pressure. The separation column in HPLC is composed of material with very small pore sizes, thereby increasing the separation efficiency. Compounds are eluted from the column at different times based on their polarity. Eluted compounds are subjected to a detector such as ultraviolet/visible (UV/Vis) spectrophotometer or diode array detector (DAD) which quantifies the compounds by measuring the absolute absorbance under a pre-defined and set wavelength [112].

2.3.1.7 Dissolution

Solid dosage forms must be changed into solution form in vivo to allow adequate absorption and distribution to the site of action. Dissolution measures the release of the API from the formulation under simulated conditions using a dissolution test apparatus [107]. Dosage units are placed in dissolution vessels filled with appropriate solvents and agitated for 30-60 minutes using a basket (apparatus I) or paddle stirrer (apparatus II). Samples are taken and subjected to pharmacopeial assay (e.g. HPLC assay) to measure the absolute quantity of the dissolved drug [113].

2.4 Medication errors

The US National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) defines a medication error as 'any preventable event that may cause or lead to inappropriate use or patient harm while the medicine is under control of the health care professional, patient, or consumer' [81]. Medication errors can occur at any stage of medication such as prescribing, preparation, dispensing, administration, and monitoring. Medication errors may be in different forms such as wrong dose, missed dose, or skipped patient monitoring [114].

Medication errors are an important cause of MRH [115]. About 50% of preventable MRH are caused by medication errors [116]. Medication errors affect over 7 million patients in a year. At least one patient dies in a day due to medication errors in the USA [117]. Medication errors are also associated with negative economic impacts [118]. The total cost of managing medication errors is estimated between 5 to 21 billion pounds in Europe alone [116]. There is limited data on the prevalence of medication errors in LMICs, but it is estimated that impact associated with medication errors would be more than 2-fold in terms of mortality [117].

2.5 Importance of standard treatment guidelines

Poor health care practices, inadequate resources such as medicines and health care professionals and poor communication among health care workers are among the factors contributing to high incidence of MRH especially in LMICs [119,120]. Standard treatment guidelines (STGs) provide evidence-based guidance on systematic prescribing, dispensing, administration of medicines and necessary patient monitoring [121]. This improves rational use of medicines, quality of care and significantly reduces the incidence of medication

errors, adverse drug reactions and mortality [121]. Further, STGs help in achieving more accurate forecasting of medicine demand and improve efficiency in the medicine supply chain. This therefore, helps to reduce medicine stock outs and health costs [122].

CHAPTER THREE: MATERIALS AND METHODS

3.0 Chapter Overview

In this chapter, we provide details of the approach taken to address each research question in this study. We here discuss the design of the studies and how the study places were selected, description of study populations and applied sampling methods and calculation of the sample size. The chapter also provides details on how data was collected, managed and the statistical analysis applied to answer each research question.

3.1 Study Design and Setting

The studies in this thesis combined cross sectional and retrospective study designs. All studies were conducted in Zomba, Machinga and Nsanje districts. The districts were randomly sampled among the 13 districts in southern region of Malawi using RAND function in Microsoft Excel. For each district, we targeted to select a district hospital (secondary hospital), four public primary health facilities (health centres), four faith-based primary health facilities and four private pharmacies by stratified random sampling. Since Zomba district does not have a district hospital, we included Zomba Central Hospital. Further, there were only three faith-based primary health care facilities in Nsanje district, and only two private pharmacies (one in Zomba and another one in Machinga) permitted us to conduct the study at their premises. Thus, the studies were conducted in 29 health facilities.

Study I was conducted in all public, faith-based, and private health facilities at all levels of care (primary, secondary, and tertiary level health facilities). Study II, III and IV involved hospitalized patients and therefore, were conducted at Zomba Central Hospital, Machinga

and Nsanje District Hospitals. This is because primary level facilities do not have inpatient care services. The other facilities were included in Study I were Nkasala, Thondwe, Machinjiti, St Luke's, Makwapala, Chamba, Mayaka, Matiya health centres and Good Health Pharmacy in Zomba; Chididi, Mbenje, Tengani, Phokera, Kalemba, Sankhulani, and Trinity in Nsanje; and Med Bag Pharmacy, Gawanani, Machinga, Mpiri, Mposa, Chikweo, Namandanje, Namanja and Nayuchi health centres in Nsanje. The geographical distribution of the study sites is shown in **Figure 2** below.

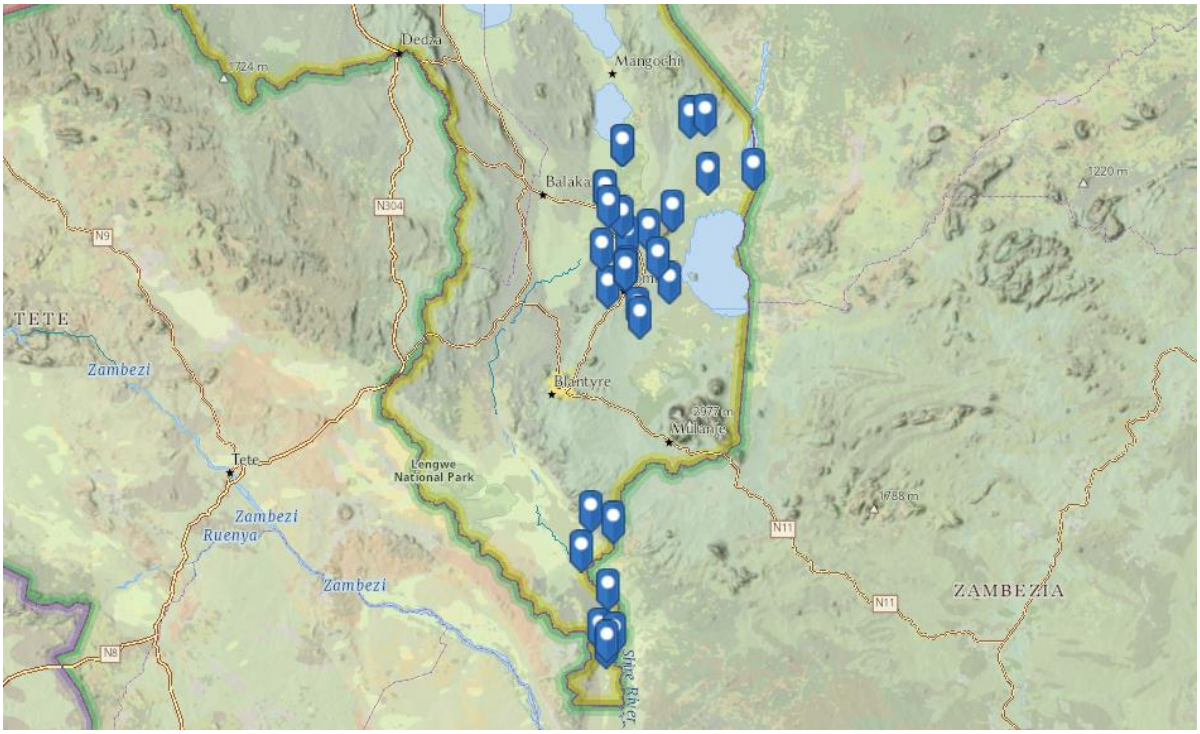

Figure 2 Map of Southern Malawi showing geographical distribution of study sites

Created by ArcGIS https://www.arcgis.com/index.html#

3.2 Population and sample size

Apart from bacterial infections, malaria is another common disease which is endemic across the country affecting both children and adults [123]. Over the past decade, there has also been an increase in the prevalence of non-communicable diseases such as hypertension

and diabetes [62,63]. We therefore compared the prevalence of SF antibiotics with antimalarials, antihypertensives and antidiabetics in study I. A total of 293 medicine samples of commonly used medicines among antibiotics, antimalarials, antihypertensives and antidiabetics were sampled. Our definition of a sample was: part of a medicine batch (minimum of 20 dosage units) collected at a particular facility at a specified point in time. The selection of the medicines was in accordance with the Malawi Essential Medicines List (MEML) and the Malawi Standard Treatment guidelines (MSTG) of 2015, which was the latest version at the time of study. We included oral medicines used as first line or alternative treatments for common bacterial infections, malaria, hypertension and diabetes mellitus type II in Malawi [124]. For antimalarial medicines, further guidance was sourced from the Malawi National Malaria Guidelines 2013 [125] that result in addition of Malawi's second line antimalarial medicine (artesunate/amodiaquine) and first line antimalarial for pregnant women (Quinine oral tablets). Medicines included in the study were: amoxicillin, azithromycin, cefuroxime, ciprofloxacin, flucloxacillin among antibiotics; quinine, fixed dose combination of artemether/lumefantrine, artesunate/amodiaquine, sulfadoxine/pyrimethamine among antimalarils amlodipine, atenolol, Enalapril, methyldopa and Hydrochlorothiazide among antihypertensives; and metformin and glibenclamide among antidiabetic medicines.

Study II, III and IV involved hospitalized adult patients. A total of 322 patient records were randomly sampled across the three facilities. Sample size was determined using a single population proportion formula $n=p(1-p) *Z^2/d^2$ [126]. We assumed 30% as expected ADR prevalence (p) [127], 0.05 margin of error (E) and 1.96 Z value corresponding to 0.05 significance level.

3.2.1 Inclusion Criteria

- Hospitalized patients in the medical ward.
- Age ≥ 18 years old.
- Prescribed antibiotic medicines as the main treatment

3.2.2 Exclusion criteria

- Medical records with missing information such as medication charts and demographic data.
- Readmissions where previous medical records were not available.

On the availability of antibiotic medicines, we purposively selected 16 antibiotic medicines among the first- and second-line recommended treatments for common bacterial infections in Malawi as stated in the latest edition of Malawi Standard Treatment Guidelines (MSTG) [124]. We included gentamicin, ceftriaxone, erythromycin, azithromycin, clarithromycin, metronidazole, amoxicillin, cloxacillin, flucloxacillin, benzyl penicillin, benzathine penicillin, ciprofloxacin, nalidixic acid, co-trimoxazole, doxycycline and meropenem. Unlike the other antibiotics, meropenem and clarithromycin are purportedly only found in tertiary level hospitals, as they are reserved for rare and life-threatening conditions caused by multi-drug resistant bacteria [128].

3.3 Data Collection

3.3.1 Data for quality of medicines

For study I, we collected basic information of the medicines such as trade name, strength of dosage units, batch numbers, expiry date, and stated manufacturer from the labeling on the primary or secondary packages using a data collection form. To acquire the minimum amount of dosage units for conducting each of the required pharmaceutical tests, we

targeted to collect at least 80 dosage units from the sample container and transported the samples to the Kamuzu University of Health Sciences for quality analysis. Where the available stock at facility was low, fewer but more than 20 dosage units were collected.

3.3.1.1 Visual inspection

All the dosage units per sample were subjected to visual inspection guided by a checklist. This involved physically assessing each dosage unit for the presence of any defects such as non-uniformity of color, size and shape, or presence of breakages, cracks, abrasions and any visible microbial or particulate contaminants.

3.3.1.2 GPHF Minilab® protocols

Three dosage units per sample were subjected to semi-quantitative analysis of the content of API using thin TLC according to the Global Pharma Health Fund (GPHF) minilab® protocols test [129]. Triplicate test samples were spotted on a TLC plate using a 2µl capillary tube and compared with standard spotting of both 80% and 100% concentration on the same plate. A sample failed the test if at least one of the sample spotting presented a difference in terms of travel distance, size, and intensity of spot with reference to the standard spotting. **Table 1** below indicates the conditions for running TLC using GPHF minilab®.

Table 1: Summary of analytical conditions used for GPHF Minilab test

Medicine Sample	Solvent	Mobile phase	Detection
Amlodipine 5 or 10mg	Methanol	Water: Acetonitrile: Acetic acid (50:25:25)	UV light
Amoxicillin 250 or 500mg	Acetone	Ethyl acetate: Acetic acid: Water (60:20:20)	Iodine stain
Atenolol 50mg	Methanol	Methanol: Ammonia (90:10)	UV light
Ciprofloxacin 250 or 500mg	Methanol	Methanol: Acetone: Toluene: Ammonia (50:12.5:12.5:25)	UV light
Enalapril 5 or 10mg	Ethanol	Acetic acid: Water: Butanol (15:25:60)	UV light
Glibenclamide 5mg	Methanol: Ethyl acetate (50:50)	Ethy acetate: Methanol: Toluene: ammonia (60: 30: 5: 5)	U/V light
Gentamicin	Water	13.5M ammonia: chloroform: methanol (1:1:1)	Ninhydrin stain
Hydrochlorothiazide 25mg	Acetone	Ethyl acetate	U/V light
Lumefantrine/artemether 120mg/20mg	Acetone	Ethyl acetate: Acetic acid: Toluene (10: 15:75)	U/V light and Iodine stain
Metformin 500mg	Water	Acetic acid: Butanol: water (10:40:50)	U/V light
Methyldopa 250mg	Methanol	Acetone: Acetic acid: Toluene: Water (25:25:25:25)	Iodine stain
Quinine 300mg	Methanol	Methanol: Ammonia (95:5)	UV light
Sulfadoxine/pyrimethamine 500mg/50mg	Methanol	Ethyl acetate: Methanol (75:25)	UV light and Iodine stain

3.3.1.3 Disintegration time testing

The ZT 31 Erweka® instrument was used for disintegration time test. We used water as medium and a temperature of 37ºC for all types of medicine samples. Six dosage units per sample were run for the test and all the dosage units were required to completely disintegrate (state at which no residue of dosage form is observed, except tablet or capsule coatings) within 30 minutes to pass the test.

3.3.1.4 Pharmacopeial assay methods

Twenty dosage units per sample were subjected to a pharmacopeial assay. We used Agilent® 1120 High Performance Liquid Chromatography (HPLC) or Biobase® Ultra-violet/ Visible (UV/Vis) spectrophotometry according to methods provided in the British and Indian Pharmacopeia [130,131]. In general, all 20 dosage units were weighed individually and crushed into powder. An aliquot of the powder was weighed and dissolved into a suitable solvent and further diluted to a desirable concentration. For HPLC, standard drugs were prepared under similar conditions used for sample preparation. All samples were filtered using EDM PTFE Millipore® filters, 0.45µm filters before injecting for analysis.

The amount of API present in the sample upon HPLC analysis was determined using the following equation:

$$\%\ determination\ of\ drug\ content = \frac{A_t}{A_s} \times \frac{W_s}{W_t} \times P_M;$$

Where A_t and A_s are the peak areas for the sample and standard solution respectively, W_t and W_s are the weights in final dilution of the sample and standard solution respectively and P_M is the potency of the main ingredient for the reference standard.

For U/V Vis assay, we used the following equation:

$$\%\ determination\ of\ drug\ content = \frac{A_t}{A\ (1\%,1cm)} \times \frac{10mg/ml}{W_t} \times 100\%;$$

Where A_t is the absorbance of the sample, W_t is the weight of sample in final dilution and A (1%,1cm) is the specific absorbance (defined as the maximum absorbance of 1% solution or 10mg/ml standard sample) at the pre-determined wavelength [132].

Table 2 indicates the analytical conditions for each sample during assay analysis.

Table 2: Summary of HPLC assay methods used in the study

Medicine sample	Column type	Mobile phase / Solvent*	Flow rate	Injection volume	Detection ƛ
Amoxicillin	C18 25cm x4.6mmx5µm	Mobile Phase A: Acetonitrile: Buffer (1:99) Mobile Phase B: Acetonitrile: Buffer (20:80) Buffer = 0.05M Potassium dihydrogen phosphate, PH adjusted to 5 using 2M sodium hydroxide (Mobile phase A:B =80:20)	1ml/min	50µl	254nm
Medicine sample	**Column type**	**Mobile phase / Solvent***	**Flow rate**	**Injection volume**	**Detection ƛ**
Benzylpenicillin	C18 25cm x4.6mmx5µm	Mobile phase A: 0.01M potassium dihydrogen phosphate Mobile phase B: Methanol (Mobile phase A:B =40:60)	1ml/min	50µl	225nm
Ceftriaxone	C18 25cm x4.6mmx5µm	Mobile phase A: Acetonitrile: Buffer (1:99) Mobile phase B: Acetonitrile: Buffer (20:80) Buffer = 0.2M potassium dihydrogen phosphate, adjusted to PH 5 using sodium hydroxide (Mobile phase A:B =20:80)	1ml/min	50µl	254nm
Medicine sample	**Column type**	**Mobile phase / Solvent***	**Flow rate**	**Injection volume**	**Detection ƛ**
Atenolol*		Methanol			275nm
Ciprofloxacin	C18 25cm x4.6mmx5µm	Mobile phase A: 0.245% orthophosphoric acid , adjusted to PH 3 Mobile Phase B: Acetonitrile (Mobile phase A: B = 87:13)	1.5ml/min	10µl	278nm
Metformin*		Water			232nm
Sulphadoxine/ pyrimethamine	C18 25cm x4.6mmx5µm	Mobile Phase A: 0.1% orthophosphoric acid Mobile Phase B: Acetonitrile (Mobile phase A: B = 55:45)	1.2ml/min	10µl	254nm

* Applied U/V Vis Assay

3.3.1.5 Dissolution test methods

We used PharmaTest®1200 dissolution apparatus to perform dissolution analysis according to methods provided in the British or International Pharmacopoeia [130,131]. Only amoxicillin, atenolol, ciprofloxacin, and metformin were subjected to dissolution test under the conditions stated in **Table 3**. For each medicine sample, the among of API dissolved was determined by the corresponding assay as indicated above.

Table 3: Summary of Dissolution methods used in the study

Medicine sample	**Dissolution apparatus**	**Medium (Volume)**	**Temperature /Speed**	**Sampling time**
Amoxicillin	Apparatus I	Water (900ml)	37ºC/75rmp	30 min
Atenolol	Apparatus II	Water and Methanol (900ml)	37ºC/50rmp	45 min
Ciprofloxacin	Apparatus II	Water (900ml)	37ºC/50rmp	30 min
Metformin	Apparatus II	0.68% Potassium dihydrogen phosphate adjusted to PH 6.8 by 1M NaOH (900ml)	37ºC/100rmp	30 min

3.4.1.6 List of laboratory reagents/chemicals

Table 4: Sources of laboratory reagents and chemicals used in the study

Name of reagent/chemical	Name of manufacturer	Country of Origin
Triethylamine	Fisher Chemicals	United Kingdom
Acetone	Glassworld	South Africa
Acetonitrile Analytical grade	Glassworld	South Africa
Acetonitrile HPLC grade	Merck KGaA	Germany
Methanol Analytical grade	Glassworld	South Africa
Methanol HPLC grade	Merck KGaA	Germany
Orthophosporic acid 85%	ACE Chemicals	South Africa
Potasium dihydrogen phosphate	ACE Chemicals	South Africa
Butan-1-ol	Skylabs	South Africa
Buffer solution PH 4	Skylabs	South Africa
Buffer solution PH 7	Skylabs	South Africa
Glacial acetic acid HPLC grade	Fisher Scientific	United Kingdom
Hydrochloric acid 32%	Kayla Africa	South Africa
Sodium hydroxide pellets	Spanlab	India
De-ionised water	Suez® deionizer machine coupled with AU480 (Kamuzu University of Health Sciences)	Malawi
Trifluoroacetic acid	Merck KGaA	Germany
Ciprofloxacin standard (>98%)	Tokyo Chemical Company	Japan
Amoxicillin standard (>98%)	Tokyo Chemical Company	Japan
Sulphadoxine standard (>98%)	Tokyo Chemical Company	Japan
Pyrimethamine standard (>98%)	Tokyo Chemical Company	Japan
Benzylpenicillin standard (>98%)	Tokyo Chemical Company	Japan
Ceftriaxone standard (>98%)	Tokyo Chemical Company	Japan
Ammonia solution 25%	Skylabs	South Africa
Toluene	Merck KGaA	Germany
Ethyl acetate	Skylabs	South Africa

3.3.2 Data for medicine availability

For study II (Objective I only), we reviewed stock cards in medicine storage facilities to collect data on the availability of 16 targeted antibiotic medicines on the day of data collection (point availability) and over the past six months using a structured questionnaire. The overall stock out of antibiotic medicines was calculated using as n/N*100, where n is the number of medicines available within the therapeutic category and N is the total number of medicines that should be available as per the list of medicines prepared. This formula has also been applied in other similar studies [133,134]. For stock out duration for each antibiotic medicine, we calculated the days which were recording a zero stock at hand in the stock card records.

3.3.3 Patient data

For study II (Objective II and III), study III and IV, we abstracted demographics and clinical data such as patient diagnosis and prescribed medicines from case management files of eligible patients. The data was collected by the primary investigator who is a registered pharmacist with special training on the detection and assessment of ADRs. He was assisted by clinicians and other pharmacists in the study sites. For each of the facilities, there were at least a medical doctor and two pharmacy personnel (pharmacist and pharmacy technician who are holders of degree and diploma in pharmacy respectively) who were trained in pharmacovigilance and oriented on the study protocol. The clinicians were mainly consulted to clarify on the clinical assessments and interpret any laboratory tests conducted. The pharmacovigilance team lead in Malawi was also consulted during assessment of cases. The facilities use a robust health management information system (HMIS) where

responsible officers assemble all discharged filed and systematically arranges them by wards, thus making the access and retrieval of the required data simple.

Antibiotic treatment was compared with treatment protocols in of the 2015 edition of Malawi Standard Treatment Guidelines (which was the latest during the period of study) for the specified diagnosis to assess for adherence to treatment guidelines. We considered non-adherence to guidelines if the patient was prescribed and administered a medicine other than the one recommended in the MSTG for the stated diagnosis in the absence of a clear contraindication for the recommended medicine.

We further applied the global trigger tool (**appendix I**) for the detection of adverse events (AEs). This tool was developed by the Institute for Healthcare Improvement (IHI) 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, abnormal laboratory results, and changes in patient prognosis [80]. 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' [81]. This definition is applied in most of similar studies [135] as it excludes events that occur when the product is used outside the terms of marketing authorization and occupational exposure [135]. Suspected adverse drug reactions (sADRs) were identified by searching for triggers such as administration of anti-emetic medicines, and any documented events that were experienced by patients after administration of antibiotic medicines. All suspected ADRs (sADRs) were assessed using various tools as indicated in **Figure 3**.

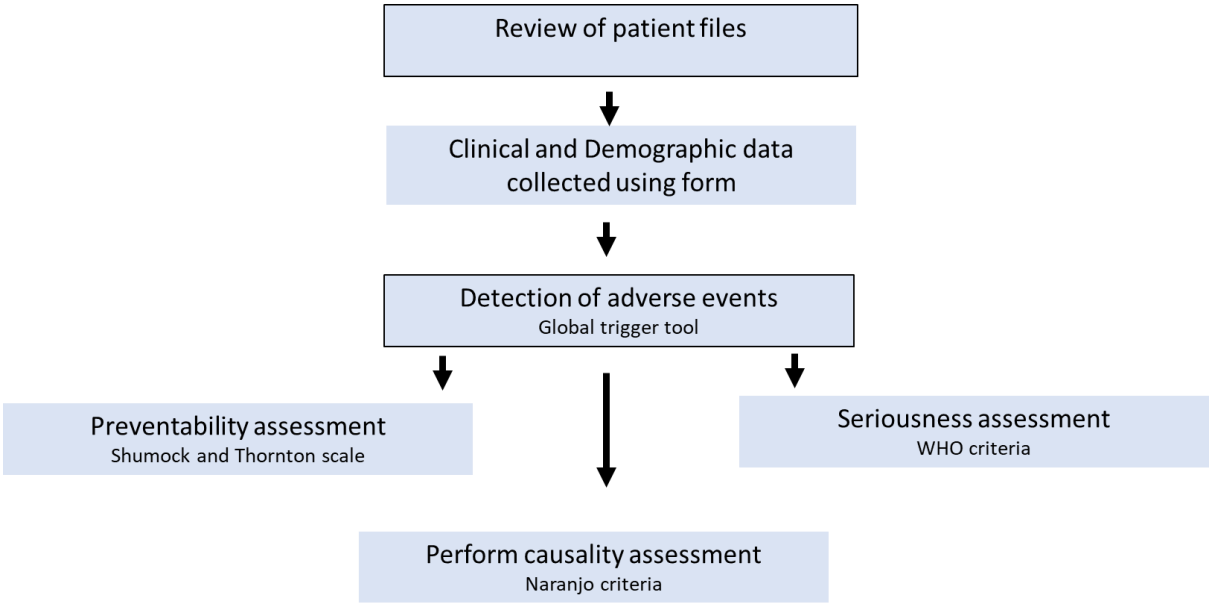

Figure 3: Tools used for assessment of suspected adverse drug reactions

Firstly, sADRs were subjected to causality assessment using Naranjo criteria (**appendix II**) [136]. The Naranjo criteria is an algorithmic causality assessment tool that uses weighted questions to categorize AEs as definite, probable, possible and unlikely or doubtful ADRs based on the gathered clinical and drug information [137]. The algorithm was developed in line with the Bradford Hill criteria for establishing a causal association in observational studies [138]. It is one of the most widely used causality assessment tool and applied in several studies [95,126,139–142] due to its simplicity and clarity of use, and reduced inter- and intra-rate dissimilarity [143,144]. A list of 10 questions is included in the algorithm to assess certain aspects such as temporal plausibility for drug exposure, consistency, specificity, biological plausibility of the event and other related patient characteristics [139]. The answers to the questions are either 'yes', 'no' or 'don't know', with scores for each answer being -1, 0, +1 or +2. **Table 5** shows a list of questions used

in the Naranjo causality assessment tool, their corresponding scores and interpretation of the scores.

Table 5: Naranjo criteria for assessment of suspected adverse drug reactions

Question	Yes	No	Do Not Know	Score
1. Are there previous conclusive reports on this reaction?	1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	2	-1	0	
3. Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	1	0	0	
4. Did the adverse event reappear when the drug was readministered?	2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	2	0	
6. Did the reaction reappear when a placebo was given?	-1	1	0	
7. Was the drug detected in blood or other fluids in concentrations known to be toxic?	1	0	0	
8. Was the reaction more severe when the dose was increased or less severe when the dose was	1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0	
10. Was the adverse event confirmed by any objective evidence?	1	0	0	
	Total Score:			

Interpretation of scores:

≥9 = Definite: The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.

5 – 8 = Probable: The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by

withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.

1-4 = Possible: The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.

0 = Doubtful/ unlikely: The reaction was likely related to factors other than a drug.

We used the WHO classification for seriousness of sADRs (**appendix III**). These criteria classify an ADR as either serious or non-serious. A serious sADR is described as an event that either causes death of patient, is life-threatening, is permanently or significantly disabling, requires or prolongs hospitalization, causes a congenital anomaly, requires a medical intervention to prevent impairment or permanent damage, or other medically important conditions [145,146]. Globally, the WHO classification for seriousness is also applied in signal prioritization and for determining which sADRs are reportable to the national PV centre [146,147].

Preventability was based on the Schumock and Thornton scale (**appendix IV**). The Shumock and Thornton scale has been used in various studies [141,142,147,148] to classify ADRs as either preventable or not preventable. It consists of seven questions with dichotomous answers (Yes or No) which seeks to establish the appropriateness of the administered drug, dosage and route of administration, performance of required therapeutic monitoring for medicines with known risks, documentation of previously occurred type B ADRs including allergies, involvement of a drug-drug interaction, and adherence to treatment [149]. The ADR is classified as preventable if any of the answers to the questions is a 'Yes'. The seven questions applied in the Shumock and Thornton scale are as follows:

1. *Was the drug involved in the ADR not considered appropriate for the patient's clinical condition?*
2. *Was the dose, route, and frequency of administration not considered appropriate for the patient age, weight, and disease state?*
3. *Was required therapeutic drug monitoring or any other necessary laboratory test not performed?*
4. *Was there history of allergy or previous reaction to the drug?*
5. *Was a drug interaction involved in this reaction?*
6. *Was a toxic serum drug level documented?*
7. *Was poor compliance involved in this reaction?*

3.4 Statistical analysis

All data were entered into Microsoft excel and exported to STATA version 14.1 for statistical analysis. Descriptive statistics were presented in terms of means, medians, interquartile ranges, frequencies, and percentages. We used skewness and kurtosis tests and histogram plots to assess the normality of numerical data. The student's t-test and Wilcoxon-Mann-Whitney test were used to assess mean differences between groups for normal and non-normal variables respectively. Chi square test or fisher's exact test (depending on sample size and cell numbers) were used to determine the association between various categorical variables. To further assess the strength of association between variables, we applied logistic regression analysis. We used both univariate and multivariate analysis where odds ratios were adjusted by controlling for potential confounding variables. A P value of < 0.05 was considered statistically significant.

CHAPTER 4 RESULTS

4.0 Chapter Overview

This chapter presents the findings of this thesis. The results are in the form of three published papers and one manuscript which was submitted to a peer reviewed journal.

4.1 Burden of and factors associated with poor quality antibiotic, antimalarial, antihypertensive and antidiabetic medicines in Malawi

4.1.1 Overview of the paper

This paper presents findings of the cross-sectional assessment on quality of antibiotics, antimalarials, antihypertensives and antidiabetic medicines. In brief, we found that the prevalence of substandard medicines is in line with the WHO estimates for LMICs. By medicine classes, the prevalence of substandard antibiotics was higher as compared with the other medicine classes. The substandard medicines were associated with local manufacturing and bulk plastic packaging. We therefore recommend to the Ministry of Health to increase awareness on SF medicines and allocation of resources for strengthening pharmaceutical quality assurance systems at the PMRA, Central Medicine Stores Trust (CMST) and all health facilities in the country.

PLOS ONE

RESEARCH ARTICLE

Burden of and factors associated with poor quality antibiotic, antimalarial, antihypertensive and antidiabetic medicines in Malawi

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Abstract

Objective

To assess the prevalence and factors associated with substandard and falsified (SF) medicines among antibiotic, antimalarial, antihypertensive and antidiabetic medicines in Malawi.

Methods

We conducted a cross-sectional study in 23 public, faith-based and private health facilities in Zomba, Machinga and Nsanje districts. We analyzed oral medicine samples of commonly used medicines among antibiotics, antimalarial, antihypertensive and antidiabetics in accordance with Malawi Essential Medicines List and local treatment guidelines. These medicines were subjected to visual inspection for any defects and screening for the content of active pharmaceutical ingredient and disintegration of dosage units. Samples that failed during screening and at least 10% of those that passed were subjected to pharmacopeia assay and dissolution test for confirmation. We used thin layer chromatography and disintegration test methods provided in the Global Pharma Health Fund minilab® for the screening purposes. We conducted confirmatory test using High-Performance Liquid Chromatography (HPLC) or ultra-violet/visible spectrophotometer and dissolution.

Results

Of the 293 medicine samples collected, 14.3% were SF medicines. Among the SF medicines were 12.5% of Amlodipine (1/8), 19.2% of Amoxicillin (5/26), 72.2% of Atenolol (8/11), 21.2% of Ciprofloxacin (7/33), 14.3% of Enalapril (1/7), 44.4% of Flucloxacillin (4/9), and 35.7% of sulfadoxine/ pyrimethamine (10/28). Medicine quality was associated with therapeutic medicine class, stated origin of manufacturer, primary packaging material and geographical location. Antimalarial and antidiabetic medicines were of better quality as compared to antibiotics, odds ratio OR 4.2 (95% CI 1.7–9.49), $p < 0.002$ and OR 5.6 (95%

Competing interests: The authors have declared that no competing interests exist.

CI 1.21–26.09), p < 0.028 respectively. In terms of stated country of origin, the prevalence of SF medicines was 30% (15/50), 33% (9/27), 26.7% (4/15) and 6.6% (8/122) for medicines stated to be manufactured in Malawi, China, Kenya and India respectively.

Conclusion

This study presents the first findings on the assessment of quality of medicines since the establishment of the national pharmacovigilance center in 2019 in Malawi. It is revealed that the problem of SF medicines is not improving and hence the need for further strengthening of quality assurance systems in Malawi.

Introduction

Substandard and falsified (SF) medicines are a global public health concerns [1]. Substandard medical products are also referred to as 'out of specification' products [2]. These are "authorized medical products that fail to meet either their quality standards or specifications or both" [3]. This is caused by limitations during manufacturing processes or post-production degradation [4]. On the other hand, falsified medical products are "medical products that deliberately or fraudulently misrepresent their identity, composition or source" [3]. Undesirable characteristics of SF medicines such as inadequate API content, may lead to harmful effects such as lack of response to treatment, adverse drug events, mortality, and antimicrobial resistance [5].

Some recent studies have started linking adverse health outcomes to the prevalence of SF medicines. A recent systematic analysis by Torloni et.al attributed the high maternal mortality in low and middle-income (LMIC) countries to the high prevalence of SF medicines used for treatment of life-threatening pregnancy complications such as eclampsia, post-partum hemorrhage and sepsis [6]. A 2017 World Health Organization review established that 169,000 children suffering from pneumonia are estimated to die every year as a result of treatment failure due to use of SF antibiotic medicines [7]. About 4% of malarial deaths among under-five patients who receive treatment in sub-Saharan Africa are also reported to occur due to use of SF medicines [8]. Furthermore, SF medicines are also associated with loss of public trust and increased individual, household or health system costs [9].

WHO estimated the prevalence of SF medicines at 10.5% in 2017 for LMIC [2]. The burden is high for African countries with a prevalence of 18.9%. The prevalence for Asian countries is 10.2%,while for other countries, the prevalence is as low as below 1% [10]. Studies done in Malawi between 2014 and 2017 have identified substandard analgesics, uterotonics, antimalarials and antibiotics in public, faith-based, private health facilities and unauthorized vendors. The median prevalence of substandard medicines was 24.7% and the range was 12.5%–88.4% [11–14]. There has also been report of falsified tablets collected from the informal markets that were mislabeled as sulphadoxine/pyrimethamine but contained paracetamol and co-trimoxazole [15].

The prevalence of SF medicines is dynamic [16]. It responds to a number of factors such as disease burden, standard treatment guidelines, and regulatory policies and enforcement [17]. The Malawi Pharmacy and Medicines Regulatory Authority (PMRA) established the national pharmacovigilance center and became a full member of the WHO programme for international drug safety monitoring (WHO-PIDM) in 2019 [18]. The goal of the WHO-PIDM is to reduce medicine-related safety problems including SF medicines through post-marketing quality monitoring and reporting [19]. However, there was limited data to assess for

improvements in prevalence of SF medicines in Malawi since 2019. Moreover, the factors associated with the quality of medicines in Malawi had not been investigated.

In this study, we aimed to comparatively assess the current burden of SF medicines among the most commonly used medicines for treatment of both infectious and non-communicable diseases. Hence, we focused on antibiotics, antimalarials, antihypertensives and antidiabetic medicines [20,21]. We also further assessed the factors that are associated with the quality of these medicines.

Materials and methods

This was a cross-sectional study conducted between July 2021 and January 2022 in 29 health facilities. The health facilities were selected in the southern region of Malawi (Zomba, Machinga and Nsanje districts) using RAND function of Excel. We adapted the guidelines for medicine quality assessment and reporting (MEDQUARG) [22]. Primary healthcare facilities were selected based on stratified random sampling. For each district, the facilities were grouped into public, faith-based and private health facility. We used the RAND function in excel to select four primary health care facility from each group. Where the facilities were ≤ 4, all of them were included in the study. Purposively, we also included each district hospital in the study for comparison. Ordinarily, each district in Malawi has one major hospital that is considered as public facility for secondary level of health care.

Furthermore, all health facilities are clustered into zones, for which each zone has one major public central hospital, which is considered as a tertiary level facility for the zone. The district health office for Zomba district only offers administrative services and bulk storage of the medicines and medical supplies for distribution to the primary health-care facilities, but does not provide patient care services. Hence, we co-opted a central hospital for the zone, which is coincidentally located within Zomba district. By these categories, there were 11 faith-based not for profit, 16 public and two private health facilities at all levels of care. Of these, 23 are primary, five are secondary and one is a tertiary level health-care facility. The primary level health-care facilities are 21 rural health-centres and two private retail pharmacies while the secondary level health-care facilities are the three major public facilities for each of the study district and two community hospitals owned by faith-based organizations. As already highlighted, the only tertiary level facility in the study is a public facility.

In total, 293 medicine samples of commonly used medicines among antibiotics, antimalarials, antihypertensives and antidiabetics were sampled (see S1 Table). The selection of the medicines was in accordance with the Malawi Essential Medicines List (MEML) and the Malawi Standard Treatment guidelines (MSTG) of 2015, which was the one in use at the time of study. The use of MSTG/MEML in the selection of medicines was supplemented with the 150 Central Medical Stores Trust (CMST) Tracer list of items. The 150 CMST tracer list of items is a compilation of 150 items that must be available all the times whenever a customer (health facility) orders medicines. We included oral medicines used as first line or alternative treatments for common bacterial infections, malaria, hypertension and diabetes mellitus type II in Malawi [23]. For antimalarial medicines, further guidance was sourced from the Malawi National Malaria Guidelines 2013 [24] that resulted in addition of Malawi's second line antimalarial medicine (artesunate/amodiaquine) and first line antimalarial for pregnant women (Quinine oral tablets). As summarized in Table 1 of results section, the selected medicines were Amoxicillin (n = 26), Azithromycin (n = 11), Cefuroxime (n = 1), Ciprofloxacin (n = 33), and Flucloxacillin (n = 9) among antibiotics, Quinine (n = 1), fixed dose combinations of Artemether/Lumefantrine (n = 99), Artesunate/Amodiaquine (n = 1), and sulfadoxine/pyrimethamine (= 25) among antimalarials, Amlodipine (n = 8), Atenolol (n = 11), Enalapril (n = 7),

Table 1. Characteristics of medicine samples.

Variable	Characteristic	MEML category[a]	Public Health Facilities (N = 16) [189 samples]	CHAM facilities (N = 11) [79 samples]	Licensed retail pharmacies (N = 2) [25 samples]	Total Number of Samples	Samples tested using visual/TLC testing methods	Samples tested according to pharmacopoeia monographs
Medicine type (International Nonproprietary Names)	Amlodipine 5 and 10mg tablet	DVA	3	3	2	8	8	0
	Amoxicillin 250 or 500mg capsule/tablet	HVA	17	8	1	26	26	14
	Artesunate/ Amodiaquine 100mg/ 270mg tablet	DVA	0	1	0	1	1	
	Atenolol 50/100mg tablet	DVA	8	2	1	11	11	11
	Azithromycin 250/ 500mg tablet	DEA	7	2	2	11	11	0
	Cefuroxime 500mg tablet	N/A	0	0	1	1	1	0
	Ciprofloxacillin 250/ 500mg tablet	DVA	24	7	2	33	33	15
	Enalapril 5/10mg tablet	DVA	4	1	2	7	7	0
	Flucloxacillin 250mg capsule	DVA	7	0	2	9	9	0
	Glibenclamide 5mg tablet	DVA	12	4	1	17	17	0
	Hydrochlorothiazide 25mg tablet	DVA	7	6	1	14	14	0
	Lumefantrine/ Artemether 120mg/ 20mg tablet	HVA	67	30	2	99	99	0
	Metformin 500mg tablet	DVA	12	2	4	18	18	14
	Methyldopa 250mg tablet	DEA	5	3	1	9	9	0
	Quinine sulfate 300mg tablet	DVA	0	0	1	1	1	0
	Sulfadoxine/ pyrimethamine 500mg/ 25mg tablet	HVA	16	10	2	28	28	10
Total medicine number of samples			189	79	25	293	293	64

[a] The Malawi Essential Medicines List (MEML) of 2015 specifies the level of health institution at which the medicine is normally permitted for use: H = at health centre, district hospital and central hospital levels; D = at district hospital and central hospital levels only; C = at central hospital level only. N = level of use not specified. The 'therapeutical priority' code categorizes medicines based on therapeutic importance of each medicine by the use of: V = vital medicines which are potentially life-saving, of major public health relevance and having significant withdraw side-effects, E = essential medicines which are effective against less severe, but nonetheless significant forms of illness; N = non-essential medicines which are used for minor self-limiting illness and are often of questionable efficacy. The third categorization of 'procurement system' has two codes: 'A' = medicines required by a large number of patients as such to be routinely procured and stocked by CMST; and 'B' = medicines required for a limited number of patients and not routinely stocked by CMST).

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methyldopa (n = 9) and Hydrochlorothiazide (n = 14) among antihypertensives and Metformin (n = 18) and Glibenclamide (n = 17) among antidiabetic medicines. From the selected medicines, the only child friendly formulation in our sample was dispersible artemether/ lumefantrine.

Basic information of the medicines such as trade name, strength of dosage units, batch numbers, expiry date, and stated manufacturer were collected from the labeling on the primary or secondary packages using a data collection form. In order to acquire the minimum amount of dosage units for conducting each of the required pharmaceutical tests, we targeted to collect at least 80 dosage units from the sample container and transported the samples to the Kamuzu University of Health Sciences for quality analysis. Where the available stock at facility was low, fewer but more than 20 dosage units were collected. All the dosage units per sample were subjected to visual inspection. Nine dosage units were subjected to screening of which three were analyzed using thin layer chromatography (TLC) and six were subjected to disintegration test. For confirmation, 20 dosage units were subjected to pharmacopeia assay for absolute determination of content of active pharmaceutical ingredient (API) and three for dissolution.

Firstly, we visually inspected the medicines for presence of any visual defects such as non-uniformity of color, size and shape, or presence of breakages and any contaminants. For screening purposes, we conducted semi-quantitative analysis of the content of API using thin layer chromatography (TLC) according to the Global Pharma Health Fund (GPHF) minilab® protocols test [25], and disintegration test as outlined in pharmacopoeia. Medicine samples that failed to comply during screening tests were subjected to pharmacopeia assay and dissolution analysis for confirmation. In addition, we ensured that at least 10% of the remaining samples that complied upon screening were also confirmed by assay and dissolution. These samples were randomly selected according to medicine type, based on the availability of reagents and reference standards. We used Agilent® 1120 high performance liquid chromatography (HPLC) or Biobase® Ultra-violet/ Visible (UV/Vis) spectrophotometry to determine the content of API while PharmaTest® 1200 dissolution apparatus was used to perform dissolution analysis according to methods provided in the British or Indian Pharmacopoeia [26,27].

A medicine sample was considered substandard if the sample dosage units failed to meet the specifications for either content or release of the API. For TLC, triplicate test samples were spotted and compared with standard spotting of both 80% and 100% concentration on the same plate. A sample failed the test if at least one of the sample spotting presented a difference in terms of travel distance, size and intensity of spot with reference to the standard spotting. Six dosage units were run for disintegration test. All the dosage units were required to disintegrate within 30 minutes to pass the test. For the assay and dissolution tests, we used the specifications provided in the US pharmacopeia for determining whether the medicine was substandard or complied to the specifications [4,28]. Overall, we considered a medicine as substandard if the sample was non-compliant to either the specifications for the API content or dissolution upon confirmation. For a few samples including Flucloxacillin (n = 3), Amlodipine (n = 1) and Enalapril (n = 1), the pharmacopeia confirmation was not performed due to unavailability of reference standards.

Descriptive statistics were used for determining the prevalence of SF medicines. Chi square test was used for comparison of the test results among different variables. The extent to which variables were associated with the quality of the medicines was analyzed using logistic regression.

Ethical considerations

This study was given ethical clearance by the College of Medicine Research and Ethics Committee (COMREC) under approval number P.11/20/3199. We also sought approval from the Pharmacy and Medicines Regulatory Authority (PMRA) and the directorates of health and social services (DHSS) in all the three participating districts before data collection. Furthermore, during medicine sample collection, consent was sought from each respondent. In the

majority of cases the respondent was also the in-charge of the facility. The respondents were provided with written participant information sheet and an oral explanation about the study before signing the consent forms. The participants in this study were mostly health workers employed by various institutions and were above eighteen years of age. No personal data was recorded during this study.

Results

Characteristics of medicine samples

Of the 293 medicine samples collected (Table 1, Fig 1), 27.3% (n = 80) were antibiotics: Amoxicillin (n = 26), Azithromycin (n = 11), Cefuroxime (n = 1), Ciprofloxacin (n = 33), and Flucloxacillin (n = 9), 44% (n = 129) were antimalarials: Quinine (n = 1), fixed dose combinations of Artemether/ Lumefantrine (n = 99), Artesunate/Amodiaquine (n = 1), and sulfadoxine/ pyrimethamine (= 25), 16.7% (n = 49) were antihypertensives: Amlodipine (n = 8), Atenolol (n = 11), Enalapril (n = 7), methyldopa (n = 9) and Hydrochlorothiazide (n = 14) and 12% (n = 35) were antidiabetic medicines, which were Metformin (n = 18) and Glibenclamide (n = 17). About 17.5% (n = 53) of the samples were claimed to be locally manufactured while 82.5% (n = 240) were claimed to be imported from various countries as indicated in Fig 2; Austria (n = 2), China (n = 27), England (n = 1), India (n = 137), Kenya (n = 21), Morocco (n = 1), Netherlands (n = 2), Switzerland (n = 27), Tanzania (n = 3), Turkey (n = 1), and Uganda (n = 17). In terms of health facilities, 27% (n = 79) of the samples were from faith-based health facilities, 8.5% (n = 25) from private pharmacies and 64.5% (n = 189) from public health facilities. The majority of the samples (77.8%, n = 228) were from health centres which provide primary health care services and mostly found in rural settings (Fig 1).

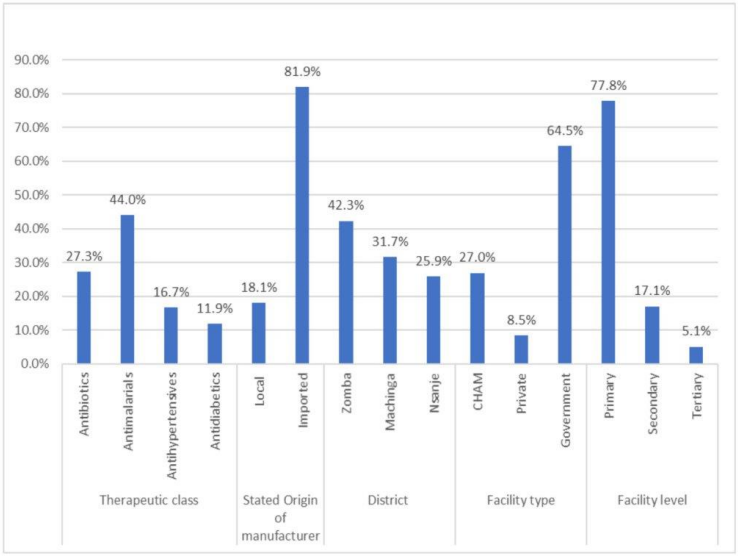

Fig 1. Showing samples tested based on category.

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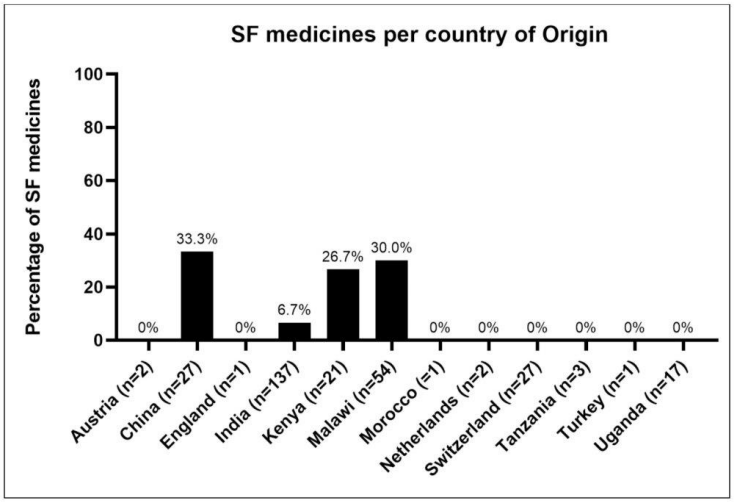

Fig 2. Showing stated country of origin of SF medicines.

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Prevalence of SF medicines

All the 293 medicine samples collected were subjected to visual inspection and disintegration. Based on availability of reference standards, 262 samples were further screened using thin layer chromatography (TLC), which performs semi-quantitative analysis of the API content. Of the medicines samples that were fully screened, 14.3% (n = 38) were found to be substandard medicines (Table 2). The substandard medicines were 12.5% of Amlodipine (1/8), 19.2% of Amoxicillin (5/26), 72.2% of Atenolol (8/11), 21.2% of Ciprofloxacin (7/33), 14.3% of Enalapril (1/7), 44.4% of Flucloxacillin (4/9), and 35.7% of sulfadoxine/ pyrimethamine (10/28). The SF medicines were associated with medicine type (by generic name) ($p < 0.001$), therapeutic class of the medicines ($p < 0.001$), stated country of origin ($p < 0.001$) and district where these medicine samples were collected ($p < 0.042$). The statistics were adjusted based on the new denominator.

Of the 38 SF medicines, 32 samples were confirmed using through pharmacopeia assay or dissolution test (see S2 Table). Except for sulfadoxine/pyrimethamine (SP) tablets, all the samples presented with non-extreme deviations from the acceptable ranges. For the ten SP samples, there was notably higher than the declared content (more than 120% of label claim) of pyrimethamine while sulfadoxine was available in extremely lower amounts (below 80% of label claim) for all the samples subjected to HPLC assay. Apparently, all the SP samples were stated to be manufactured by the same one company from China. Of special note is that the purportedly names of the manufacturers as extracted from the packaging have been omitted to ensure anonymity. However, for all the samples that failed confirmatory tests, we reported to the Pharmacy and Medicines Regulatory Authority with the details of the manufacturers and where the medicines were sampled for further action.

Table 2. Prevalence of out-of-specification medicines.

Variable	Characteristic	Number of samples	Visual analysis, n (%)	TLC, n (%)	Disintegration, n (%)	Dissolution, n (%)	Pharmacopoeia Assay, n (%)	Overall non-compliance rate, n (%)
Medicine type (INN)	Amlodipine 5mg or 10mg tablet	8	0(0)	1 (12.5)	0 (0)			1 (12.5)
	Amoxicillin 250mg/ 500mg tablet/capsule	26	0 (0)	0 (0)	5 (19.2)	5 (35.7)	5 (35.7)	5 (19.2)
	Artesunate/Amodiaquine	1	0 (0)	-	0 (0)			
	Atenolol	11	6 (54.6)	0 (0)	0 (0)	5 (45.5)	4 (36.4)	8(72.7)
	Azithromycin	11	0 (0)	-	0 (0)			-
	Cefuroxime	1	0 (0)	-	0 (0)			-
	Ciprofloxacillin	33	0 (0)	3 (9.1)	4 (12.1)	2 (20)	6 (42.9)	7(21.2)
	Enalapril	7	0 (0)	1 (14.3)	0 (0)			1 (14.3)
	Flucloxacillin	9	0 (0)	-	4 (44.4)			4 (44.4)
	Glibenclamide	17	0 (0)	0 (0)	0 (0)			0 (0)
	Hydrochlorothiazide	14	0 (0)	0 (0)	0 (0)	0 (0)		0 (0)
	Lumefantrine/Artemether	99	0 (0)	0 (0)	0 (0)			0 (0)
	Metformin	18	1 (5.6)	0 (0)	0 (0)	0 (0)	2 (11.1)	2 (11.1)
	Methyldopa	9	0 (0)	0 (0)	0 (0)			-
	Quinine sulfate	1	0 (0)	0 (0)	0 (0)			-
	Sulfadoxine/ pyrimethamine	28	0 (0)	2 (7.1)	3 (10.7)		10 (100)	10 (35.7)
Therapeutic class	Antibiotics	80	0 (0)	3 (5.1)	13 (16.3)	7 (29.2)	11 (39.3)	16 (25.4)
	Antimalarials	129	0 (0)	2 (1.2)	3 (2.3)		10 (100)	10 (7.8)
	Antihypertensives	49	6 (12.2)	2 (5)	0 (0)	5 (26.3)	4 (36.4)	10 (25)
	Antidiabetics	35	1 (2.9)	0 (0)	0 (0)	0 (0)	2 (11.1)	2 (5.7)
Stated Origin of manufacturer	Local	53	7 (13.2)	3 (6.1)	6 (11.3)	9 (37.5)	10 (34.5)	15 (30.6)
	Imported	240	0 (0)	4 (1.9)	10 (4.2)	3 (9.7)	17 (44.7)	23 (10.6)
District	Zomba	124	5 (4.1)	2 (1.9)	8 (6.5)	7 (29.1)	13 (37.1)	19 (17.3)
	Machinga	93	0 (0)	1 (1.2)	3 (3.2)	2 (13.3)	6 (40)	7 (8.3)
	Nsanje	76	2 (2.7)	4 (5.6)	5 (6.6)	3 (18.8)	8 (47.1)	12 (16.7)
Facility type	Government	189	6 (3.2)	6 (3.5)	10 (5.3)	9 (23.7)	20 (41.7)	27 (15.7)
	CHAM	79	1 (1.3)	1 (1.4)	4 (5.1)	3 (20)	6 (46.2)	8 (11)
	Private	25	0 (0)	0 (0)	2 (8)	0 (0)	1 (16.7)	3 (14.3)
Facility level	Primary	228	3 (1.3)	7 (3.4)	13 (5.7)	6 (17.1)	20 (44.4)	11 (5.7)
	Secondary	50	3 (6)	0 (0)	3 (6)	5 (29.4)	6 (31.6)	27 (13)
	Tertiary	15	1 (6.7)	0 (0)	0 (0)	1 (33.3)	1 (33.3)	2 (16.7)
All	NA	293	7 (2.4)	7 (2.7)	16 (5.5)	12 (21.8)	27 (40.3	38 (14.3)
Total number of samples		**293**	**293**	**262**	**293**	**55**	**67**	

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Factors associated with substandard (quality of) medicines

Results of the logistic regression analysis for possible factors affecting quality of medicines such as therapeutic class, stated origin of manufacturer, primary packaging material, storage stores, and location of health facility are presented in Table 3. Odds ratios (OR) for complying to quality specifications were compared with antibiotic medicine class, local manufacturing, bottle primary packaging, ordinary storage stores and Zomba district respectively as reference characteristics.

Table 3. Factors associated with SF medicines in southern Malawi.

			Compliance to Quality specifications		
Variable	**Comparator**	**Characteristic**	**OR**	**95% Conf. Interval**	**P value**
Therapeutic class	Antibiotics	Antimalarials	4.2	1.7–9.49	0.002
		Antihypertensives	1.02	0.41–2.54	0.964
		Antidiabetics	5.6	1.21–26.09	0.028
Stated country of Origin for manufacturer	Local	Imported	3.72	1.78–7.84	0.001
Primary packaging	Bottle	blisters	5.05	2.33–10.91	<0.000
Storage	Ordinary drug store	SIAB	0.84	0.42–1.69	0.63
District	Zomba	Machinga	2.29	1.02–6.74	0.026
		Nsanje	1.04	0.47–2.31	0.915

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Medicine samples from Machinga districts had better-quality medicines, OR 2.29 (95% CI 1.02–6.74), p< 0.026) as compared to those sampled from Zomba district while there was no significant difference with those sampled from Nsanje district, OR 1.04 (95% CI 0.47–2.31), p < 0.915.

In terms of therapeutic medicine class, antibiotic medicines had the highest rate of non-compliance to quality specifications after adjustment basing on confirmatory tests. Antidiabetic medicines had the highest quality OR 5.6 (95% CI 1.21–26.09), p < 0.028 and were seconded by antimalarial medicines with OR 4.2 (95% CI 1.7–9.49), p < 0.002. The quality of antihypertensive medicines was comparable to antibiotic medicines with OR 1.02 (95% CI 0.41–2.54), p < 0.964. We further analyzed the quality of the medicines by therapeutic class per district and found that only results for antimalarial medicines were significant in Nsanje district, p < 0.003. The rest of the medicine classes per each district, except antihypertensives in Zomba, had OR > 1 in comparison with antibiotics but the results were not statistically significant.

We also found imported medicines to have better quality in comparison with locally manufactured medicines, OR 3.72 (CI 1.78–7.84), p < 0.001 and also medicines primarily packed in blister packs were of better quality as compared to medicines packaged directly in bottles, OR 5.05 (95% CI 2.33–10.91), p < 0.000. On further stratified analysis per district, the good quality of the medicines for imported medicines was significant for Zomba and Nsanje districts, OR 2.75 (95% CI 1.3–7.8), p < 0.046 and OR 6.5 (95% CI 1.67–25.18), p < 0.007. In terms of packaging, the results were significant in Zomba and Machinga with OR 5.7 (95% CI 1.68–17.8), p < 0.005 and OR 5.7 (95% CI 1.04–31.8), p < 0.045 respectively.

Origin of substandard medicines in Malawi

All the detected substandard medicines were manufactured in Africa and Asian countries (Fig 2). There was a significant variation in the proportion of SF medicines among the countries where the medicine samples were manufactured (P< 0.001). Prevalence of SF medicines was rampant for medicines claimed to be locally manufactured (30%), from China (33%), Kenya (26.7%) and India (6.6%).

Discussion

Routine post-marketing surveillance of medicine quality is not common in resource limited countries such as Malawi [29]. Thus, with respect to the WHO Global Benchmarking tool for evaluation of national regulating systems of medical products, majority of LMICs are at lower levels (level 1 or 2) of maturity as they lack resources to maintain strong and active systems and structures that can enable them to achieve properly documented integrated monitoring

activities at various levels. Another major challenge of national medicines regulatory authorities in LMICs is lack of human resource [30]. As such, the quality of medicines on the market remains a concern. Our study found that 14.3% of the antibiotics, antimalarial, antihypertensive and antidiabetic medicines in our sample were substandard based on tests for content and in-vitro release of API. The medicine classes analyzed in the study are crucial as they are used for treatment of diseases with a high morbidity and mortality in Malawi and other LMICs. For instance, more than 50% of prescriptions in LMICs contain antibiotic medicines [31]. On the other hand, Malaria is one of the leading cause of death in Malawian children under the age of five years [32]. It is also revealed that the burden of hypertension and diabetes is increasing in Malawi [33]. Therefore, the compromised quality of medicines analyzed in this study have potential to cause hazardous effects on the public health.

Previous studies done in Malawi found SF medicine prevalence of 45.5% and 13% in 2014 and 2017 respectively among antibiotic medicines. In these studies, the sampled antibiotics included co-trimoxazole, phenoxymethylpenicillin, Ciprofloxacin, Amoxicillin/Clavulanic acid, chloramphenicol and Cefuroxime [11,13]. In this study, we sampled Amoxicillin, Azithromycin, Cefuroxime, Ciprofloxacin and Flucloxacillin and found a prevalence of SF medicines of 25.4%. This is 1.79-fold lower than the prevalence in 2014 but 1.9-fold higher than results if the study done in 2017. The continued high prevalence of SF antibiotics is worrisome for low-income countries such as Malawi. This is based on the fact that the country is burdened with high infectious diseases which requires quality treatment using antibiotics. The poor-quality antibiotics may therefore contribute to mortality and antimicrobial resistance due to under-dosing in individual patients.

In 2015, a study by Chikowe et.al found a very high prevalence of 88.8% substandard antimalarial medicines [12] while in 2017 study by Khuluza et.al the prevalence of SF medicines was 9% among antimalarial medicines [13]. Both studies included samples artemether/lumefantrine, Sulphadoxine/ Pyrimethamine, Quinine and Artesunate/ Amodiaquine medicines and these were also included our study. In the current findings, we found a slightly lower prevalence (7.8%) than the 2017 prevalence of SF medicines among antimalarial medicines. The methods applied in these three studies are similar and therefore the variations might be likely attributable to times that these studies were conducted and thereby further confirming that the prevalence of SF medicines is dynamic and therefore continuous efforts to curb the burden are necessary.

In the past studies, little attention was given to the quality of medicines for treatment of non-communicable diseases in Malawi and sub-Saharan Africa. In this study, we also included antihypertensive medicines such as Amlodipine, Atenolol, Enalapril, Methyldopa and Hydrochlorothiazide and oral antidiabetic medicines such as Metformin and Glibenclamide. The prevalence of SF medicines among antihypertensives was 25%, which is comparable to the high prevalence of SF medicines among antibiotics. Antidiabetics on the other hand, have a lower prevalence of 5.7%. Though most studies have found that antimalarial and antibiotics are mostly to be substandard and falsified in low-income countries, this study has found that the problem is also prevalent in non-communicable disease (NCD) medicines, especially the antihypertensives. This requires strong post marketing surveillance system targeting medicines for treatment of all medicines regardless of the disease that they are intended to treat.

The factors associated with SF medicines in this study were therapeutic medicine class, stated country of origin, primary packaging material, and geographical area. Previous studies have shown that there is disproportionality in the burden of SF medicines across the globe, with low-income countries recording a high prevalence of SF medicines used for treatment of infectious diseases such as antibiotics while in high-income countries, the burden is low and mostly concern expensive medicines for lifestyle use such as steroids and treatments erectile dysfunction [10,34]. Further, it is postulated that economic factors such as high market

demand as propelled by the disease burden, play a role in proliferation of SF medicines [17]. Antibiotics and antimalarial medicines are among the most commonly used medicines in Malawi and therefore we expected to have higher prevalence of SF medicines for these therapeutic classes. Our results however, found a high prevalence of SF medicines among antibiotics (25.4%) and a low prevalence of SF medicines among antimalarials (7.8%). The low prevalence of SF medicines among antimalarial medicines is probably due to a more controlled supply chain system for medicines and medical supplies for special public health programs such as Malaria, HIV and Tuberculosis. In Malawian public and faith-based health care facilities, antimalarial medicines are sourced from a limited number of World Health Organization prequalified suppliers and the distribution and storage of these medicines is closely monitored. This may be the reason for the observed low prevalence of SF medicines for the antimalarials in the study.

On the other hand, incidence of non-communicable diseases is also escalating in LMICs [20,21]. Consistent with the increased demand, it was observed in the study that there was also high prevalence of SF medicines for antihypertensive medicines (25%). Although the prevalence of SF medicines for antidiabetic medicines was relatively low (5.7%), the current results raise a signal for an emerging concern of the quality of medicines for treatment of non-communicable diseases (NCDs) in Malawi.

Our results revealed that locally manufactured medicines are likely to be of poor quality as compared to imported medicines. This may be attributable to inadequate regulatory supervision on the part of Medicine regulator and lack of adequate resources to enable manufacturing and quality control processes that are fully compliant to current good manufacturing practices (cGMP) in local pharmaceutical companies. An assessment of pharmaceutical quality assurance systems showed that there is poor compliance to the WHO set guidelines for quality assurance in LMICs [35]. This is even likely to be more prominent in countries with relatively weaker regulatory framework such as Malawi [36]. In Malawi, the regulatory authority has put in place strong efforts and guidelines to ensure good quality of medicines. This include active surveillance, raising awareness to health care professionals and ensuring that reporting tools are available for reporting suspected SF medicines in health facilities. However, challenges such as inadequate human and financial resources are affecting such activities.

Blister packaging offers additional protection to tablet and capsule dosage units through prevention of direct contact with atmospheric air, humidity and sunlight; which are the major factors that facilitate the deterioration of medicines on storage [37–39]. Our results provide further evidence on this, as it was found that medicine samples that used blisters for primary packaging were of significantly better quality as compared to those that used bottles for primary packaging. With an annual mean temperature of 28˚C (www.worlddata.info/africa/malawi), the southern region of Malawi may be considered as an area with unfavorable conditions for storage of medicines without temperature control mechanisms. The normal acceptable range for storage of most of oral solid dosage forms is 15˚C to 25˚C, but depends on the manufacturer's recommendation which must be based on formal stability studies [40]. It is therefore important to emphasize on the need for compliance to storage requirements of the medicines as stated by the manufacturer's labelling for all medicine types.

Based on the assertion that higher temperatures are more likely to cause a higher degradation rate for medicines, we expected a higher prevalence of poor-quality medicines in Nsanje district, which records the highest temperatures across the year in the southern Malawi. On the contrary, Zomba which relatively records lower temperatures had the highest prevalence of poor-quality medicines. This difference could be likely due to the storage practices of medicines in the health facilities. For instance, despite the higher temperatures in the district, 77% of the study sites in Nsanje district use the 'Storage in a box' (SIaB) units while only 43% and

32% of study facilities in have the SIaB in Zomba and Machinga respectively. SIAB units are prefabricated medicine storage rooms designed to easily control temperature by installing them using insulated wall panels, double roofing and heat reflector painting. The SIaB units are a USAID initiative, which was aimed at improving the storage conditions and capacity for health facilities in resource-limited places such as Malawi. These storage units offer better conditions than ordinary medicine stores as they are pre-also contain air conditioners and built-in room thermometers for continuous monitoring of the daily storage conditions [41].

The factors associated with SF medicines provides insights into possible challenges of the supply chain system in Malawi. The Central Medical Stores Trust (CMST) procures, stores and distributes medicines and medical supplies for public and faith-based health institutions in Malawi [42]. This centralized system is advantageous in resource limited settings like Malawi as it provides a single route of entry of medicines into the supply chain which can be easily monitored for any possible quality defects. It is therefore important to strengthen the measures for countering SF medicines from the CMST level down the supply chain system. For medicines that are supplied outside the CMST system, the same level of regulatory supervision need to be established and implemented across the country, to avoid that there are different standards between the public and private sector.

Limitations of the study

In this study, not all the medicine samples were subjected to pharmacopeia analysis; HPLC and UV-VIS spectrometry for analysis of API content and dissolution tester for analysis of the release of API which are considered as gold standard techniques. However, we ensured that at least 10% of samples and those that failed upon TLC and disintegration testing were confirmed by the pharmacopeia methods. As highlighted, a few medicines that failed the screening stage, were not verified by the pharmacopeia analysis. This is due to lack of reference standards due to procurement challenges as the study was done when COVID-19 pandemic was at the peak in Malawi.

Conclusion

This study presents the first results on the assessment of quality of medicines since the establishment of the national pharmacovigilance centre in 2019 in Malawi. It is revealed that the problem of SF medicines is not improving and therefore the measures that are implemented in order to curb this problem needs further strengthening. It is also recommended that the capacity of the National Regulatory Authority is strengthened, for better carrying out essential regulatory tasks including post marketing surveillance.

Supporting information

S1 Table. List of all medicines collected for the study.
(DOCX)

S2 Table. Description of all medicines that failed test.
(DOCX)

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References

1. Akpobolokemi T., Martinez-Nunez R. T., and Raimi-Abraham B. T., "Tackling the global impact of substandard and falsified and unregistered/unlicensed anti-tuberculosis medicines," *J. Med. Access*, vol. 6, 2022, https://doi.org/10.1177/23992026211070406 PMID: 36204519
2. World-Health-Organization, "Global Surveillance and Monitoring System for substandard and falsified medical products," *World Health Organization*, 2017. https://apps.who.int/iris/handle/10665/326708 (accessed Sep. 05, 2022).
3. World Health Organization, "Member State mechanism on substandard / spurious / falsely—labelled / falsified / counterfeit medical products," *Exec. Board Agenda item*, vol. 19, no. 140th session Agenda Item 8.6, p. 1, 2017, [Online]. Available: https://apps.who.int/iris/handle/10665/273272.
4. Hauk C., Hagen N., and Heide L., "Identification of substandard and falsified medicines: Influence of different tolerance limits and use of authenticity inquiries," *Am. J. Trop. Med. Hyg.*, vol. 104, no. 5, pp. 1936–1945, 2021, https://doi.org/10.4269/ajtmh.20-1612 PMID: 33788775
5. Johnston A. and Holt D. W., "Substandard drugs: A potential crisis for public health," *Br. J. Clin. Pharmacol.*, vol. 78, no. 2, pp. 218–243, 2014, https://doi.org/10.1111/bcp.12298 PMID: 24286459
6. Torloni M. R., Bonet M., Betrán A. P., Ribeiro-Do-Valle C. C., and Widmer M., "Quality of medicines for life-threatening pregnancy complications in low- And middleincome countries: A systematic review," *PLoS One*, vol. 15, no. 7 July, pp. 1–18, 2020, https://doi.org/10.1371/journal.pone.0236060 PMID: 32649710
7. World-Health-Organization(WHO), "A Study on the Public Health and Socioeconomic Impact of substandard and falsified medical products," *World Health Organization*, 2017. https://www.who.int/publications/i/item/9789241513432 (accessed Sep. 05, 2022).

8. Renschler J. P., Walters K. M., Newton P. N., and Laxminarayan R., "Estimated Under-Five Deaths Associated with Poor-Quality Antimalarials in Sub-Saharan Africa," vol. 92, no. Suppl 6, pp. 119–126, 2015, https://doi.org/10.4269/ajtmh.14-0725 PMID: 25897068

9. Aminu N., Sha'aban A., Abubakar A., and Gwarzo M. S., "Unveiling the Peril of Substandard and Falsified Medicines to Public Health and Safety in Africa: Need for All-Out War to End the Menace," *Med. Access @ Point Care*, vol. 1, no. 1, 2017, https://doi.org/10.5301/maapoc.0000023

10. Ozawa S., Chen H., Lee Y. A., Higgins C. R., and Yemeke T. T., "Characterizing Medicine Quality by Active Pharmaceutical Ingredient Levels: A Systematic Review and Meta-Analysis across Low- and Middle-Income Countries," vol. 106, no. 6, pp. 1778–1790, 2022, https://doi.org/10.4269/ajtmh.21-1123 PMID: 35895431

11. Khuluza F., "In-vitro evaluation of the quality of paracetamol and co-trimoxazole tablets used in Malawi based on pharmacopoeial standards," *Malawi Med. J.*, vol. 26, no. 2, pp. 38–41, 2014, [Online]. Available: https://pubmed.ncbi.nlm.nih.gov/25157315/. PMID: 25157315

12. Chikowe I., Osei-Safo D., Harrison J. J. E. K., Konadu D. Y., and Addae-Mensah I., "Post-marketing surveillance of anti-malarial medicines used in Malawi," *Malar. J.*, vol. 14, no. 1, pp. 1–11, 2015, https://doi.org/10.1186/s12936-015-0637-z PMID: 25890029

13. Khuluza F., Kigera S., and Heide L., "Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi," *Am. J. Trop. Med. Hyg.*, vol. 96, no. 5, pp. 1124–1135, 2017, https://doi.org/10.4269/ajtmh.16-1008 PMID: 28219993

14. Hagen N., Khuluza F., and Heide L., "Quality, availability and storage conditions of oxytocin and misoprostol in Malawi," *BMC Pregnancy Childbirth*, vol. 20, no. 1, pp. 1–18, 2020, https://doi.org/10.1186/s12884-020-2810-9 PMID: 32223759

15. Khuluza F., Kigera S., Jähnke R. W. O., and Heide L., "Use of thin-layer chromatography to detect counterfeit sulfadoxine/pyrimethamine tablets with the wrong active ingredient in Malawi," *Malar. J.*, vol. 15, no. 1, pp. 1–7, 2016, https://doi.org/10.1186/s12936-016-1259-9 PMID: 27075749

16. McManus D. and Naughton B. D., "A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: A focus on context, prevalence, and quality," *BMJ Glob. Heal.*, vol. 5, no. 8, pp. 1–9, 2020, https://doi.org/10.1136/bmjgh-2020-002393 PMID: 32859648

17. G. J. B. and L. O. Gostin, "Countering the problem of falsified and substandard medicines," 2013. http://nap.edu/18272 (accessed Sep. 05, 2022).

18. Jusot V., Chimimba F., Dzabala N., Menang O., Cole J., and Gardiner G., "Enhancing Pharmacovigilance in Sub—Saharan Africa Through Training and Mentoring: A GSK Pilot Initiative in Malawi," *Drug Saf.*, no. 0123456789, 2020, https://doi.org/10.1007/s40264-020-00925-4 PMID: 32239447

19. Olsson S., "The role of the WHO programme on international drug monitoring in coordinating worldwide drug safety efforts," *Drug Saf.*, vol. 19, no. 1, pp. 1–10, 1998, https://doi.org/10.2165/00002018-199819010-00001 PMID: 9673854

20. Bowie C., "The burden of disease in Malawi," *Malawi Medical Journal*, 2007. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3345623/ (accessed Sep. 05, 2022).

21. Gowshall M. and Taylor-robinson S. D., "The increasing prevalence of non-communicable diseases in low-middle income countries: the view from Malawi," pp. 255–264, 2018, [Online]. Available: https://doi.org/10.2147/IJGM.S157987 PMID: 29988742

22. Newton P. N. et al., "Guidelines for field surveys of the quality of medicines: A proposal," *PLoS Med.*, vol. 6, no. 3, pp. 0252–0257, 2009, https://doi.org/10.1371/journal.pmed.1000052 PMID: 19320538

23. Ministry-of-Health, "Malawi Standard Treatment Guidelines. Incorporating Malawi Essential Medicines List," 2015. https://extranet.who.int/ncdccs/Data/MWI_D1_Malawi-Standard-Treatment-Guidelines-Essential-Medicines-List-2015.pdf.

24. Ministry-of-Health-National-Malaria-Programme, "Guidelines for the treatment of malaria in Malawi," 2013. https://www.severemalaria.org/sites/mmv-smo/files/content/attachments/2017-03-03/Malawi 2013 Edition of Malaria Treatment Guidelines.pdf (accessed Sep. 05, 2022).

25. GPHF-Minilab™, "Protection against counterfeit medicines," *GPHF-Minilab*, 2016. https://www.gphf.org/en/minilab/index.htm (accessed Sep. 05, 2022).

26. British-Pharmacoeia-Commission, "British Pharmacopoeia," *TSO information and publishing solutions*, 2013. https://www.worldcat.org/title/british-pharmacopoeia-2013/oclc/809536883 (accessed Sep. 05, 2022).

27. The-Indian-Pharmacopoeia-Commission, "Indian Pharmacopoeia," *Indian Pharmacopoeia*, 2007. https://www.pharmaresearchlibrary.com/wp-content/uploads/2013/03/IP2007-Vol-1.pdf (accessed Sep. 05, 2022).

28. United-States-Pharmacopeia-Convention, *The United States Pharmacopeia. The National Formulary*. 2018.

29. Hajjou M. et al., "Monitoring the quality of medicines: results from Africa, Asia, and South America," *Am. J. Trop. Med. Hyg.*, vol. 92, no. 6, pp. 68–74, 2015, https://doi.org/10.4269/ajtmh.14-0535 PMID: 25897073

30. Khadem Broojerdi A., Baran Sillo H., Ostad Ali Dehaghi R., Ward M., Refaat M., and Parry J., "The World Health Organization Global Benchmarking Tool an Instrument to Strengthen Medical Products Regulation and Promote Universal Health Coverage," *Front. Med.*, vol. 7, no. August, pp. 1–7, 2020, https://doi.org/10.3389/fmed.2020.00457 PMID: 32974367

31. Sulis G. et al., "Antibiotic prescription practices in primary care in low- And middle-income countries: A systematic review and meta-analysis," *PLoS Med.*, vol. 17, no. 6, pp. 1–20, 2020, https://doi.org/10.1371/journal.pmed.1003139 PMID: 32544153

32. Chilanga E., Collin-Vézina D., MacIntosh H., Mitchell C., and Cherney K., "Prevalence and determinants of malaria infection among children of local farmers in Central Malawi," *Malar. J.*, vol. 19, no. 1, pp. 1–10, 2020, https://doi.org/10.1186/s12936-020-03382-7 PMID: 32854713

33. Price A. J. et al., "Prevalence of obesity, hypertension, and diabetes, and cascade of care in sub-Saharan Africa: a cross-sectional, population-based study in rural and urban Malawi," *Lancet Diabetes Endocrinol.*, vol. 6, no. 3, pp. 208–222, 2018, https://doi.org/10.1016/S2213-8587(17)30432-1 PMID: 29371076

34. P. Elizabeth, "Antimicrobial resistance: What does medicine quality have to do with it?" 2015, [Online]. https://amr-review.org/sites/default/files/ElizabethPisaniMedicinesQualitypaper.pdf.

35. Van Assche K. et al., "Pharmaceutical quality assurance of local private distributors: A secondary analysis in 13 low-income and middleincome countries," *BMJ Glob. Heal.*, vol. 3, no. 3, pp. 1–10, 2018, https://doi.org/10.1136/bmjgh-2018-000771 PMID: 29915671

36. Orubu E. S. F., Ching C., Zaman M. H., and Wirtz V. J., "Tackling the blind spot of poor-quality medicines in Universal Health Coverage," *J. Pharm. Policy Pract.*, vol. 13, no. 1, pp. 1–10, 2020, https://doi.org/10.1186/s40545-020-00208-4 PMID: 32670594

37. Shukla S., Halli P., Khalid M. K., and Lundström M., "Waste Pharmaceutical Blister Packages as a Source of Secondary Aluminum," *Jom*, vol. 74, no. 2, pp. 612–621, 2022, https://doi.org/10.1007/s11837-021-05038-6

38. Berard V., Fiala C., Cameron S., Bombas T., Parachini M., and Gemzell-Danielsson K., "Instability of misoprostol tablets stored outside the blister: A potential serious concern for clinical outcome in medical abortion," *PLoS One*, vol. 9, no. 12, pp. 1–13, 2014, https://doi.org/10.1371/journal.pone.0112401 PMID: 25502819

39. Hagen N., Bizimana T., Kayumba P. C., Khuluza F., and Heide L., "Stability of misoprostol tablets collected in Malawi and Rwanda: Importance of intact primary packaging," *PLoS One*, vol. 15, no. 9 September, pp. 1–15, 2020, https://doi.org/10.1371/journal.pone.0238628 PMID: 32877459

40. K. Shafaat et al., "An overview: storage of pharmaceutical products," *World Journal of Pharmacy and Pharmaceutical Sciences*, 2013. https://www.researchgate.net/profile/Brajesh-Kumar-23/publication/258833887_an_overview_storage_of_pharmaceutical_products/links/00b7d5290e8cc7ee09000000.pdf.

41. USAID-Global-Health-Supply-Chain-Program, "Impact assessment of Pharmacy assistant graduates in Malawi health centres. A mixed method, quasi-experiemental evaluation of matched health facilities with and without pharmacy assistants," 2019. https://www.villagereach.org/wp-content/uploads/2021/11/Malawi_PA-Impact-Assessment-2019_FINAL-redesigned-for-website.pdf.

42. Khuluza F., Kadammanja P., Simango C., and Mukhuna M., "Did drug availability in Malawian central hospitals improve after the conversion of central medical stores to a trust?," *African J. Pharm. Pharmacol.*, vol. 10, no. 9, pp. 145–150, 2016, https://doi.org/10.5897/AJPP2015.4470

4.2 Effect of antibiotic medicines availability on adherence to standard treatment guidelines among hospitalized adult patients in Southern Malawi

4.2.1 Overview of the paper

Treatment guidelines are an important tool for improving rational prescribing of medicines. This paper presents the findings on point availability of antibiotic medicines and longitudinally over a six-months duration. We found lower than recommended level of antibiotic medicine availability in secondary level health facilities. Antibiotic stock outs significantly affected the adherence to the Malawi Standard Treatment Guidelines. Further, we also found a high use of 'Watch' antibiotics against the WHO recommendation of ensuring more than 60% of prescriptions being from the 'Access' class. We therefore recommend the Ministry of Health to ensure adequate budget allocation to improve the supply of antibiotic medicines and to intensify policy measures to improve rational prescribing of medicines and the adherence to STGs. There is a need to enforce the WHO recommendation that states that at least 60% of antibiotic prescriptions being from the access list to control the spread of antibacterial resistance.

PLOS ONE

RESEARCH ARTICLE

Effect of antibiotic medicines availability on adherence to standard treatment guidelines among hospitalized adult patients in southern Malawi

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Abstract

Background

Antibiotic resistance is a global public health problem. High and inappropriate use of antibiotic therapy exacerbate the risk of antibiotic resistance. We assessed the effect of availability of antibiotic medicines on adherence to standard treatment guidelines among hospitalized adult patients in Southern Malawi.

Methods

A cross-sectional study was done to assess the availability of 16 antibiotics among the first-line recommended treatments for common bacterial infections in Malawi. Data for up to six-month duration was extracted from stock card records in Machinga and Nsanje District Hospitals and Zomba Central Hospital. This was complemented by a retrospective review of 322 patient management files from medical wards to assess adherence to the Malawi Standard Treatment Guidelines (MSTG). Investigators abstracted data such as patient demographics, diagnoses, and prescribed therapy using a data collection form that resulted in analyzing 304 patient files. Data was entered into Microsoft excel and analyzed using STATA 14.1. Point availability, stock-out duration and adherence to treatment guidelines were presented in terms of frequencies and percentages. Chi-square test or Fisher's exact test was applied to assess the association between variables and adherence to treatment guidelines.

Results

Point availability of antibiotics was 81.5%, 87.7%, and 42.8% for Zomba Central, Machinga and Nsanje District Hospitals respectively. Over a period of six months, 12.5% of antibiotic medicines were stocked out for at least one day at Zomba (Median stock out days = 0, (IQR

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0–0 days), while 64.3% were stocked out at Machinga (Median stock out days = 21, IQR 0–31 days) and 85.7% were stocked out at Nsanje District Hospital (Median stock out days = 66.5, IQR 18–113 days). Overall, adherence to MSTG was 79.6%, (95% CI, 73.3–84.9%). By facilities, adherence to guidelines at Zomba Central Hospital was 95.9% (95% CI, 89.7–98.9%) while at Nsanje and Machinga District Hospitals was 73.2% (95% CI, 59.7–84.2%) and 54.2% (95% CI, 39.2–68.6%) respectively. Adherence to treatment guidelines was associated with health facility, presence of laboratory test results, antibiotic spectrum, and WHO-AWaRe category of the medicine, p<0.005. Adherence was lower for antibiotics that were stocked out than antibiotics that were not stocked out during the study period (63.8%, 95% CI 48.5–77.3% vs 84.4%, 95% CI 77.7–89.8%), p< 0.002.

Conclusion

We found unstable availability of antibiotic medicines in hospitals which might contribute to the sub-optimal adherence to standard treatment guidelines. This is a setback to efforts aimed at curbing antibiotic resistance in Malawi.

Background

Bacterial infections are amongst the leading causes of mortality globally [1]. Nearly 13% of deaths around the world are attributed to bacterial infections [2]. There are concerns of increasing incidences of antibiotic resistance due to the haphazard use of antibiotic therapy [3, 4]. In 2019, it was estimated that about five million deaths were associated with antibiotic resistance globally. Deaths associated with antibiotic resistance were highest in sub-Saharan Africa, with 98.9 deaths per 100,000 while in high-income countries the rate was 55.7 deaths per 100,000 [5]. The high burden of antibiotic resistance in low and middle-income countries (LMICs) is attributed to both high and inappropriate use of antibiotics [6]. In addition, an unstable supply of essential medicines in LMICs influences the inappropriate selection of antibiotic therapy [7].

A study conducted across 20 LMICs observed that more than 60% of out-patient pediatric patients were prescribed antibiotics, but their availability was as low as 40% in the majority of the countries [8]. In Malawi, the availability of essential medicines is limited as only about 50% of essential medicines were constantly available in public health facilities in 2017 [9]. Medicine availability may, however, vary depending on the type of medicine, health facility and season. For instance, the availability (in public health facilities) of adult formulation of amoxicillin, a commonly prescribed oral beta-lactam antibiotic [10, 11] was 60% in 2015 [12], while in 2017 another study revealed a higher availability of 100% [9]. Data for the two cross sectional studies was collected at different times. In addition, the latter study focused on public health facilities located in Blantyre and Lilongwe cities, while the other study focused on Blantyre city as well as three other surrounding rural districts.

Constant availability of medicines is one of the key indicators of a country's performance towards universal health coverage [13]. Essential medicine lists provide guidance on the prioritized medicines that are supposed to be in sufficient supply at all times in order to meet the healthcare needs of a country [14]. On the other hand, standard treatment guidelines are necessary to ensure the rational use of these medicines [15]. Adherence to treatment guidelines significantly reduces mortality and morbidity [16]. Furthermore, it improves cost-effectiveness and medicine supply chain efficiency [15].

Implementation of the essential medicine list concept in Malawi has been affected by several challenges such as higher medicine prices than what most hospitals can afford, inefficient procurement systems, and poor healthcare infrastructure [17]. The latest edition of the Malawi Essential Medicine List (MEML) was published in 2015 and is incorporated with the Malawi Standard Treatment Guidelines (MSTG) [18]. Due to the high prevalence of infectious diseases, the MEML gives much attention to antimicrobial agents, of which the majority are antibiotics [17]. Thus, as is the case in other LMICs, most prescriptions in Malawi are antibiotic therapy [19–21]. The Malawi antimicrobial resistance strategy was established in 2017 and aimed at achieving 100% optimization of the use of antibiotic therapy by 2022 [22]. In this study, we evaluated the availability of selected antibiotic medicines and its influence on adherence to national guidelines (MSTG) for prescribing antibiotics among hospitalized adult patients.

Methods

Study design and setting

A cross sectional study was conducted to collect data on point availability of antibiotic medicines in February 2022. This was supplemented by data on medicine stock-outs in the past six months. To assess the adherence of therapy to national standard treatment guidelines, we retrospectively reviewed records for patients admitted to medical wards. The study was conducted in two secondary-level health facilities (district hospitals) in the Machinga and Nsanje districts and a tertiary-level health facility (central hospital) in Zomba district. The districts were randomly selected among 13 districts in southern Malawi using RAND function in Microsoft Excel.

Criteria for selection of antibiotic medicines

We purposively selected first-line antibiotics for common bacterial infections as stated in the 2015 Malawi Standard Treatment Guidelines (MSTG) which was the latest version at the time of the study [18]. Common bacterial infections in Malawi include: sepsis, respiratory tract infections such as pneumonia, sinusitis, and bronchitis, HIV and AIDS complications such as meningitis, urinary tract infections such as cystitis and urethritis, cellulitis and other skin conditions, and sexually transmitted diseases such as syphilis and genital ulcers [23–29]. In this study, we included the first line antibiotic therapy for these common conditions as recommended in the MSTG. **S1 Table** provides more details on the treatment protocols for the conditions. Thus, we included gentamicin, ceftriaxone, erythromycin, azithromycin, clarithromycin, metronidazole, amoxicillin, cloxacillin, flucloxacillin, benzylpenicillin, benzathine benzylpenicillin, ciprofloxacin, nalidixic acid, co-trimoxazole, doxycycline and meropenem. The selected antibiotics represent 45.7% of all antibiotics in adult formulations (N = 35) in the MEML. Unlike the other antibiotics, meropenem and clarithromycin are mostly found in tertiary level hospitals, as they are reserved for rare and life-threatening conditions caused by multi-drug resistant bacteria [30]. As such, the availability of meropenem and clarithromycin was only assessed at tertiary hospital and not the secondary (district) level hospitals. As for both benzathine benzylpenicillin and benzylpenicillin, they were included as they are used for two different conditions. Benzathine benzylpenicillin is mainly used as first-line treatment for sexually transmitted diseases in Malawi while benzylpenicillin is for routine infections. This is because the addition of benzathine makes the combination more long-acting as such ideal for sexually transmitted diseases unlike benzylpenicillin which needs four time administration.

Study population and sampling

A total of 322 patient records were randomly sampled across the facilities. The sample size was determined using a single population proportion formula: $n = p(1\text{-}p)\ ^*Z^2/d^2$ [31]. We estimated p as 30%, 0.05 margin of error (E) and 1.96 Z value corresponding to 0.05 significance level. The inclusion criteria were hospitalized patients with aged $\geq$ 18 years old, who were given antibiotics as the main treatment. Medical records with missing information such as medication charts and demographic information were excluded from the study.

Data collection

FKC, HMN, and FK reviewed stock cards in medicine storage facilities to collect data on the availability of antibiotic medicines on the day of data collection (point availability) and over the past six months using a data collection form (**S2 Table**). This data included stock remaining on the shelf and the number of stocked-out days within the six-month duration for each medicine type. Stocked-out days were obtained by counting the number of days the product was not available for use in the stock card from the day the balance was zero to the day when they received a new supply. A new supply would be received from either Central Medical Stores Trust, private pharmaceutical suppliers, or other health facilities in line with the Malawi Health Commodity Logistics Management system Standard Operating Procedures Manual [32]. A stock card (also called an inventory control card) is a stock-keeping record that is used for recording the inflow and outflow of pharmaceuticals in Malawi [33]. Generally, stock cards are kept in the Pharmacy for seven years before they are sent for archiving at the central office, as such all information for this study was available in the facilities. FKC, HMN, and FK further abstracted demographics and clinical data such as patient diagnosis and prescribed therapy from case management files of eligible patients. Antibiotic treatment was compared with treatment protocols in the 2015 edition of Malawi Standard Treatment Guidelines for the specified diagnosis, to assess for adherence to treatment guidelines.

Statistical analysis

All data were entered into Microsoft Excel and analyzed in STATA version 14.1. Availability of medicines was described in terms of percentages of antibiotic medicines that were not available on the day of data collection or at least one day in the past six months. Furthermore, stock-out days for each medicine type were described in terms of frequencies. Antibiotic regimens that were not in line with the MSTG were quantified and Chi-square test was used to assess the association between variables and adherence to the guidelines. Only in cases where the cell number was $\leq$ 5, Fisher's exact test was applied.

Results

Classification of antibiotic medicines

Availability of medicines was assessed among 16 antibiotics. These were five penicillin antibiotics, three macrolides, two quinolones, one aminoglycoside, one cephalosporin, one nitroimidazole, one tetracycline, one carbapenem and one fixed dose combination of sulfonamide and trimethoprim. According to the WHO Access, Watch and Reserve (AWaRe) classification [34], 56% (9/16) were access antibiotics, 38% (6/16) were watch antibiotics, and one antibiotic was unclassified. Anatomical, chemical, and therapeutic categories are shown in **Table 1**. According to Malawi Essential Medicines List (MEML), 87.5% (14/16) of the antibiotic medicines were classified as vital medicines, 12.5% (2/16) were essential medicines and none of the antibiotics was classified as non-essential medicine. In terms of level of access, all the antibiotic

Table 1. Classifications of antibiotic medicines.

Antibiotic name (generic)	Dosage form	Antibiotic class	ATC code[1]	Spectrum of activity	AWARE category	MEML category[2]
Gentamycin	Injectable	Aminoglycoside	J01GB03	Broad	Access	HVA
Ceftriaxone	Injectable	Cephalosporin	J01DD04	Broad	Watch	DVA
Erythromycin	Solid (Tabs or caps)	Macrolide	J01FA01	Broad	Watch	HVA
Azithromycin	Solid (Tabs or caps)	Macrolide	J01FA10	Broad	Watch	DEA
Clarithromycin	Solid (Tabs or caps)	Macrolide	J01FA09	Broad	Watch	CVA
Metronidazole	Solid or injectable	Nitroimidazole	J01XD01 or J01AB01	Broad	Access	HVA
Amoxicillin	Solid (Tabs or caps)	Penicillin	J01CA04	Broad	Access	HVA
Cloxacillin	Solid (Tabs or caps)	Penicillin	J01CF02	Broad	Access	DEA
Flucloxacillin	Solid (Tabs or caps)	Penicillin	J01CF05	Narrow	Access	DVA
Benzyl penicillin	Injectable	Penicillin	J01CE01	Narrow	Access	HVA
Benzanthine penicillin	Injectable	Penicillin	J01CE08	Narrow	Access	HVA
Ciprofloxacin	Solid (Tabs or caps)	Quinolone	J01MA02	Broad	Watch	DVB
Nalidixic acid	Solid (Tabs or caps)	Quinolone	J01MB02	Narrow	Unclassified	DVA
Cotrimoxazole	Solid (Tabs or caps)	Sulfonamide-trimethoprim-combination	J01EE01	Broad	Access	HVA
Doxycycline	Solid (Tabs or caps)	Tetracycline	J01AA02	Broad	Access	HVA
Meropenem	Injectable	Carbapenem	J01DH02	Broad	Watch	CVA

[1]ATC = Anatomical, therapeutic and chemical classification.

[2]The Malawi Essential Medicines List (MEML) of 2015 specifies the level of health institution at which the medicine is normally permitted for use: H = at health centre, district hospital and central hospital levels; D = at district hospital and central hospital levels only; C = at central hospital level only; N = level of use not specified. The 'therapeutical priority' code categorizes medicines based on therapeutic importance of each medicine by the use of: V = vital medicines which are potentially life-saving, of major public health relevance and having significant withdraw side-effects; E = essential medicines which are effective against less severe, but nonetheless significant forms of illness; N = non-essential medicines which are used for minor self-limiting illness and are often of questionable efficacy. The third categorization of 'procurement system' has two codes: 'A' = medicines required by a large number of patients as such to be routinely procured and stocked by CMST; and 'B' = medicines required for a limited number of patients and not routinely stocked by CMST).

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medicines were required to be available at both district and central hospitals except for meropenem and clarithromycin which were designated to be available at central hospitals only.

Patient characteristics

From the 322 patient files, 18 files were excluded due to missing data; thus, a final total of 304 patient files were analyzed. Of the 304 patients, 48% were female with a mean age of 45.9 years, range (18–96 years), while 52% were male with a mean age of 46.1 years, range (18–92 years). Antibiotics were used for treatment in 71.4% (n = 217) of cases while they were used for prophylaxis in 28.6% (n = 87) of the cases (**Table 2**). No bacterial culture or antibiotic sensitivity test was conducted to aid in the diagnosis and selection of antibiotics respectively. Full blood count (FBC) was done in 56.6% (n = 172) of the patients. Only broad-spectrum antibiotics were used in 71.7% (n = 218) of patients while narrow-spectrum antibiotics were used in 7.6% (n = 23) of patients. The remaining 20.7% (n = 63) received a combination of broad and

Table 2. Patient's characteristics and reasons for receiving antibiotic therapy.

Variable	Characteristic	Antibiotics used for treatment n (%)	Antibiotics used for prophylaxis n (%)
Age	Years	43 (30–62)[1]	46 (35–60)[1]
Sex	Male	113 (52.1)	45 (51.7)
	Female	104 (47.9)	42 (48.3)
Facility	ZA CTL	99 (71.7)	39 (28.28)
	MGH DHO	55 (65.5)	29 (34.5)
	NE DHO	63 (76.8)	19 (23.2)
Antibiotic types given	Number per prescription	1 (1–2)[1]	1 (1–2)[1]
Antibiotic spectrum	Broad spectrum antibiotics	159 (72.9)	50 (27.1)
	Narrow spectrum antibiotics	10 (43.5)	13 (56.5)
	Broad + Narrow spectrum antibiotics	48 (76.2)	15 (23.8)
WHO AWaRe group	Access group	49 (65.3)	26 (34.7)
	Watch group	101 (71.63)	40 (28.4)
	Access + Watch group	67 (76.1)	21 (23.9)
Full Blood count	Done	126 (73.3)	46 (26.7)
	Not done	91 (68.9)	41 (31.1)
Bacterial culture	Done	0 (0)	0 (0)
	Not done	217 (71.4)	87 (28.6)
Sensitivity test	Done	0 (0)	0 (0)
	Not done	217 (71.4)	87 (28.6)

[1]Presented as Median (Interquartile range)

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narrow spectrum antibiotics. Among those who received broad-spectrum antibiotics only, 72.9% (n = 159) were for treatment whilst 27.1% (n = 50) were for prophylaxis. Of those who received narrow spectrum antibiotics, 43.5% (n = 10) were for treatment while 56.5% (n = 13) were for prophylaxis. By AWARE classification, 24.6% (n = 75) received access antibiotics, 46.4% (n = 141) watch antibiotics and 29% (n = 88) received a combination of access and watch antibiotics. Among those who received access antibiotics, 65.3% (n = 49) were for treatment while 34.7% (n = 26) were for prophylaxis. For those who received watch antibiotics, 71.6% (n = 101) were for treatment while 28.4% (n = 40) were for prophylaxis.

Medicine availability

There was a significant variation in antibiotic availability among facilities, $p < 0.035$. On the days of data collection, 81.5% (13/16) of the antibiotics were available at Zomba Central Hospital, 87.7% (12/14) at Machinga District Hospital, and 42.8% (6/14) were available at Nsanje District Hospital (**Fig 1**). Medicines that were not available at Zomba were erythromycin, clarithromycin, and cloxacillin. For Machinga, medicines that were not available were cloxacillin and nalidixic acid while for Nsanje, it was gentamycin, erythromycin, azithromycin, metronidazole, amoxicillin, cloxacillin, ciprofloxacin, and nalidixic acid. Zomba Central Hospital had the lowest rate of stock-outs in the past six months from the day of data collection. Only 12.5% (2/16) of the medicines were stocked out for at least one day. On the other hand, 64.3% (9/14) and 85.7% (12/14) of the medicines were stocked out at Machinga and Nsanje district hospitals respectively.

Stock out duration

Stock out duration was highest at Nsanje, followed by Machinga and Zomba. Median stock out days were 66.5 days (IQR 18–113 days), 21 days (IQR 0–31 days), and 0 days (IQR 0–0

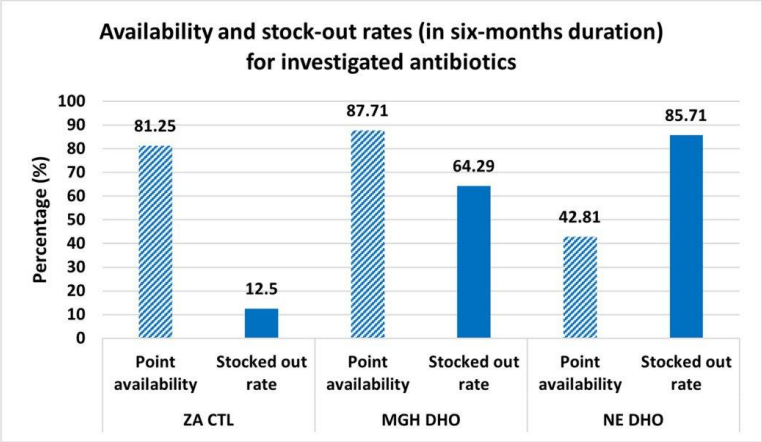

Fig 1. Percentage of investigated antibiotics which were available on the day of data collection and for which stock-outs were reported in six-month duration. ZA CTL = Zomba Central Hospital, MGH DHO = Machinga District Hospital, NE DHO = Nsanje District Hospital.

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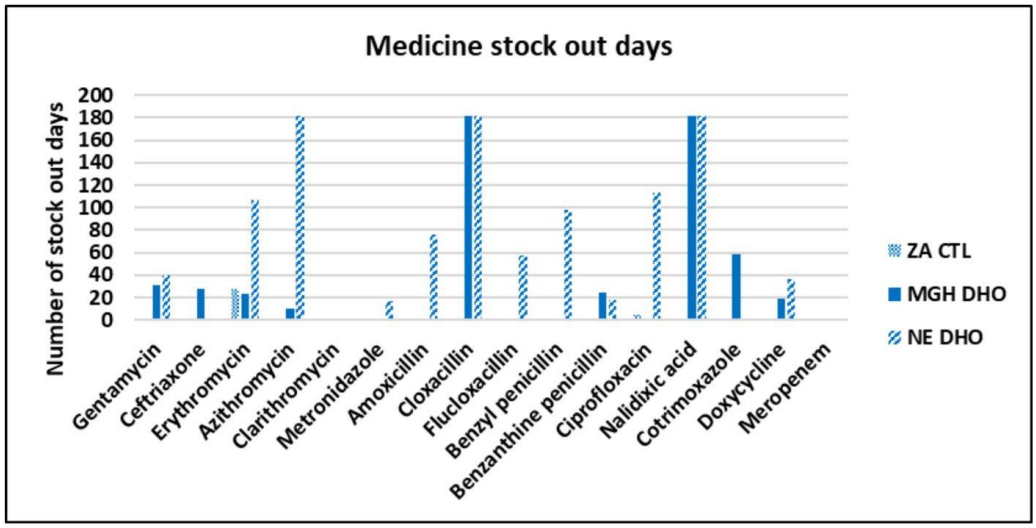
days) for Nsanje, Machinga and Zomba respectively. For Zomba Central Hospital, only erythromycin and ciprofloxacin had stock outs for 28 and five days respectively. Medicines with highest stock out days at Machinga District Hospital were cloxacillin and nalidixic acid, which were not available for the entire six month-duration (Fig 2). These were followed by cotrimoxazole (59 days), gentamicin (31 days), ceftriaxone (28 days), benzathine benzylpenicillin (25 days) erythromycin (23 days), doxycycline (19 days) and azithromycin (10 days). Nsanje District Hospital had the highest level of antibiotic stock outs. Azithromycin, cloxacillin and nalidixic acid were not available for the whole six month-duration and were followed by ciprofloxacin (113 days), erythromycin (107 days), benzylpenicillin (98 days), amoxicillin (76 days), flucloxacillin (57 days), gentamicin (40 days), doxycycline (37 days), and metronidazole (17 days).

Use of antibiotic therapy

Common diagnoses among participants were sepsis (25.7%), pneumonia (19.7%), meningitis (4.9%), cellulitis (3.6%) and peptic ulcers (3.0%). A total of 471 antibiotic medicines were prescribed. The most prescribed antibiotic was ceftriaxone (46.7%, n = 220). This was followed by metronidazole (22.5%, n = 106), benzylpenicillin (13.0%, n = 61), gentamicin (6.4%,n = 30), amoxicillin (4.3%, n = 20), cotrimoxazole (1.5%, n = 7), doxycycline (1.3%, n = 6), flucloxacillin (1.1%, n = 5), erythromycin (0.9%, n = 4), amoxicillin/clavulanic acid (0.4%, n = 2), azithromycin (0.2%, n = 1) and benzathine benzylpenicillin (0.2%, n = 1) (Fig 3). Among the participants, 52.3% received single antibiotic therapy while 45.7% received a combination therapy of antibiotics. Common antibiotic combinations were ceftriaxone and metronidazole (17.4%, n = 53); benzyl penicillin and gentamicin (5.3%, n = 16); and amoxicillin and metronidazole (4.3%, n = 13) (S1 Fig).

By facilities, ceftriaxone was the most prescribed antibiotic at Zomba (75.6%, n = 132) and Nsanje (32%, n = 48), while benzyl penicillin was the most prescribed antibiotic at Machinga (28.5%, n = 42). In terms of patient diagnosis, ceftriaxone was mostly prescribed for sepsis



ZA CTL = Zomba Central Hospital, MGH DHO = Machinga District Hospital, NE DHO = Nsanje District Hospital

Fig 2. Stock out duration for various antibiotic medicines per facility in six-month duration. ZA CTL = Zomba Central Hospital, MGH DHO = Machinga District Hospital, NE DHO = Nsanje District Hospital.

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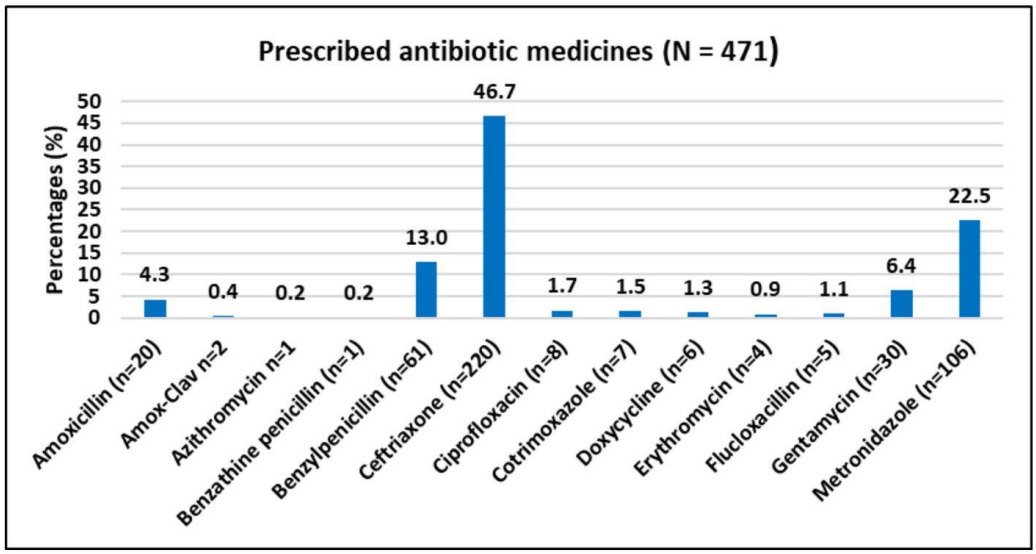

Fig 3. Prescribed antibiotic therapy in the study.

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Table 3. Prescribed antibiotics by facility and diagnosis.

Name of antibiotic	By facility n, (%)			By diagnosis n, (%)					
	Zomba N = 174	Machinga N = 147	Nsanje N = 150	Sepsis N = 118	Pneumonia N = 88	Meningitis N = 20	Cellulitis N = 21	Peptic ulcers N = 17	Others N = 207
Amoxicillin	5 (2.9)	2 (1.4)	13 (8.7)	5 (4.2)	1 (1.1)	0 (0)	0 (0)	4 (23.5)	10 (4.9)
Amox- Clav	2 (1.2)	0 (0)	0 (0)	0 (0)	2 (2.3)	0 (0)	0 (0)	0 (0)	0 (0)
Azithromycin	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)
Benzathine benzylpenicillin	0 (0)	0 (0)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.5)
Benzylpenicillin	1 (0.6)	42 (28.5)	18 (12)	15 (12.7)	11 (12.5)	1 (5)	3 (14.3)	4 (11.8)	29 (14.0)
Ceftriaxone	132 (75.9)	40 (27.2)	48 (32)	60 (50.9)	50 (56.9)	14 (70)	8 (38.1)	3 (17.7)	85 (41.1)
Ciprofloxacin	1 (0.6)	4 (2.7)	3 (2)	2 (1.7)	1 (1.1)	2 (10)	0 (0)	0 (0)	3 (3.1)
Cotrimoxazole	1 (0.6)	1 (0.7)	5 (3.3)	2 (1.7)	1 (1.1)	1 (5)	1 (4.8)	0 (0)	2 (1.0)
Doxycycline	0 (0)	0 (0)	6 (4)	3 (2.5)	0 (0)	0 (0)	0 (0)	0 (0)	3 (1.45)
Erythromycin	2 (1.15)	1 (0.7)	1 (0.7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	4 (1.9)
Flucloxacillin	1 (0.6)	0 (0)	4 (2.7)	1 (0.9)	0 (0)	0 (0)	3 (14.3)	0 (0)	1 (0.5)
Gentamycin	1 (0.6)	20 (13.6)	9 (6)	8 (6.8)	8 (9.1_	2 (10)	0 (0)	1 (5.9)	11 (5.3)
Metronidazole	28 (16.1)	36 (24.5)	42 (28)	22 (18.6)	14 (15.9)	0 (0)	6 (28.6)	7 (41.2)	57 (27.5)

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(50.9%, n = 60), pneumonia (56.9%, n = 50), meningitis (70%, n = 14), and cellulitis (38.1%, n = 8). In peptic ulcers, the most prescribed antibiotics were metronidazole (41.2%, n = 8) and amoxicillin (23.5%, n = 4) (**Table 3**).

Adherence to treatment guidelines

Only 66% (201/304) of cases were assessed for adherence of antibiotic prescribing to treatment guidelines, as the MSTG does not include adequate information on the use of antibiotics for prophylaxis and other uncommon conditions. Adherence to MSTG was associated with health facility, presence of laboratory test results (FBC), spectrum of prescribed antibiotics, and WHO-AWaRe classification of the medicine, $p<0.005$. Overall, adherence to MSTG was 79.6%, (95% CI, 73.3–84.9%). By facilities, adherence to guidelines at Zomba was 95.9% (95% CI, 89.7–98.9%) while at Nsanje and Machinga was 73.2% (95% CI, 59.7–84.2%) and 54.2% (95% CI, 39.2–68.6%) respectively (**Table 4**). There was high adherence to MSTG for management of meningitis with 93.3% (95% CI, 68–99.8%) of the cases being treated according to the guidelines. The adherence was 90.9% (95% CI, 58.7–99.7%) for cellulitis, 83.3% (95% CI, 71.4–91.7%) for pneumonia, 79.5% (95% CI, 68.8–87.8%) for sepsis, 44% (95% CI, 13.7–78.8%) for peptic ulcers and 71.4% (95% CI, 51.3–86.8%) for miscellaneous conditions such as urinary tract infections, syphilis, and dysentery. There was 93.2% (95% CI, 87.9–96.7%) adherence on the prescribing of broad-spectrum antibiotics while for narrow-spectrum antibiotics adherence was 10% (95% CI, 2.5–44.5%). By AWARE classification, adherence for access antibiotics was 27.3% (95%, 14.9–42.8%), while for watch antibiotics was 98% (95% CI, 92.8–99.7%). Adherence to MSTG was lower for antibiotics that were stocked out (63.8%, 95% CI 48.5–77.3%) than antibiotics that were not stocked out during the study period (84.4%, 95% CI 77.7–89.8%), $p< 0.002$.

Discussion

This study was conducted at one tertiary (central) hospital and two secondary-level (district) hospitals in southern Malawi. We found that the selected tertiary-level facility had better

Table 4. Adherence of antibiotic treatment to Malawi Standard Treatment Guidelines.

Variable	Characteristic	Total	Adherence to MSTG		P value[1]
			Yes	No	
Age	<30	57	40 (70.2)	17 (29.8	0.133
	31–45	52	41 (78.8)	11 (21.2)	
	46–64	42	37 (88.1)	5 (11.9)	
	> 65	50	42 (84.1)	8 (16.0)	
Sex	Female	95	79 (83.2)	16 (16.8)	0.236
	Male	106	81 (76.4)	25 (23.6)	
Facility	ZA CTL	97	93 (95.9)	4 (4.1)	<0.001
	MGH DHO	48	26 (54.2)	22 (45.8)	
	NE DHO	56	41 (73.2)	15 (26.8)	
Diagnosis	Sepsis	78	62 (79.5)	16 (20.5)	0.072
	Pneumonia	60	50 (83.3)	10 (16.7)	
	Meningitis	15	14 (93.3)	1 (6.7)	
	Cellulitis	11	10 (90.9)	1 (9.1)	
	Peptic ulcers	9	4 (44.4)	5 (55.6)	
	Others	28	20 (71.4)	8 (28.6)	
FBC test	Not Done	81	55 (67.9)	26 (32)	0.001
	Done	120	105 (87.5)	15 (12.5)	
Diagnosis by system	Cardiovascular	1	1 (100)	0 (0)	0.031
	Central Nervous	16	14 (87.5)	2 (12.5)	
	Dermatological	20	17 (85.0)	3 (15.0)	
	Gastrointestinal	17	8 (47.1)	9 (52.9)	
	Immune	77	61 (79.2)	16 (20.8)	
	Respiratory	66	55 (83.3)	11 (16.7)	
	Urogenital	4	4 (100)	0 (0)	
Spectrum	Broad	148	138 (93.2)	10 (6.8)	<0.001
	Narrow	10	1 (10)	9 (90)	
	Broad + Narrow	43	21 (48.8)	22 (51.2)	
WHO AWARE	Access	44	12 (27.3)	32 (72.7)	<0.001
	Watch	97	97(98.0)	2 (2.0)	
	Access + Watch	58	51 (87.9)	7 (12.1)	

[1]P values are based on chi-square test. Where the cell number was ≤5, Fisher's exact test was used. P values ≤ 0.05 were considered significant.

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availability of the required antibiotics compared with the two district hospitals, with one having much worse availability.

Despite the differences in the level of patient care, all public health facilities procure most of their medicines through the Central Medicine Stores Trust (CMST) with few exceptions [35]. During the period of data collection, the central hospitals were allowed to purchase any medicine/pharmaceutical product that was not available at CMST from private pharmaceutical suppliers, unlike district hospitals. Between 2019 and 2023, budget allocation for pharmaceutical purchases has been between 20 and 30 million US$ per year of which approximately 40% is meant for four central hospitals while the rest is shared among the 28 districts [36, 37]. The flexibility by central hospitals to use their budgetary allocation in purchasing from private suppliers and the increased share of the budget best explains the higher availability of antibiotics in central hospitals than in district hospitals.

The availability of antibiotics at Nsanje District Hospital was very poor as compared to Machinga District Hospital. As noted, the point availability was below 50% at Nsanje District

Hospital. In addition, more than 80% of the antibiotics were stocked out within a six-month duration. This could be partially attributed to tropical cyclone Ana and cyclone Dumako which heavily hit the district in January and February 2022 respectively [38]. The disaster resulted in disruption of healthcare delivery including pharmaceutical logistics and supply as most of the roads were rendered impassable. All public health facilities in Malawi receive medical supplies once a month from CMST, as such, the impassable roads meant that there were very few deliveries of normal supply to Nsanje. Moreover, healthcare workers including pharmacy personnel were temporarily re-deployed to various camps where they provided relief healthcare services [38] and thus, affecting quantification and procurement of pharmaceuticals.

The MEML classifies medicines as non-essential, essential, and vital (see legend of Table 1). On the other hand, WHO classifies antibiotic medicines as access, watch, and reserve antibiotics (AWaRe classification) [39]. Most of the antibiotic medicines in MEML are categorized as vital medicines. In our study, only azithromycin and cloxacillin were classified as essential medicines. Both azithromycin and cloxacillin had poor availability at district hospitals but were constantly available at central hospital. By WHO AWaRe categories, the availability of antibiotics did not vary significantly between classes. As noted, 51.8% of access antibiotics were stocked out within six months, and 42.9% of watch antibiotics were stocked out within the same duration. It is most likely that procurement of antibiotics in Malawi does not consider the WHO AWaRe classifications as at the time of the study, few guiding documents aligned the MEML with the WHO AWaRe principles. On the other hand, the latest edition of the WHO model EML was compiled based on the AWaRe classification. This was done with the intentions of improving not just the access to antibiotic therapy but also the quality of antibiotic use, as a way of minimizing antibiotic resistance [40]. The incorporation of the AWARE category in the current 2023 MSTG is a positive development for the future of antibiotic procurement and prescribing in Malawi [41].

The 2015 MSTG provided limited information on the use of antibiotics for prophylaxis and uncommon conditions. The adherence to MSTG for such cases was therefore not assessed in the study. Consistent with other LMICs and previous studies done in Malawi, sepsis and pneumonia were the most common diagnoses in this study [1, 42]. However, the level of diagnostic certainty was low as the diagnoses were all based on clinical presentations without laboratory confirmation [43]. Only FBC was applied in 57% of cases in this study. However, studies have reported a low sensitivity and specificity in the diagnosis of bacterial infections using FBC [44]. As further noted in this study, no sensitivity test or bacterial culture was conducted. This could be one of the reasons for more prescriptions of broad-spectrum antibiotics than narrow-spectrum antibiotics.

Globally, it is recommended that adherence to treatment guidelines for prescribing antibiotics should be >95%. In this study, we found varying rates of adherence to MSTG among the facilities. The adherence to MSTG was assessed based on the records of prescribed antibiotic regimens to patients. Although nurses record in the patient management files when administering the medicines (by indicating the time of administration), it was difficult to confirm retrospectively whether the medicines were administered correctly. Zomba Central Hospital had the highest and optimal level of adherence to guidelines with 95.9% of antibiotics prescribed according to the MSTG. The adherence to guidelines for Zomba Central Hospital was higher than the results of a study conducted at Queen Elizabeth Central Hospital (QECH) in Blantyre district in 2018, which found 84% adherence to antibiotic prescriptions to treatment guidelines [42]. The QECH is one of the four major referral and teaching hospitals in Malawi [45]. Adherence to MSTG was sub-optimal for both Machinga and Nsanje District Hospitals (54.2% and 73.2% respectively).

In this study, we noted that most of the antibiotic therapies that were not in line with the MSTG were combination therapies as compared to single antibiotic therapies. Nevertheless, some of the common antibiotic combinations were rational. For instance, the combination of ceftriaxone with metronidazole is recommended for sepsis if the presumed or known source is intrabdominal. A combination of amoxicillin and metronidazole is also a standard care for the eradication of *Helicobacter pylori* in peptic ulcers [18]. Availability of first-line antibiotics was significantly associated with the level of adherence to MSTG. As noted, although for the two district hospitals, the availability of antibiotics medicines was better in Machinga, the overall adherence to MSTG was poorer as compared to Nsanje District Hospital. This was because Machinga experienced the longest duration for stock out of ceftriaxone, which is the agent of choice for severe sepsis and pneumonia. This could therefore explain why more cases were managed without following guidelines at Machinga District Hospital as compared to Nsanje District Hospital.

The WHO set a target that more than 60% of antibiotics prescribed at the national level should be from the Access category [46]. Although the choice of ceftriaxone is justifiable in most cases according to the MSTG, the overuse of the antibiotic in Malawi is a concern. Ceftriaxone is categorized as a Watch antibiotic by WHO. Thus, the use of this antibiotic needs to be controlled since it has an increased risk of inducing resistance [34]. In addition, cephalosporin antibiotics have been reported to induce cross-resistance with penicillin antibiotics, which are commonly prescribed in primary care in Malawi [11].

Limitations

This study focused on a few facilities which were only one central and two district hospitals. Primary health center facilities, which serve most of the population in these districts, were not included in the study. The retrospective study design for assessing adherence to guidelines is also another limitation as the data may be biased by missing information in the case management files. In addition, the study did not explore further other possible factors that affected clinician's decisions on the selection of antibiotics.

Conclusion

The current study revealed that stock out of antibiotic medicines is still a challenge across facilities. The linkage between availability and adherence to standard treatment guidelines suggests that poor availability of medicines may be one of the contributing factors to inappropriate use of antibiotic therapy and consequently increase the risk of antibiotic resistance. Further studies that can validate these findings are necessary for further guidance in antibiotic selection and prescribing policy. In addition, we also recommend the adoption of WHO AWaRe classification to help minimize the overuse of antibiotics with a high risk of antibiotic resistance.

Supporting information

S1 Checklist. STROBE statement—checklist of items that should be included in reports of observational studies.
(DOCX)

S1 Table. Antibiotic treatment protocols for common bacterial infections in Malawi based on 2015 Malawi Standard Treatment Guidelines.
(PDF)

S2 Table. Data collection forms.
(PDF)

S1 Fig. Showing combination of antibiotics prescribed.
(PNG)

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References

1. Bhattarai S, Sharma BK, Subedi N, Ranabhat S, Baral MP. Burden of Serious Bacterial Infections and Multidrug-Resistant Organisms in an Adult Population of Nepal: A Comparative Analysis of Minimally Invasive Tissue Sampling Informed Mortality Surveillance of Community and Hospital Deaths. Clin Infect Dis. 2021; 73(Suppl_5):S415–S421. https://doi.org/10.1093/cid/ciab773 PMID: 34910184
2. Ikuta K. S. et al., "Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019," *Lancet*, vol. 400, no. 10369, pp. 2221–2248, 2022, https://doi.org/10.1016/S0140-6736(22)02185-7 PMID: 36423648
3. Barbosa TM, Levy SB. The impact of antibiotic use on resistance development and persistence. Drug Resist Updat. 2000; 3(5):303–311. https://doi.org/10.1054/drup.2000.0167 PMID: 11498398
4. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018; 115(15):E3463–E3470. https://doi.org/10.1073/pnas.1717295115 PMID: 29581252
5. Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis [published correction appears in Lancet. 2022 Oct 1; 400(10358):1102]. Lancet. 2022; 399(10325):629–655. https://doi.org/10.1016/S0140-6736(21)02724-0 PMID: 35065702

6. Sartelli M C Hardcastle T, Catena F, et al. Antibiotic Use in Low and Middle-Income Countries and the Challenges of Antimicrobial Resistance in Surgery. Antibiotics (Basel). 2020; 9(8):497. Published 2020 Aug 9. https://doi.org/10.3390/antibiotics9080497 PMID: 32784880

7. Kamere N, Rutter V, Munkombwe D, et al. Supply-chain factors and antimicrobial stewardship. Bull World Health Organ. 2023; 101(6):403–411. https://doi.org/10.2471/BLT.22.288650 PMID: 37265674

8. Knowles R, Sharland M, Hsia Y, et al. Measuring antibiotic availability and use in 20 low- and middle-income countries. Bull World Health Organ. 2020; 98(3):177–187C. https://doi.org/10.2471/BLT.19.241349 PMID: 32132752

9. Khuluza F, Haefele-Abah C. The availability, prices and affordability of essential medicines in Malawi: A cross-sectional study. PLoS One. 2019; 14(2):e0212125. Published 2019 Feb 12. https://doi.org/10.1371/journal.pone.0212125 PMID: 30753219

10. Ewing AC, Davis NL, Kayira D, et al. Prescription of Antibacterial Drugs for HIV-Exposed, Uninfected Infants, Malawi, 2004–2010. Emerg Infect Dis. 2019; 25(1):103–112. https://doi.org/10.3201/eid2501.180782 PMID: 30561313

11. Dixon J, MacPherson EE, Nayiga S, et al. Antibiotic stories: a mixed-methods, multi-country analysis of household antibiotic use in Malawi, Uganda and Zimbabwe. BMJ Glob Health. 2021; 6(11):e006920. https://doi.org/10.1136/bmjgh-2021-006920 PMID: 34836911

12. Khuluza F and Heide L. Availability and affordability of antimalarial and antibiotic medicines in Malawi. *PLoS One*, vol. 12, no. 4, pp. 1–15, 2017, https://doi.org/10.1371/journal.pone.0175399 PMID: 28419126

13. Bigdeli M, Laing R, Tomson G, and Babar ZUD. Medicines and universal health coverage:Challenges and opportunities. *J. Pharm. Policy Pract.*, vol. 8, no. 1, pp. 1–3, 2015, https://doi.org/10.1186/s40545-015-0028-4 PMID: 25825675

14. World Health Organization. WHO model list of essential medicines - 22nd list, 2021. *Tech. Doc.*, p. 2021, 2021, [Online]. Available: https://www.who.int/publications/i/item/WHO-MHP-HPS-EML-2021.02.

15. Govender T, Suleman F, Perumal-Pillay VA. Evaluating the implementation of the standard treatment guidelines (STGs) and essential medicines list (EML) at a public South African tertiary institution and its associated primary health care (PHC) facilities. J Pharm Policy Pract. 2021; 14(1):105. Published 2021 Dec 14. https://doi.org/10.1186/s40545-021-00390-z PMID: 34906236

16. Kruger M. The importance of standard treatment guidelines in paediatric practice in Africa [Editorial]. *Public Heal. Action*, vol. 3, no. 2, pp. 94–94, 2013, https://doi.org/10.5588/pha.13.0042 PMID: 26393006

17. Aitken M. Understanding the Role and Use of Essential Medicines Lists. IMS Inst. *Healthc. Informatics*, no. April, pp. 13, 16–39, 2015, [Online]. Available: https://www.farmaindustria.es/web_en/wp-content/uploads/sites/3/2015/04/IIHI_Essential_Medicines_Report_2015-Web3.pdf.

18. Ministry-of-Health. Malawi Standard Treatment Guidelines. Incorporating Malawi Essential Medicines List 2015. https://extranet.who.int/ncdccs/Data/MWI_D1_Malawi-Standard-Treatment-Guidelines-Essential-Medicines-List-2015.pdf.

19. Alabi ME and Essack SY. Antibiotic prescribing amongst South African general practitioners in private practice: an analysis of a health insurance database. *JAC-Antimicrobial Resist.*, vol. 4, no. 5, pp. 1–8, 2022, https://doi.org/10.1093/jacamr/dlac101 PMID: 36196441

20. Sulis G, Adam P, Nafade V, et al. Antibiotic prescription practices in primary care in low- and middle-income countries: A systematic review and meta-analysis. PLoS Med. 2020; 17(6):e1003139. Published 2020 Jun 16. https://doi.org/10.1371/journal.pmed.1003139 PMID: 32544153

21. Siachalinga L, Godman B, Mwita JC, et al. Current Antibiotic Use Among Hospitals in the sub-Saharan Africa Region; Findings and Implications. Infect Drug Resist. 2023; 16:2179–2190. Published 2023 Apr 13. https://doi.org/10.2147/IDR.S398223 PMID: 37077250

22. Government of Malawi. Antimicrobial Resistance Strategy 2017–2022. 2018, [Online]. Available: https://www.who.int/publications/m/item/malawi-antimicrobial-resistance-strategy-2017-2022.

23. Musicha P, Cornick JE, Bar-Zeev N, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi (1998–2016): a surveillance study. Lancet Infect Dis. 2017; 17(10):1042–1052. https://doi.org/10.1016/S1473-3099(17)30394-8 PMID: 28818544

24. Makoka MH, Miller WC, Hoffman IF, et al. Bacterial infections in Lilongwe, Malawi: aetiology and antibiotic resistance. BMC Infect Dis. 2012; 12:67. Published 2012 Mar 21. https://doi.org/10.1186/1471-2334-12-67 PMID: 22436174

25. Kayambankadzanja RK, Lihaka M, Barratt-Due A, et al. The use of antibiotics in the intensive care unit of a tertiary hospital in Malawi. BMC Infect Dis. 2020; 20(1):776. Published 2020 Oct 19. https://doi.org/10.1186/s12879-020-05505-6 PMID: 33076857

26. Gordon S and Graham S. Epidemiology of respiratory disease in Malawi. *Malawi Med. J.*, vol. 18, no. 3, pp. 134–146, 2007, https://doi.org/10.4314/mmj.v18i3.10918 PMID: 27529007

27. Wall EC, Everett DB, Mukaka M, et al. Bacterial meningitis in Malawian adults, adolescents, and children during the era of antiretroviral scale-up and Haemophilus influenzae type b vaccination, 2000–2012. Clin Infect Dis. 2014; 58(10):e137–e145. https://doi.org/10.1093/cid/ciu057 PMID: 24496208

28. Kanyama C, Chagomerana MB, Chawinga C, et al. Implementation of tuberculosis and cryptococcal meningitis rapid diagnostic tests amongst patients with advanced HIV at Kamuzu Central Hospital, Malawi, 2016–2017. BMC Infect Dis. 2022; 22(1):224. Published 2022 Mar 5. https://doi.org/10.1186/s12879-022-07224-6 PMID: 35247971

29. Zachariah R, Nkhoma W, Harries AD, et al. Health seeking and sexual behaviour among patients with sexually transmitted infections—the importance of traditional healers. Malawi Med J. 2002; 14(2):15–17. https://doi.org/10.4314/mmj.v14i2.10761 PMID: 27528933

30. Lewis J. M., Lester R., Mphasa M., Banda R., Thomson N. R., and Feasey N., "Emergence of carbapenemase producing Enterobacteriaceae, Malawi," *J. Antimicrob. Resist.*, pp. 225–227, 2020, https://doi.org/10.1016/j.jgar.2019.12.017.Emergence

31. Sendekie AK, Netere AK, Tesfaye S, Dagnew EM, Belachew EA. Incidence and patterns of adverse drug reactions among adult patients hospitalized in the University of Gondar comprehensive specialized hospital: A prospective observational follow-up study. PLoS One. 2023; 18(2):e0282096. Published 2023 Feb 24. https://doi.org/10.1371/journal.pone.0282096 PMID: 36827307

32. Ministry of Health and John Snow. Malawi Health Commodities Logistics Management System Standard Operating Procedures Manual. no. 1. 2015.

33. USAID-Deliver Project. The Logistics Handbook: A Practical Guide for the Supply Chain Management of Health Commodities. 2011, [Online]. Available: http://deliver.jsi.com/dlvr_content/resources/allpubs/guidelines/LogiHand.pdf.

34. The WHO AWaRe (Access, Watch, Reserve) antibiotic book. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. ISBN 978-92-4-006238-2 (electronic version). Available at: https://www.who.int/publications/i/item/9789240062382

35. Khuluza F, Kadammanja P, Simango C, and Mukhuna M. Did drug availability in Malawian central hospitals improve after the conversion of central medical stores to a trust?. *African J. Pharm. Pharmacol.*, vol. 10, no. 9, pp. 145–150, 2016, https://doi.org/10.5897/AJPP2015.4470

36. UNICEF Malawi. Malawi 2022/23 Health Budget Brief. 2022, [Online]. Available: https://www.unicef.org/esa/media/11821/file/UNICEF Malawi Health Budget Brief 2022-2023.pdf.

37. Chitsulo L. "Malawi drug budget dwindling,". The Nation Newspaper. Blantyre, Feb. 22, 2022. Available from: https://mwnation.com/malawi-drug-budget-dwindling/#:~:text=The%20sector%20allocation%20represents%209.7,of%20the%20country's%20total%20budget.

38. Mailosi A, Mwalwanda S, Hassan C, et al. Experiences from Cyclone Anna and Cyclone Dumako: A short report. Afr J Prim Health Care Fam Med. 2022; 14(1):e1–e4. Published 2022 Dec 14. https://doi.org/10.4102/phcfm.v14i1.3761 PMID: 36546498

39. Zanichelli V, Sharland M, Cappello B, Moja L, Getahun H, Pessoa-Silva C, et al. The WHO AWaRe (Access, Watch, Reserve) antibiotic book and prevention of antimicrobial resistance. Bull World Health Organ. 2023 Apr 1; 101(4):290–6. https://doi.org/10.2471/BLT.22.288614 Epub 2023 Feb 10. PMCID: PMC10042089.

40. Sharland M, Zanichelli V, Ombajo LA, et al. The WHO essential medicines list AWaRe book: from a list to a quality improvement system. Clin Microbiol Infect. 2022; 28(12):1533–1535. https://doi.org/10.1016/j.cmi.2022.08.009 PMID: 36007869

41. Ministry-of-Health. Malawi Standard Treatment Guidelines. Incorporating Malawi Essential Medicines List. vol. 6th Edition, 2023.

42. Sibande GT, Banda NPK, Moya T, Siwinda S, Lester R. Antibiotic guideline adherence by Clinicians in medical wards at Queen Elizabeth Central Hospital (QECH), Blantyre Malawi. Malawi Med J. 2022; 34(1):3–8. https://doi.org/10.4314/mmj.v34i1.2 PMID: 37265826

43. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics for infectious diseases [published correction appears in Clin Infect Dis. 2014 May; 58(9):1346]. Clin Infect Dis. 2013;57 Suppl 3(Suppl 3):S139-S170. https://doi.org/10.1093/cid/cit578 PMID: 24200831

44. Günay Y,Taşdöven İ, Kozan R,Koca Ş, and Çağlar E. Investigation of predictive value of complete blood count in the diagnosis of acute complicated appendicitis. *Haseki Tip Bul.*, vol. 57, no. 1, pp. 26–31, 2019, https://doi.org/10.4274/haseki.galenos.2018.4567

45. Gadama Y, Kamtchum-Tatuene J, Benjamin L, Phiri T, Mwandumba HC. The significant gap between international standards and stroke management practices at Queen Elizabeth Central Hospital

(Malawi): An audit report. Malawi Med J. 2019; 31(4):249–255. https://doi.org/10.4314/mmj.v31i4.6 PMID: 32128035

46. Simmons B, Ariyoshi K, Ohmagari N, et al. Progress towards antibiotic use targets in eight high-income countries. Bull World Health Organ. 2021; 99(8):550–561. https://doi.org/10.2471/BLT.20.270934 PMID: 34354310

4.3 Adverse drug reactions related with antibiotic medicines in Malawi: A retrospective analysis of prevalence and associated factors

4.3.1 Overview of the paper

In this paper, we present the occurrence and characteristics of adverse drug reactions (ADRs) related to antibiotic therapy. Using active methods, we detected suspected ADRs and applied various tools to perform causality, seriousness, and preventability assessments. In summary, we found a high burden of serious antibiotic related ADRs such as convulsions than reported in other countries. We recommend the National PV centre to supplement the spontaneous reporting scheme with active surveillance methods and ensure that the reporting tools are accessible and convenient in all health facilities to improve the detection of safety signals.

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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%).

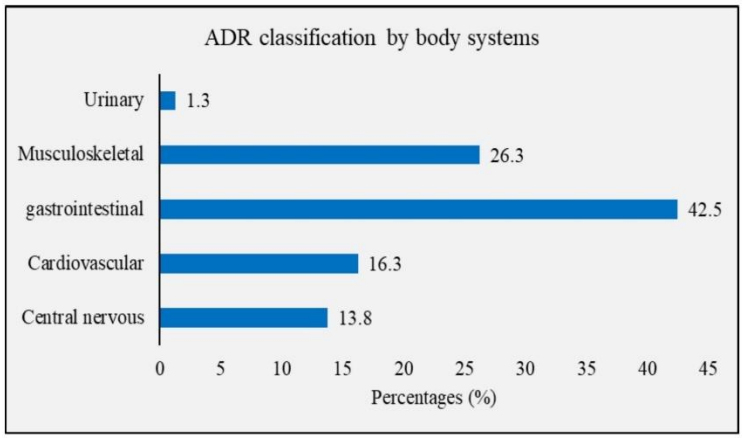

Figure 1 Occurrence of suspected adverse drug reactions (s(ADRs) by body systems. The sADRs were classified according to the anatomical system and presented in terms of percentages.

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.

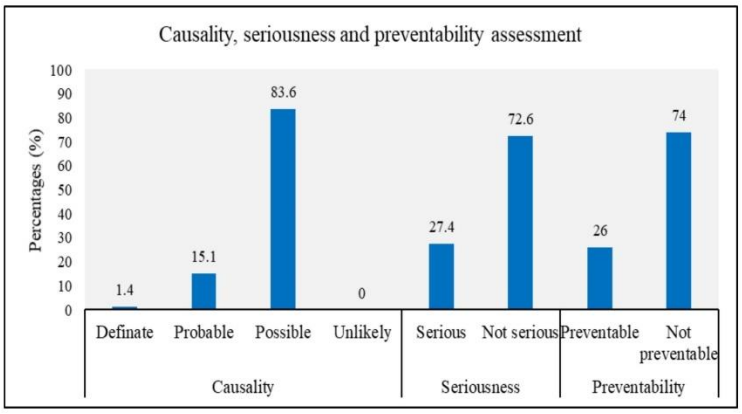

Figure 2 ADR Classification according to causality, seriousness, and preventability. The Naranjo scale, the World Health Organization classification and the Schumock and Thornton scale were applied to perform causality, seriousness and preventability assessments respectively.

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.

References

1. Walter SR, Day RO, Gallego B. et al. The impact of serious adverse drug reactions: a population-based study of a decade of hospital admissions in New South Wales, Australia. *Br J Clin Pharmacol*. 2017;83(2):416–426. doi:10.1111/bcp.13124
2. Yadesa TM, Kitutu FE, Deyno S, et al. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: a systematic review and meta-analysis. *SAGE Open Med*. 2021;9:205031212110390. doi:10.1177/20503121211039099
3. Insani WN, Whittlesea C, Alwafi H, et al. Prevalence of adverse drug reactions in the primary care setting: a systematic review and meta-analysis. *PLoS One*. 2021;16(5):1–24. doi:10.1371/journal.pone.0252161
4. Fattinger K, Roos M, Vergères P, et al. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. *Br J Clin Pharmacol*. 2000;49(2):158–167. doi:10.1046/j.1365-2125.2000.00132.x
5. Montastruc JL, Lafaurie M, de Canecaude C, et al. Fatal adverse drug reactions: a worldwide perspective in the World Health Organization pharmacovigilance database. *Br J Clin Pharmacol*. 2021;87(11):4334–4340. doi:10.1111/bcp.14851
6. Giardina C, Cutroneo PM, Mocciaro E, et al. Adverse drug reactions in hospitalized patients: results of the FORWARD (Facilitation of Reporting in Hospital Ward) Study. *Frontiers in Pharmacology*. 2018;9:1–12.
7. Pouyanne P, Haramburu F, Imbs JL, et al. Admissions to hospital caused by adverse drug reactions: cross sectional incidence study. *Br Med J*. 2000;320(7241):1036. doi:10.1136/bmj.320.7241.1036
8. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356(9237):1255–1259. doi:10.1016/S0140-6736(00)02799-9
9. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. *J Pharmacol Pharmacother*. 2013;4(1_suppl):73–77. doi:10.4103/0976-500X.120957
10. Osanlou R, Walker L, Hughes DA, et al. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. *BMJ Open*. 2022;12(7):1–7. doi:10.1136/bmjopen-2021-055551
11. Sulis G, Adam P, Nafade V, et al. Antibiotic prescription practices in primary care in low- And middle-income countries: a systematic review and meta-analysis. *PLoS Med*. 2020;17(6):1–20. doi:10.1371/journal.pmed.1003139
12. Siachalinga L, Godman B, Mwita JC, et al. Current antibiotic use among hospitals in the sub-Saharan Africa region; findings and implications. *Infection and Drug Resistance*. 1909;1:0–3.
13. Klein EY, Van Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc Natl Acad Sci U S A*. 2018;115(15):E3463–E3470. doi:10.1073/pnas.1717295115
14. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf*. 2014;5(6):229–241. doi:10.1177/2042098614554919
15. Mohsen S, Dickinson JA, Somayaji R. Update on the adverse effects of antimicrobial therapies in community practice. *Can Fam Physician*. 2020;66(9):651–659.
16. Tamma PD, Avdic E, Li DX, et al. Association of adverse events with antibiotic use in hospitalized patients. *JAMA Intern Med*. 2017;177(9):1308–1315. doi:10.1001/jamainternmed.2017.1938
17. Kiguba R, Karamagi C, Bird SM. Antibiotic-associated suspected adverse drug reactions among hospitalized patients in Uganda: a prospective cohort study. *Pharmacol Res Perspect*. 2017;5(9237):1–16. doi:10.1002/prp2.298

18. Jo HG, Jeong K, Ryu JY, et al. Fatal events associated with adverse drug reactions in the Korean national pharmacovigilance database. *J Pers Med*. 2021;12(1):5. doi:10.3390/jpm12010005
19. Kayambankadzanja RK, Lihaka M, Barratt-Due A, et al. The use of antibiotics in the intensive care unit of a tertiary hospital in Malawi. *BMC Infect Dis*. 2020;20(1):1–7. doi:10.1186/s12879-020-05505-6
20. Kumwenda P, Adukwu EC, Tabe ES, et al. Prevalence, distribution and antimicrobial susceptibility pattern of bacterial isolates from a tertiary Hospital in Malawi. *BMC Infect Dis*. 2021;21(1):1–10. doi:10.1186/s12879-020-05725-w
21. Gebeyehu E, Bantie L, Azage M. Inappropriate use of antibiotics and its associated factors among urban and rural communities of Bahir Dar city administration, northwest Ethiopia. *PLoS One*. 2015;10(9):1–14. doi:10.1371/journal.pone.0138179
22. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010;340(may18 2):1120. doi:10.1136/bmj.c2096
23. Endashaw Hareru H, Sisay D, Kassaw C, et al. Antibiotics non-adherence and its associated factors among households in southern Ethiopia. *SAGE Open Med*. 2022;10:205031212210904. doi:10.1177/20503121221090472
24. Rolfes L, van Hunsel F, Taxis K, et al. The impact of experiencing adverse drug reactions on the patient's quality of life: a retrospective cross-sectional study in the Netherlands. *Drug Saf*. 2016;39(8):769–776. doi:10.1007/s40264-016-0422-0
25. Berhe DF, Taxis K, Haaijer-Ruskamp FM, et al. Impact of adverse drug events and treatment satisfaction on patient adherence with antihypertensive medication – a study in ambulatory patients. *Br J Clin Pharmacol*. 2017;83(9):2107–2117. doi:10.1111/bcp.13312
26. Makwero MT. Delivery of primary health care in Malawi. *African J Prim Heal Care Fam Med*. 2018;10:1–3.
27. Kröner-Fresenius-Stiftung E. Capacity building in physiotherapy for the south-eastern region of Malawi in Zomba as its centre, https://www.ekfs.de/en/humanitarian-funding/currently-funded-projects/capacity-building-in-Physiotherapy. (2021, accessed 24, October 2023.).
28. Griffin F, Resar R. IHI global trigger tool for measuring adverse events. *IHI Innov Ser white Pap*. 2009;1:1–44.
29. Montané E, Santesmases J. Adverse drug reactions. *Med Clini*. 2020;154(5):178–184. doi:10.1016/j.medcli.2019.08.007
30. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245. doi:10.1038/clpt.1981.154
31. Bethesda MD. Adverse drug reaction probability scale (naranjo) in drug induced liver injury. *Natl Institutes Heal US Dept Heal Hum Serv*. 2019;1:1–5.
32. World_Health_Organisation. Safety of Medicines: a guide to detecting and reporting adverse drug reactions. *World Health Organization Geneva*, (2002); Available from: https://apps.who.int/iris/handle/10665/67378. Accessed July 17, 2024.
33. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. *Hosp Pharm*. 1992;27(6):538.
34. Shegena EA, Nigussie KA, Tamukong R, et al. Prevalence and factors associated with adverse drug reactions among heart failure patients hospitalized at Mbarara Regional Referral Hospital, Uganda. *BMC Cardiovasc Disord*. 2022;22(1):1–13. doi:10.1186/s12872-022-02937-7
35. Alomar MJ. Factors affecting the development of adverse drug reactions (Review article). *Saudi Pharm J*. 2014;22(2):83–94. doi:10.1016/j.jsps.2013.02.003
36. Noorda NMF, Sallevelt BTGM, Langendijk WL, et al. Performance of a trigger tool for detecting adverse drug reactions in patients with polypharmacy acutely admitted to the geriatric ward. *Eur Geriatr Med*. 2022;13(4):837–847. doi:10.1007/s41999-022-00649-x
37. Ji HH, Song L, Xiao JW, et al. Adverse drug events in Chinese pediatric inpatients and associated risk factors: a retrospective review using the Global Trigger Tool. *Sci Rep*. 2018;8(1):1–7. doi:10.1038/s41598-018-20868-2
38. Pandya AD, Patel K, Rana D, et al. Global trigger tool: proficient adverse drug reaction autodetection method in critical care patient units. *Indian J Crit Care Med*. 2020;24(3):172–178. doi:10.5005/jp-journals-10071-23367
39. Khan LM, Al-harthi SE, Osman AM, et al. Dilemmas of the causality assessment tools in the diagnosis of adverse drug reactions. *Saudi Pharm J*. 2016;24(4):485–493. doi:10.1016/j.jsps.2015.01.010
40. Seger D, Barker K, McNaughton C. Misuse of the naranjo adverse drug reaction probability scale in toxicology, *Clin Toxicol*. 2013;6. doi:10.1016/j.earlhumdev.2006.05.022
41. Knight LK, Lehloenya RJ, Sinanovic E, et al. Cost of managing severe cutaneous adverse drug reactions to first-line tuberculosis therapy in South Africa. *Trop Med Int Heal*. 2019;24(8):994–1002. doi:10.1111/tmi.13275
42. Martínez-Domínguez J, Sierra-Martínez O, Galindo-Fraga A, et al. Antibiotic prescription errors: the relationship with clinical competence in junior medical residents. *BMC Med Educ*. 2022;22(1):1–14. doi:10.1186/s12909-022-03499-0
43. Cruz AT, Mahajan P, Bonsu BK, et al. Accuracy of complete blood cell counts to identify febrile infants 60 days or younger with invasive bacterial infections. *JAMA Pediatr*. 2017;171(11):1–8. doi:10.1001/jamapediatrics.2017.2927
44. Günay Y, Taşdöven İ, Kozan R, et al. Investigation of predictive value of complete blood count in the diagnosis of acute complicated appendicitis. *Haseki Tip Bul*. 2019;57(1):26–31. doi:10.4274/haseki.galenos.2018.4567
45. Cižman M, Plankar Srovin T. Antibiotic consumption and resistance of gram-negative pathogens (collateral damage). *GMS Infect Dis*. 2018;6:Doc05. doi:10.3205/id000040
46. Melander RJ, Zurawski DV, Melander C. Narrow-spectrum antibacterial agents. *Medchemcomm*. 2018;9(1):12–21. doi:10.1039/C7MD00528H
47. Alhawassi TM, Krass I, Bajorek B, et al. A systematic review of the prevalence and risk factors for adverse drug reactions in the elderly in the acute care setting. *Clin Interv Aging*. 2014;9:2079–2086. doi:10.2147/CIA.S71178
48. Muirhead GJ, Wilner K, Colburn W, et al. The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil citrate. *Br J Clin Pharmacol Suppl*. 2002;53(Suppl 1):21S–30S. doi:10.1046/j.0306-5251.2001.00029.x
49. Liao PJ, Mao CT, Chen TL, et al. Factors associated with adverse drug reaction occurrence and prognosis, and their economic impacts in older inpatients in Taiwan: a nested case-control study. *BMJ Open*. 2019;9(5):1–10. doi:10.1136/bmjopen-2018-026771
50. Drug-interaction-checker. Medscape, https://reference.medscape.com/drug-interactionchecker. (accessed 15, January 2023.).
51. Hoogervorst-Schilp J, Langelaan M, Spreeuwenberg P, et al. Excess length of stay and economic consequences of adverse events in Dutch hospital patients. *BMC Health Serv Res*. 2015;15(1):1–7. doi:10.1186/s12913-015-1205-5
52. Classen DC. Adverse drug events in hospitalized patients excess length of stay, extra costs, and attributable mortality. *JAMA J Am Med Assoc*. 1997;277:301.
53. Lerch M, Nowicki P, Manlik K, et al. Statistical signal detection as a routine pharmacovigilance practice: effects of periodicity and resignalling criteria on quality and workload. *Drug Saf*. 2015;38(12):1219–1231. doi:10.1007/s40264-015-0345-1

54. Insani WN, Pacurariu AC, Mantel-Teeuwisse AK, et al. Characteristics of drugs safety signals that predict safety related product information update. *Pharmacoepidemiol Drug Saf*. 2018;27(7):789–796. doi:10.1002/pds.4446
55. Electronic-medicines-compendium. Summary of product characteristics, https://www.medicines.org.uk/emc/. (2023, accessed 15, January 2023.).
56. Joint_Formularly_Commitee. *British National Formulary 83*. London. 2022. doi: 10.1002/jps.3030470133
57. Hoffman RS. Understanding the limitations of retrospective analyses of poison center data. *Clin Toxicol*. 2007;45(8):943–945. doi:10.1080/15563650701233370
58. Jusot V, Chimimba F, Dzabala N, et al. Enhancing pharmacovigilance in sub - Saharan Africa through training and mentoring: a GSK pilot initiative in Malawi. *Drug Saf*. 2020;43(6):583–593. doi:10.1007/s40264-020-00925-4

4.4 Substandard and falsified antibiotics and their clinical outcomes among hospitalized patients in southern Malawi: A pilot study

4.4.1 Overview of the paper

In this final paper, we assessed the clinical outcomes among patients who received antibiotics with optimal amount of API vs antibiotics with lower than the required API content. In brief, we found that antibiotic medicines with sub-optimal API content caused fewer adverse effects, and the patient recovery was lower than patients who took antibiotics with optimal amount of API. Although this was a biologically plausible pattern, the results were not statistically significant. We therefore recommend further studies to investigate and characterize the adverse events associated with poor quality antibiotics. This will help to provide a basis for signal detection for possible SF medicines in clinical settings.

frontiers

Substandard antibiotics and their clinical outcomes among hospitalized patients in southern Malawi: A pilot study

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Scope Statement

The burden of substandard antibiotics is high in Malawi and other low-middle-income countries, but there is limited evidence of their clinical impact. In this study, we assessed the quality of antibiotics and associated clinical outcomes among hospitalized patients in southern Malawi. Our study fits well with Frontier Pharmacology, especially Drugs outcomes research as it is providing the impact of low quality medicines on clinical outcomes

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

Credit Author Statement

Adamson Sinjani Muula: Conceptualization, Data curation, Funding acquisition, Methodology, Project administration, Supervision, Validation, Visualization, Writing - review & editing. **Elizabeth Kampira**: Formal Analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing - review & editing. **Frider Chimimba**: Data curation, Formal Analysis, Investigation, Methodology, Resources, Supervision, Validation, Writing - review & editing. **Francis Kachidza Chiumia**: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Project administration, Resources, Validation, Visualization, Writing - original draft, Writing - review & editing. **Felix Khuluza**: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Happy Magwaza Nyirongo**: Data curation, Formal Analysis, Investigation, Methodology, Validation, Visualization, Writing - original draft.

Keywords

Substandard medicines, parenteral antibiotic medicines, clinical outcomes, adverse drug reactions, Patient recovery

Abstract

Word count: 270

Substandard and falsified antibiotics affect the lives of patients and promote drug resistance. We assessed the quality of antibiotics and associated clinical outcomes among hospitalized patients in southern Malawi.A cross-sectional study involving review of retrospective records was conducted among hospitalized adult patients at Zomba central, Machinga and Nsanje district hospitals in October 2022 and January 2024. We reviewed patient management files for eligible patients to assess patient recovery and occurrence of adverse drug reactions (ADRs) using a global trigger tool.Trained pharmacy personnel recorded antibiotic medicines that were issued to the patients, and the medicines were sampled and subjected to pharmacopeial test for content of active pharmaceutical ingredients using high performance liquid chromatography.Of the 224 reviewed files, ADRs occurred in 18.3% % (n=41) of patients while 12.05% (n=27) did not recover from their illness. One benzylpenicillin sample was found out of specifications with only 61.8% of declared amount of active ingredient. Among patients who received benzylpenicillin with optimal API content, 15.8% experienced ADRs while 10.5% failed to recover from illness. For patients who received benzylpenicillin containing lower than required amount of API, only 7.1% experienced an ADR while 14.3% failed to recover from illness. These differences were, however, not statistically significant. Patient outcomes were significantly associated with age and Charlson comorbidity index (CCI), p <0.05.The present findings provide preliminary insights on the potential negative clinical impact of substandard antibiotic medicines. We therefore recommend a larger prospective study to further validate these findings and encourage stakeholders to be more vigilant on the quality of antibiotic medicines as one of the key measures of improving clinical outcomes and preventing antibiotic resistance in Malawi.

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Ethics statements

Studies involving animal subjects

Generated Statement: No animal studies are presented in this manuscript.

Studies involving human subjects

Generated Statement: The studies involving humans were approved by This study was approved 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.. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Inclusion of identifiable human data

Generated Statement: No potentially identifiable images or data are presented in this study.

Data availability statement

Generated Statement: The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

Generative AI disclosure

No Generative AI was used in the preparation of this manuscript.

Substandard antibiotics and their clinical outcomes among hospitalized patients in southern Malawi: A pilot study

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Abstract

Background

Substandard and falsified antibiotics affect the lives of patients and promote drug resistance. We assessed the quality of antibiotics and associated clinical outcomes among hospitalized patients in southern Malawi.

Methods

A cross-sectional study involving review of retrospective records was conducted among hospitalized adult patients at Zomba central, Machinga and Nsanje district hospitals in October 2022 and January 2024. We reviewed patient management files for eligible patients to assess patient recovery and occurrence of adverse drug reactions (ADRs) using a global trigger tool. Trained pharmacy personnel recorded antibiotic medicines that were issued to the patients, and the medicines were sampled and subjected to pharmacopeial test for content of active pharmaceutical ingredients using high performance liquid chromatography.

Results

Of the 224 reviewed files, ADRs occurred in 18.3% % (n=41) of patients while 12.05% (n=27) did not recover from their illness. One benzylpenicillin sample was found out of specifications with only 61.8% of declared amount of active ingredient. Among patients who received benzylpenicillin with optimal API content, 15.8% experienced ADRs while 10.5% failed to recover from illness. For patients who received benzylpenicillin containing lower than required amount of API, only 7.1% experienced an ADR while 14.3% failed to recover from illness. These differences were, however, not statistically significant. Patient outcomes were significantly associated with age and Charlson comorbidity index (CCI), $p < 0.05$.

Conclusion

The present findings provide preliminary insights on the potential negative clinical impact of substandard antibiotic medicines. We therefore recommend a larger prospective study to further validate these findings and encourage stakeholders to be more vigilant on the quality of antibiotic medicines as one of the key measures of improving clinical outcomes and preventing antibiotic resistance in Malawi.

Keywords

Substandard medicines, parenteral antibiotic medicines, clinical outcomes, adverse drug reactions, patient recovery

Background

Substandard and falsified (SF) medicines pose major risks to global public health[1]. The prevalence of SF medicines varies by region and range from as low as <5% to as high as >50%[2] with studies reporting a disproportionally higher prevalence of SF medicines in low-middle income countries (LMICs). Most studies done in LMICs, have found antibiotic medicines as one of the classes with a high prevalence of SF medicines [3–6]. It is estimated that antibiotic consumption in LMICs would reach up to 168 billion defined daily doses (DDDs) in the next decade[7]. This is a health concern as antibiotic medicines overuse increases the emergence of antibiotic resistance and occurrence of adverse drug reactions (ADRs). Antibiotic resistance is associated with the death of over 5 million people globally every year[8], while antibiotic-related ADRs contribute to more than 50% of individual case safety reports[9, 10].

SF medicines may contain lower or higher declared content of active ingredients, misrepresented ingredients and/or contain impurities[11]. This may lead to sub-therapeutic exposure of antibiotics to bacteria and therefore further increase the risk of antibiotic resistance[12]. Furthermore, SF medicines are also associated with a higher risk of adverse drug reactions which eventually affect patient's quality of life and adherence to treatment[11]. The SF antibiotics increases the risk of death among patients by almost four-fold[1]. In 2017, the World Health Organization (WHO), estimated that, on the assumption of 10% prevalence of SF antibiotic medicines, about 72,000 deaths occurred due to lower activity of active ingredients and over 169,000 deaths occurred due to no drug activity among children presenting with pneumonia[13].

Previous studies conducted in Malawi have consistently shown a high prevalence of SF antibiotic medicines ranging from 13 - 45.5%, between 2014 and 2022. These studies mostly

focused on oral antibiotics with amoxicillin, ciprofloxacin, cefuroxime, co-trimoxazole, flucloxacillin and azithromycin[14–16]. The burden of SF medicines may still be under-estimated in Malawi as some of the samples in the reported studies were tested using less sensitive screening techniques such as thin layer chromatography (TLC) compared to pharmacopeial assay methods such as high performance liquid chromatography (HPLC)[17].

Studies have suggested that linkage of clinical outcomes to medicine batches using pharmacovigilance databases (for individual case safety reports) can offer an effective method for detection of possible SF medicines[18, 19]. This study was therefore conducted to assess antibiotic ADRs and associate them with the medicine quality to provide insights of safety signals which would be used as triggers for detection of SF antibiotic medicines. Further, the study provides insights on the extent to which clinical outcomes are affected by SF medicines, as limited observational studies have been conducted.

Methods

Study design and setting

A cross-sectional study involving review of retrospective case management files for hospitalized patients who were prescribed antibiotic medicines was done in Zomba, Machinga and Nsanje districts in October 2022 and January 2024. The study districts were randomly selected in Microsoft Excel among 13 districts in the southern region of Malawi as described in another publication by our team which was addressing other objectives [16]. We further conducted a cross-sectional study to analyze quality of antibiotic medicines administered to the patients using medicine ordering records at the pharmacy kept by trained pharmacy personnel.

Study population and sampling

We retrospectively reviewed 224 case files for patients who were randomly selected among hospitalized patients in medical wards in all study districts. We focused on patients who were administered with parenteral antibiotics and whose batch was traceable for sampling. All re-admissions were excluded from the study. Ceftriaxone and benzylpenicillin were selected for sampling as these were among the most administered parenteral antibiotic medicines among hospitalized patients in all the three facilities.

Data Collection and analysis

Patient management files for eligible participants were reviewed by investigators who were guided by senior clinicians at the study sites. The clinicians interpreted clinical assessments and the patient's laboratory results. Prior to study inception, these clinicians were trained on pharmacovigilance principles and oriented on the study protocol by the investigators. Demographics and clinical data such as age, sex, stated diagnosis and prescribed antibiotics were collected. Suspected ADRs were detected using a global trigger tool. This tool was developed by the Institute for Healthcare Improvement (IHI) 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, abnormal laboratory results, and changes in patient prognosis[20]. Suspected ADRs were subjected to causality assessment using the Naranjo criteria[21]. We further classified patients based on their outcomes and whether they had recovered or were recovering from the illness. Recovered or recovering patients were those whose admission complaints were alleviated or improved during treatment respectively. Not recovered patients were those who did not show any improvement, were referred to a higher-level facility, or died after treatment was started. Furthermore, we calculated

the Charlson co-morbidity index based on the presenting co-morbidities for each patient using the CCI algorithm (Supplementary file 1). The CCI algorithm applies weighted scores depending on patient characteristics such as age and seriousness of presenting co-morbidities such as HIV/AIDs, history of cardiovascular accident and cancer[22, 23].

Trained pharmacy personnel provided records for the medicine batches which were issued to the wards during the time of admission of the patients. We therefore sampled the medicines for quality analysis. Unlike parenteral medicines which are issued on a daily or weekly basis from the main pharmacy, oral medicines are issued in bulk and kept within the wards for longer duration. Thus, it was difficult to confirm the batch that was administered to patients during their time of hospital stay. Oral antibiotic medicines were therefore not sampled and all patients who were given oral medicines, or a combination of both oral and parenteral medicines were removed from the analysis.

Sampled parenteral antibiotic medicines were subjected to pharmacopeial assay for absolute quantification of API. We used pharmacopeial assay methods outlined in the British Pharmacopoeia. For both benzylpenicillin and ceftriaxone, we used a stainless-steel column (25cm x 4.6mm) packed with octadecylsilyl silica gel (5µm) (Reprisals C18) for high-performance liquid chromatography (HPLC). The mobile phase for benzylpenicillin assay consisted of 6.8% w/v potassium dihydrogen phosphate and methanol adjusted to pH3 using orthophosphoric acid and detection was done at wavelength of 254nm. For ceftriaxone, the mobile phase consisted of 0.2M potassium dihydrogen phosphate buffer combined with acetonitrile, and detection was done at a wavelength of 225nm. Our methods were internally validated by ensuring that linearity of the standard curve R^2>0.995 and precision was RSD <1%.

Data Management and statistical analysis

Data was entered and cleaned in Microsoft Excel and imported to STATA 14.1 for statistical analysis. Laboratory test results for antibiotic medicine quality were entered as categorical data. For descriptive analysis, numerical variables were presented as means, medians, and interquartile range while frequencies and percentages were calculated for categorical variables.

Ethics

This study was approved 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 (Zomba Central Hospital) or Directorates of Health and Social Services for Machinga and Nsanje before data collection. The study was approved in line with the Principles of the Declaration of Helsinki. No details were collected to identify patients and clinicians in the study.

Results

Patient's demographic characteristics

Of the 224 patients included in the study, 60.71% (n=136) were female and 39.29% (n=88) were male. The median age for females was 43 years (IQR 35-63 years) and 43.5 years (IQR 30-63.5 years) among males. The most common diagnosis was sepsis (26.34%, n=59), followed by pneumonia (20.09%, n=45) and meningitis (7.59%, n=17) **(Table 1).** More patients were given ceftriaxone (79.5%, n=178), followed by benzylpenicillin (20.5%, n =46). Overall, median Charlson co-morbidity index (CCI) among the patients was 1 (IQR 0-3.5). By sex, the median CCI was 1 (IQR 0-4) among female and 0 (0-3) among male patients.

Table 1 Patient's demographic characteristics and prescribed antibiotics

Variable	Characteristics	Frequency	Percentage (N=224)
Age	Median, IQR	43	30-60*
Sex	Female	136	60.71
	Male	88	39.29
Charlson Score	Median, IQR	1	0 - 3.5*
Facility	Facility 1	96	42.86
	Facility 2	71	31.7
	Facility 3	57	25.45
Diagnosis	Sepsis	59	26.34
	Pneumonia	45	20.09
	Meningitis	17	7.59
	Cellulitis	8	3.57
	Peptic ulcers	7	3.13
	Others	88	39.29
Antibiotics prescribed	Benzylpenicillin	46	20.5
	Ceftriaxone	178	79.5

*Numerical summaries presented as Median and interquartile range (IQR)

Quality of administered antibiotics

We collected samples of antibiotic medicines given to the patients in the study. A total of nine batches of parenteral antibiotic medicines (that included six batches of ceftriaxone and three of benzylpenicillin) were sampled and subjected to a test for the content of active pharmaceutical ingredients (API). Among the antibiotics tested, we found one sample of out-of-specification benzylpenicillin. This sample was claimed to originate from China and contained only 61.8% of the declared amount of API. The other samples of benzylpenicillin were from China and India and contained 95% and 98% of the declared API respectively. Ceftriaxone samples from all the three facilities were stated to be manufactured in India. The determined API contents for ceftriaxone samples ranged from 102 – 120% **(Table 2)**.

Table 2 Antibiotic samples and test results for API content

Sample ID	Medicine name	ATC CODE[1]	Strength	Dosage form	MEML category[2]	WHO AWaRe classification[3]	Stated country of origin	Assay % determination
Cef 101	Ceftriaxone	J01DD04	1000mg	IV/IM powder	DVA	Watch	India	116.9
Cef 102	Ceftriaxone	J01DD04	1000mg	IV/IM powder	DVA	Watch	India	119
Cef 103	Ceftriaxone	J01DD04	1000mg	IV/IM powder	DVA	Watch	India	120.3
Cef 104	Ceftriaxone	J01DD04	1000mg	IV/IM powder	DVA	Watch	India	103
Cef 105	Ceftriaxone	J01DD04	1000mg	IV/IM powder	DVA	Watch	India	110
Cef 106	Ceftriaxone	J01DD04	1000mg	IV/IM powder	DVA	Watch	India	102.5
Benzyl 101	Benzylpenicillin	J01CE01	5MU	IV/IM powder	HVA	Access	China	95.4
Benzyl 102	Benzylpenicillin	J01CE01	5MU	IV/IM powder	HVA	Access	China	61.8[4]
Benzyl 103	Benzylpenicillin	J01CE01	5MU	IV/IM powder	HVA	Access	India	98

[1] ATC = Anatomical, therapeutic, and chemical classification (https://www.whocc.no/atc_ddd_index/)

[2] Malawi Essential Medicines Lists (EML) classifies medicines according to the level of healthcare facilities where the medicines are expected to be found, the importance of the condition treated and procurement system. H = found

at health centre, district hospital and central hospital levels; D = found at district hospital and central hospital levels only; C = found at central hospital level only. By importance, V = vital medicines and E = essential medicines. By procurement system A= medicines required by a large number of patients as such to be routinely procured and stocked by CMST and B= medicines required for a limited number of patients and not routinely stocked by CMST

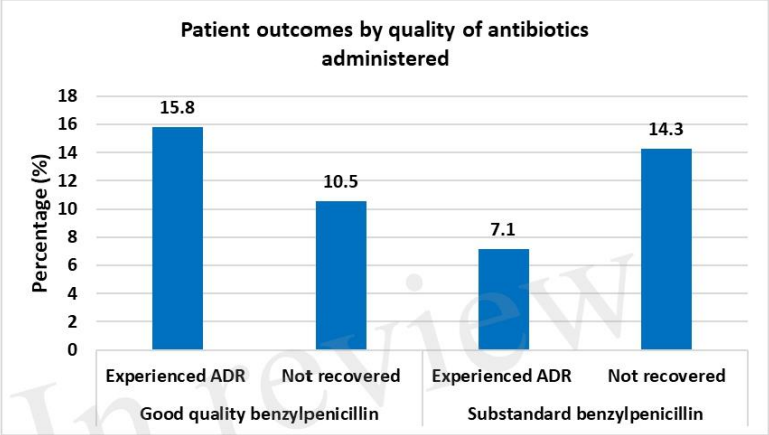
[3] WHO classifies antibiotic medicines according to the risk of inducing resistance. Access categories comprise of antibiotics which are narrow spectrum and routinely used with low risk of resistance. Watch medicines are broad spectrum antibiotics with a higher risk of inducing resistance. Reserve antibiotics are last resort used in multi-drug-resistant infections

[4]Extreme deviation with low API content

Patient clinical outcomes

Of the 224 patients, suspected ADRs occurred in 18.3% (n=41) of patients while 12.05% (n=27) did not recover from their illness. By causality assessment, 2.4% (n=1) were certain, 17.1% (n=7) probable, and 80.1% (n=33) possible ADRs. Among patients who received benzylpenicillin with optimal API content, 15.8% experienced ADRs while 10.5% failed to recover from illness. For patients who received benzylpenicillin containing a lower than required amount of API, only 7.1% experienced an ADR while 14.3% failed to recover from illness **(Figure 1).**

Figure 1 Clinical Outcomes for patients administered with benzylpenicillin of different quality status by the content of active pharmaceutical ingredient



Patient outcomes were significantly associated with age and CCI. The mean age among patients who did not recover was 55.7 years (95% CI 48.2 – 63.1 years) vs 44.8 years (95% CI 41.9 – 47.7 years) among patients who recovered. Mean CCI was 3.1 (95% CI 2.0 – 4.2) among patients who did not recover vs 1.8 (95% CI 1.5 – 2.2) among patients who recovered. Although there was a lower ADR rate among patients who were given antibiotics with lower amount of API (7.1%) as compared to patients who were given antibiotics with optimal amount of API (18.5%), the difference was not statistically significant, $p < 0.203$ **(Table 3)**. Similarly, the difference in failure to recover was not statistically significant between the group of patients who were given antibiotics with lower API content (14.3%%) and who were given antibiotics with optimal amount of API (11.4%%), $p < 0.502$.

A multivariate logistic regression analysis was performed to assess the influence of possible confounders, but the results were not statistically significant (supplementary table 1).

Table 3 Clinical outcomes among patients and associated factors

Association with the occurrence of ADRs	**Factor**	**Characteristic**	**With ADRs (N=41)**	**Without ADRs (N=183)**
	Age	Mean ±SD	50.6± 24.2	45.1± 19.7
	Charlson Score	Mean ±SD	1.92± 2.5	2 ± 2.2
	Antibiotic quality	Optimal API	34 (18.48)	150 (81.52)
		Low API	1 (7.14)	13 (92.86)
	Diagnosis	Sepsis	9 (15.25)	50 (84.75)
		Pneumonia	8 (17.78)	32 (82.22)
		Meningitis	6 (35.29)	11 (64.71)
		Cellulitis	2 (25)	6 (75)
		Peptic ulcers	1 (14.29)	6 (85.71)
		Others	15 (17.05)	73 (82.95)
	Antibiotics given	Benzylpenicillin	8 (17.39)	38 (82.61)
		Ceftriaxone	33 (18.54)	145 (81.46)
Association with patient recovery	**Factor**	**Characteristic**	**Not recovered (N=27)**	**Recovered (N=197)**
	Age	Mean ±SD	55.7± 18.7	44.8± 20.6
	Charlson Score	Mean ±SD	3.11± 2.7	1.83± 2.4
	Antibiotic quality	Optimal API	21 (11.41)	163 (88.59)
		Low API	2 (14.29)	12 (85.71)
	Diagnosis	Sepsis	5 (8.47)	54 (91.53
		Pneumonia	6 (13.33)	39 (86.67)
		Meningitis	1 (5.88)	16 (94.12)
		Cellulitis	1 (12.5)	7 (87.5)
		Peptic ulcers	2 (28.57)	5 (71.43)
		Others	12 (13.64)	76 (86.36)
	Antibiotics given	Benzylpenicillin	4 (8.7)	42 (91.3)
		Ceftriaxone	23 (12.92)	155 (87.08)

Discussion

In this study, we sampled and tested antibiotic medicines based on records of batches administered to our study patients. Tests were conducted on the content of API using pharmacopeial HPLC methods for ceftriaxone and benzylpenicillin samples. By the API content, deviations from the specifications are classified as either extreme or non-extreme. Extreme substandard medicines contain API of <80%, while non-extreme substandard medicines contain API between 80% to the lowest required content, which is usually (but not always) 90%[24, 25].

Most studies on the quality of antibiotics have assessed oral dosage forms such as amoxicillin, ciprofloxacin and metronidazole, but few studies have reported on the quality of parenteral antibiotics such as ceftriaxone and benzylpenicillin[27]. Generally, the prevalence of substandard oral antibiotics has been reported to be very high in LMICs including Malawi but a study in Rwanda, showed that parenteral antibiotics contributed to only 5.1% of the substandard antibiotic medicines[28]. This is consistent with the findings in this study where we only detected one sample of substandard benzylpenicillin which contained only 61.8% of the declared API content. However, this may also be attributable to the small sample size of tested batches. Furthermore, similar to other studies[28], we only tested for API content which is the most principal parameter for parenteral antibiotics while oral antibiotics are usually also subjected to tests for the release of the API from the formulation. As such, even if the API content is optimal, other oral antibiotic samples fail based on disintegration or dissolution tests[2, 16].

There is limited literature on the clinical impact of substandard medicines on patient recovery and the occurrence of adverse drug reactions. Published reports on the effects of SF medicines include clusters of death due to contamination by toxic impurities or falsification of medicines.

For example, in 2013, there were reports of more than 100 serious illnesses and deaths among patients who took dextromethorphan syrup that was contaminated with levomethorphan in Paraguay and Pakistan[29]. A similar incidence happened in 2022 when the WHO investigated reports of 22 children who died from acute kidney injury after taking cough syrups containing unacceptable amounts of ethylene glycol and diethylene glycol[30].

Augmented ADRs, which are common and related to the pharmacology of the API, pose a challenge to be linked to the quality of medicines as they present with signs and symptoms that are similar to other diseases. Similarly, lack of response to treatment (sometimes referred to as type F ADRs) may also be a challenge to be attributable to SF medicines because they are affected by several other possible factors[31, 32]. However, cluster analysis of ADRs and lack of responses that were commissioned to in the WHO vigibase® has helped in the detection of several cases of SF medicines including quetiapine which was failing to release the API (dissolution) and salbutamol which was being sold after expiry date in the United States of America[18, 19].

In our study, we found a plausible pattern of occurrence of ADRs and patient recovery. Although the findings were not statistically significant, we observed lower rates of both ADR occurrence and patient recovery among patients who were administered with benzylpenicillin containing sub-optimal amount of API as compared to patients who were administered with benzylpenicillin with optimal API content. This requires confirmation in a bigger study as it suggests that sub-therapeutic doses of antibiotics may indeed potentially contribute to lower recovery rate[33, 34], but less side effects. Ceftriaxone samples contained API content near to the upper limit (between 117-120%) and were also observed to cause a higher prevalence of ADRs. There was, however, no further evidence that the observed ADRs were dose dependent.

Significant predictors of ADRs and recovery were age and CCI. Adverse drug reactions are common among elderly patients because the pharmacokinetics of most medicines are affected due to hepatic and renal dysfunction that is associated with aging[35, 36]. The CCI is an indicator of disease complexity based on the presence of important co-morbidities[23]. It is therefore applied in studies to predict mortality among patient study participants[37]. The criteria consist of a series of questions for presence of targeted and usually serious comorbidities such as HIV/AIDS, diabetes and cancers. The responses are weighted, and a final score is given based on the responses. Patients with a high CCI score are also more likely to take concomitant medicines which may potentially interact with antibiotic medicines and affect response and occurrence of adverse drug reactions[38, 39].

Limitations

There was a sampling bias in this study as antibiotics were sampled based on exposure of the batch to the patients. Thus, limited number of samples were collected and tested. Similarly, the study also included a limited number of participants as this was also limited by the availability of records for tracing batches which were administered to patients. In the study, we did not adequately investigate other possible contributors to the lack of patient recovery and thus, the results may be biased and affected by other confounding factors. Furthermore, the use of retrospective and routinely-collected data poses a challenge of missing out important information due to possible insufficient documentation and lack of verification or direct follow up with the patients. Due to the type of study design, there was a limited number of participants who were exposed to substandard antibiotics and therefore the study power was inadequate to accurately detect statistically significant effects. Thus, the findings of this study cannot be generalized to a larger population.

Conclusion

We assessed the quality of parenteral antibiotic medicines sampled from three hospitals in southern Malawi and identified a batch of benzylpenicillin with extremely low API content. There was no significant difference in terms of patient outcomes between patients exposed to antibiotics with low API and those who took antibiotics with optimal amount of API We therefore recommend a larger prospective study to further validate our findings and encourage stakeholders to be more vigilant on quality of antibiotic medicines as one of the key measures of mitigating antibiotic resistance in Malawi.

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References

[1] Ozawa S, Higgins CR, Nwokike JI, et al. Modeling the Health and Economic Impact of Substandard and Falsified Medicines: A Review of Existing Models and Approaches. *Am J Trop Med Hyg* 2022; 107: 14–20.

[2] Ozawa S, Evans DR, Bessias S, et al. Prevalence and Estimated Economic Burden of Substandard and Falsified Medicines in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. *JAMA Netw open*; 1. Epub ahead of print 2018. DOI: 10.1001/jamanetworkopen.2018.1662.

[3] Ozawa S, Chen H, Lee YA, et al. Characterizing Medicine Quality by Active Pharmaceutical Ingredient Levels : A Systematic Review and Meta-Analysis across Low- and Middle-Income Countries. 2022; 106: 1778–1790.

[4] McManus D, Naughton BD. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: A focus on context, prevalence, and quality. *BMJ Glob Heal* 2020; 5: 1–9.

[5] Almuzaini T, Choonara I, Sammons H. Substandard and counterfeit medicines: A systematic review of the literature. *BMJ Open* 2013; 3: 1–7.

[6] Akpobolokemi T, Martinez-Nunez RT, Raimi-Abraham BT. Tackling the global impact of substandard and falsified and unregistered/unlicensed anti-tuberculosis medicines. *J Med Access* 2022; 6: 239920262110704.

[7] Klein EY, Boeckel TP Van, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *PNAS* 2018; 115: 3463–3470.

[8] Murray CJ, Ikuta KS, Sharara F, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; 399: 629–655.

[9] Mudenda W, Mudenda W, Chikatula E, et al. Prescribing Patterns and Medicine Use at

the. *Med J Zambia* 2016; 43: 94–102.

[10] Oleim SH, K Noor S, O Bushara S, et al. The Irrational Use of Antibiotics Among Doctors, Pharmacists and the Public in River Nile State, Sudan. *Sudan J Med Sci* 2019; 14: 276–288.

[11] Johnston A, Holt DW. Substandard drugs: A potential crisis for public health. *Br J Clin Pharmacol* 2014; 78: 218–243.

[12] Gulumbe BH, Adesola RO. Revisiting the blind spot of substandard and fake drugs as drivers of antimicrobial resistance in LMICs. *Ann Med Surg* 2023; 85: 122–123.

[13] World-Health-Organization(WHO). A Study on the Public Health and Socioeconomic Impact of substandard and falsified medical products. *World Health Organization*, https://www.who.int/publications/i/item/9789241513432 (2017, accessed 5 September 2022).

[14] Khuluza F, Kigera S, Heide L. Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi. *Am J Trop Med Hyg* 2017; 96: 1124–1135.

[15] Khuluza F. In-vitro evaluation of the quality of paracetamol and co-trimoxazole tablets used in Malawi based on pharmacopoeial standards. *Malawi Med J* 2014; 26: 38–41.

[16] Chiumia FK, Nyirongo HM, Kampira E, et al. Burden of and factors associated with poor quality antibiotic, antimalarial, antihypertensive and antidiabetic medicines in Malawi. *PLoS One* 2022; 17: e0279637.

[17] Pan H, Ba-Thein W. Diagnostic accuracy of global pharma health fund minilab™ in

assessing pharmacopoeial quality of antimicrobials. *Am J Trop Med Hyg* 2018; 98: 344–348.

[18] Pozsgai K, Szűcs G, Kőnig-Péter A, et al. Analysis of pharmacovigilance databases for spontaneous reports of adverse drug reactions related to substandard and falsified medical products: A descriptive study. *Front Pharmacol* 2022; 13: 1–13.

[19] Juhlin K, Karimi G, Andér M, et al. Using VigiBase to Identify Substandard Medicines: Detection Capacity and Key Prerequisites. *Drug Saf* 2015; 38: 373–382.

[20] Griffin F, Resar R. IHI Global Trigger Tool for measuring adverse events. *IHI Innov Ser white Pap* 2009; 1–44.

[21] Murali M, Suppes SL, Feldman K, et al. Utilization of the Naranjo scale to evaluate adverse drug reactions at a free-standing children's hospital. *PLoS One* 2021; 16: 1–10.

[22] Glasheen WP, Cordier T, Gumpina R, et al. Charlson Comorbidity Index : ICD-9. 12.

[23] Hall RE, Porter J, Quan H, et al. Developing an adapted Charlson comorbidity index for ischemic stroke outcome studies. *BMC Health Serv Res* 2019; 19: 1–9.

[24] WHO. Survey of the quality of Selected antimalarial medicineS circulating in Six countrieS of Sub-Saharan africa.

[25] Hagen N, Khuluza F, Heide L. Quality, availability and storage conditions of oxytocin and misoprostol in Malawi. *BMC Pregnancy Childbirth* 2020; 20: 1–18.

[26] Ministry-of-Health. Malawi Standard Treatment Guidelines. Incorporating Malawi Essential Medicines List, https://extranet.who.int/ncdccs/Data/MWI_D1_Malawi-Standard-Treatment-Guidelines-Essential-Medicines-List-2015.pdf (2015).

[27] PATH. HealthTech Report: Prevalence of counterfeit or substandard antibiotics in developing countries. 2014; 1–2.

[28] Asrade Mekonnen B, Getie Yizengaw M, Chanie Worku M. Prevalence of substandard, falsified, unlicensed and unregistered medicine and its associated factors in Africa: a systematic review. *J Pharm Policy Pract* 2024; 17: 1–20.

[29] World-Health-Organization. Global Surveillance and Monitoring System for substandard and falsified medical products. *World Health Organization*. Epub ahead of print 2017. DOI: 978-92-4-151342-5.

[30] Thiagarajan K. WHO investigates cough syrups after deaths of 66 children in Gambia. *BMJ* 2022; 379: o2472.

[31] Shrestha RT, Malabanan A, Haugen BR, et al. Adverse event reporting in patients treated with thyroid hormone extract. *Endocr Pract* 2017; 23: 566–575.

[32] Sam M, Masaba JPM, Alio D, et al. Treatment Failure and Associated Factors among Individuals on Second Line Antiretroviral Therapy in Eastern Uganda: A Retrospective Cohort Study. *Infect Dis Res Treat* 2021; 14: 117863372110145.

[33] Appaneal HJ, Shireman TI, Lopes V V., et al. Poor clinical outcomes associated with suboptimal antibiotic treatment among older long-term care facility residents with urinary tract infection: a retrospective cohort study. *BMC Geriatr* 2021; 21: 1–13.

[34] Shafrin J, Marijam A, Joshi A V., et al. Impact of suboptimal or inappropriate treatment on healthcare resource use and cost among patients with uncomplicated urinary tract infection: an analysis of integrated delivery network electronic health records. *Antimicrob*

Resist Infect Control 2022; 11: 1–13.

[35] Muirhead GJ, Wilner K, Colburn W, et al. The effects of age and renal and hepatic impairment on the pharmacokinetics of sildenafil citrate. *Br J Clin Pharmacol Suppl*; 53. Epub ahead of print 2002. DOI: 10.1046/j.0306-5251.2001.00029.x.

[36] Helldén A, Bergman U, von Euler M, et al. Erratum to: Adverse Drug Reactions and Impaired Renal Function in Elderly Patients Admitted to the Emergency Department. *Drugs Aging* 2013; 30: 1043–1045.

[37] Charlson ME, Carrozzino D, Guidi J, et al. Charlson Comorbidity Index: A Critical Review of Clinimetric Properties. *Psychother Psychosom* 2022; 91: 8–35.

[38] Arabyat RM, Alazzam OM, Al-Azzam SI, et al. Association between Charlson Comorbidity Index and polypharmacy: A retrospective database study from Jordan. *Int J Pharm Pract* 2021; 29: 580–586.

[39] Brandariz-Núñez D, Ferreiro-Gómez M, Suanzes J, et al. Prevalence of adverse drug reactions associated with emergency department visits and risk factors for hospitalization. *Farm Hosp* 2023; 47: 20–25.

CHAPTER FIVE: DISCUSSION

5.0 Chapter overview

The findings for each specific objective have been adequately discussed in each publication or manuscript included in the thesis. Here we provide an overview of how the papers relate to one another in addressing the broad study objective. We highlight the new knowledge that the studies contribute to the field of pharmacovigilance, the limitations associated with the applied methods and provide insights of the future perspectives.

5.1 Relevance of the findings to pharmacovigilance

The aim of pharmacovigilance is to contribute to the prevention of medicine safety problems through identifying challenges that affect the proper use of medicines; improving patient care and safety; enhancing public health; contributing to the risk-benefit assessment and encouraging rational and cost-effective use of medicines [10,150]. SF medicines, poor availability of medicines, non-adherence to treatment guidelines, and occurrence of ADRs (which are covered in specific objectives I – IV) are among the key threats to patient safety.

ADRs may be caused by either the intrinsic properties of the API, product excipients or impurities. Augmented (type A) ADRs are usually related to the chemical structure of the API and therefore well documented in literature [96]. SF medicines are characterized by lower or higher than the stated amount of active ingredients, inferior excipients or toxic impurities [151]. They may therefore cause a distinct pattern of adverse events, which usually occurs in clusters, such as a series of treatment failure among patients taking a certain batch of a medicine [152]. Occurrence of type B ADRs (which are not expected from the pharmacological actions of the API) may suggest problems with the product excipients or presence of toxic impurities[153]. In this study, type A ADRs include events

such as abdominal pain, nausea, and vomiting while type B ADRs include events such as convulsions and hematuria. Such type B ADRs may be suspected to be caused by SF medicines, especially when the occurrence is in clusters or more frequent than elsewhere.

Standard treatment guidelines help to enhance rational medicine use, treatment cost-effectiveness and improve patient care [122]. To ensure efficiency of use of standard treatment guidelines, the EML provides a list of medicines that are required to be available always in sufficient supply at a health facility [154]. The adherence to standard treatment guidelines is therefore regarded as one of the important indicators of quality patient care. Poor availability of antibiotics defeats the purpose of the EML and MSTG and hence, may contribute to inappropriate use of antibiotics and pose a threat to antimicrobial stewardship.

5.2 New knowledge from the study

In this thesis, we have contributed to new knowledge on the important antibiotic medicine-related problems in Malawi.

Firstly, we found the factors that are associated with SF medicines in Malawi: local manufacturing and plastic primary packaging materials. The Malawi government supports the 'Buy Malawi' campaign which has potential to improve the economy of the country through industrialization, job creation and positive balance of trade [155]. However, for pharmaceutical products, the initiative needs to be promoted along with quality assurance measure as LMICs including Malawi face challenges such as poor regulatory mechanisms, and resources that can ensure compliance to current Good Manufacturing Practices and testing of medicine quality [156]. Bulk packaging of medicines in plastic bottles may be preferred due to the reduces cost as opposed to blister packaging [156]. However, blister

packages provide better protection against moisture, sunlight and microbial contamination which are known facilitators of medicine degradation [157].

We also found an association between antibiotic medicine availability and poor adherence to the MSTG. In addition, we also found the overuse of antibiotics in the Watch List category such as ceftriaxone. Watch antibiotics have an increased risk for resistance and hence the need to control their use to prevent the spread of antimicrobial resistance [158].

Lastly, this study identified new safety signals of adverse drug reactions related to antibiotics. We detected numbness of legs, hypotension and tachycardia which have not been documented in the summary of product characteristics and other literature. In addition, we also detected unusual frequency of convulsions following ceftriaxone administration [159]. These are serious ADRs of which some are life threatening and therefore require further investigation for signal validation and subsequent risk management actions.

5.3 Importance or application of the study findings in antimicrobial stewardship

The United States of America Centre for Disease Control (CDC) proposed infection prevention, effective diagnosis and treatment, rational use of antibiotics, and preventing transmission of resistance strains as main strategies for combatting antibiotic resistance [160]. Uchil et. al, expanded on these strategies and included other important elements such as policy formulation, increasing local and international collaborations, establishment of essential medicines list and treatment guidelines, improving antimicrobial surveillance, restricting over the counter (OTC) access for antibiotics, and increasing awareness campaigns on use of antibiotics [161]. These are important and relevant measures for adoption, as part of antimicrobial stewardship in Malawi. However, our current study

findings help to provide further insights on implementation challenges for the proposed measures. For instance, rational prescribing of antibiotics may not achieve positive clinical outcomes if the dispensed medicines are of poor pharmaceutical quality. Similarly, establishing standard treatment guidelines in a country may not be enough if there is low adherence to the stated treatment protocols among prescribers.

Based on our current findings, we propose additional measures that are relevant to these local problems that we face in Malawi. Firstly, we found that the high prevalence (25.4%) of poor quality of antibiotic medicines on the Malawian market is a huge threat to achieving positive clinical outcomes and fighting antibiotic resistance. The SF antibiotics found in this study had either low content of API or poor dissolution. Thus, these medicines expose bacteria to sub-optimal doses of antibacterial agents and therefore have very great potential to induce antibiotic resistance [162]. As noted, the percentage of patients who recover upon administering antibiotics with low API content was lower. On the same note, the decreased rate of ADRs also signifies loss of potency among substandard antibiotic medicines. This is because most of the ADRs experienced by patients on antibiotic medicines are dose-related (type A ADRs).

Among antibiotic medicines that were found to be of poor quality were amoxicillin, ciprofloxacin and flucloxacillin and benzylpenicillin. These among the first line antibiotic medicines for common bacterial infections in Malawi [124]. As such, the findings indicate that majority of patients presenting with bacterial infections may be exposed to these poor-quality antibiotic medicines. For instance, amoxicillin is recommended for infections such as respiratory tract infections, tonsilitis and sepsis. Ciprofloxacin is recommended as first line treatment for urinary tract infections and gastrointestinal infections such as bacillary

dysentery and typhoid while flucloxacillin is mostly recommended for infections such as otitis media, otitis interna and musculoskeletal infections such as septic arthritis and mastitis. Benzylpenicillin is an important parenteral antibiotic medicine for treatment of serious infections such as meningitis, neurosyphilis and other respiratory tract infections [124,163]. Studies have reported between 9-18% bacterial resistance to penicillins (which include amoxicillin, flucloxacillin and benzylpenicillin) and between 12-16% resistance to ciprofloxacin in Malawi [30–32].

The essential medicines list (EML) and standard treatment guidelines (STG) are available in Malawi to provide guidance on rational use of antibiotic medicines [124]. However, there are some implementation challenges regarding the use of MEML and MSTG in combating antibiotic resistance. Of importance to note, is that the latest MEML (released in 2015) at the time of data collection did not characterize antibiotics based on the risk for inducing resistance as guided by the WHO model EML [154]. Whilst the MEML generalizes the classification of antibiotic medicines based on effectiveness of treating important illnesses (as non-essential, essential and vital medicines) [124], the WHO considers the risk of resistance as another crucial element and categorizes antibiotics as Access, Watch and Reserve (AWaRe) medicines. Access antibiotics are those that can treat most common bacterial infections with low risk of inducing resistance due to their narrow spectrum. Watch antibiotics have broader spectrum and higher risk of inducing resistance. They are therefore recommended for use in severe bacterial infections. On the other hand, Reserve antibiotics are highly active agents that are used as last resort for multi-drug resistant pathogens in severe infections [158]. The AWaRe classification of antibiotics is therefore a very important guide towards curbing antibiotic resistance but has not yet been

adopted in Malawi. This classification guides physicians and pharmacists on the resistance risk associated with the antibiotic medicines to inform their selection of the most appropriate antibiotic medicines.

WHO recommends that more than 60% of antibiotic prescriptions should be from the Access category [164]. In our study, we found that only 24.7% of hospitalized patients were on Access antibiotics, 29.1% were on a combination of Access and Watch antibiotics, while 46.4% of prescriptions were Watch antibiotics. The overuse of Watch antibiotics such as ceftriaxone poses a big threat to the transmission of bacteria resistance in Malawi.

A study conducted between 2018 and 2020 revealed 68% bacterial resistance to ceftriaxone and other third-generation cephalosporins at QECH in Blantyre. Among the patients whom resistance strains were isolated, 45% died while in hospital [165]. Haigh et. al attribute over use of ceftriaxone in Malawi to high costs and restrictive policies against access to alternative extended spectrum antibiotics [166]. For instance, a daily dose of meropenem costs over US$50 vs US$11 for ceftriaxone(126). Furthermore, Amikacin, a WHO Access antibiotic which is effective against extended spectrum beta-lactamase (ESBL) producing bacterial strains such as Escherichia coli, Klebsiella pneumoniae and Salmonella [168] is restricted to treatment of only multi-drug resistance tuberculosis (TB) through policies initiated by the national TB programme of the Ministry of Health [166,169].

Uncontrolled access to antibiotic medicines has been reported as one of the factors that increases the risk of misuse and abuse of antibiotics. Misuse and abuse of antibiotics include self-medication and off-label use of antibiotics that are intended for human use, in animals [170–173]. Measures that restrict access of the public to antibiotics without the proper guidance of medical practitioners are urgently required. While controlling

accessibility of medicines protects patients and the public from harm associated with misuse and abuse of antibiotics, poor availability of antibiotic medicines in authorized premises such as hospitals has negative impacts on delivery of patient care.

Uninterrupted supply of essential antibiotics in a country is important to achieve rational antibiotic prescribing. This allows treating patients adequately according to treatment guidelines. As noted in our finding, poor availability of first line antibiotics was significantly associated with non-adherence to MSTG. When the required antibiotic medicines are not available, prescribers may improvise by switching to broad spectrum antibiotics to easily achieve the required effectiveness of therapy [174].

Adverse drug reactions also have a significant impact on the prescribing pattern of medicines. When a patient develops an ADR, there may be dose titrations or switching to alternative medicines with tolerable adverse effects [175]. Such treatment alterations may sometimes not be in accordance with the STGs. Furthermore, patients may lose trust and often may not be adherent to the prescribed regimen [176]. The alternative treatment may also be sub-optimal for the targeted disease or have a greater risk of resistance than the first line medicines.

Based on new findings presented in this thesis, we propose a modification of the model for the strategies required to combat antibiotic resistance as illustrated in **Figure 4**.

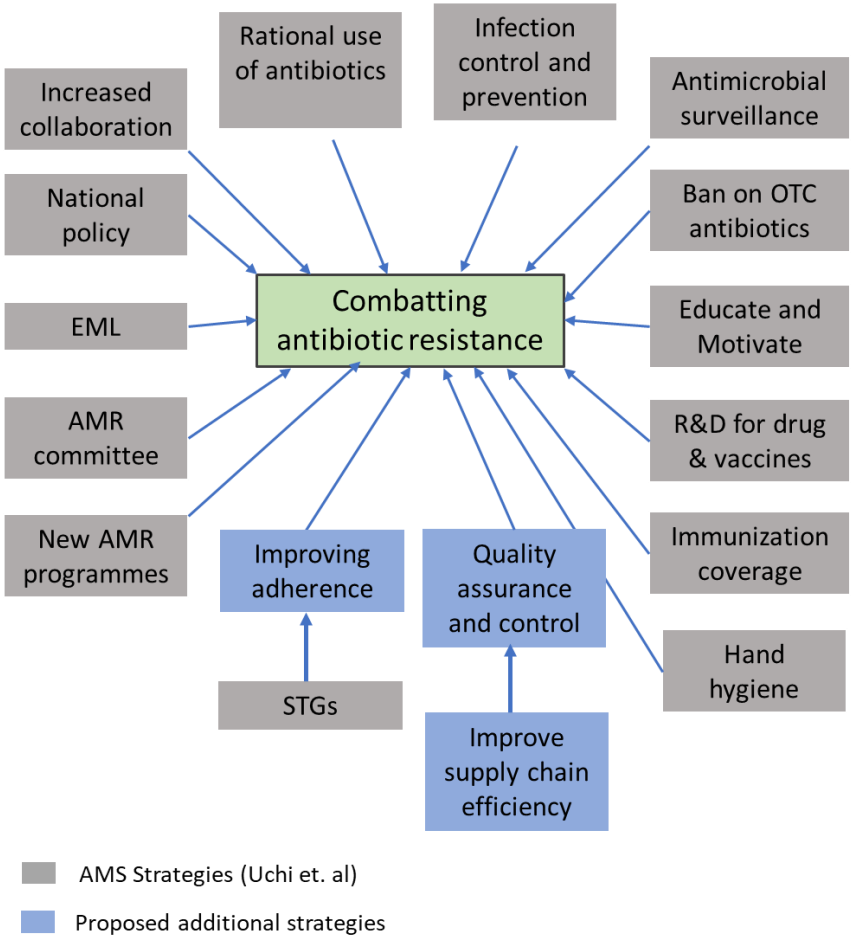


Figure 4: Model for implementing Antimicrobial Stewardship (AMS) strategies

Studies have suggested poor knowledge and access to the STGs by healthcare workers as one of the major reasons for poor adherence to the STGs [122,177]. Thus, there is a need for further enforcement of adherence to guidelines by ensuring that the MSTG is available and easily accessible in health facilities across the country. In addition, awareness and training among clinicians, pharmacists and nurses on the use of up-to-date version of the MSTG is important. Improvement of the supply chain for antibiotics would also prevent

irrational selection of antibiotics and reduce overuse of broad-spectrum antibiotics. This needs to be supplemented by strong and efficient quality control checks before the release of medicines by the manufacturer for marketing [178]. Quality of imported medicines can be ensured by sampling and screening in all entry points [179,180]. Further, post marketing surveillance by the PMRA needs to be revamped to ensure quality of medicines on the market [37].

5.2 Comparison of prevalence of SF antibiotics with other medicine classes

In objective I, we firstly confirmed our hypothesis that due to the high burden of bacterial infections and the subsequent high market demand, antibiotics are the most susceptible medicinal agents to be substandard or falsified. We found a higher burden of SF medicines among antibiotics as compared to antimalarials and antidiabetics. However, there was no significant difference between the prevalence of SF medicines between antibiotics and antihypertensives. This is consistent to our assertion, as the prevalence of antihypertension has been reported to drastically increase over the past years and hence, the expected increase in demand for antihypertensive medicines in Malawi. By 2017, about 16% (1.3 million) of adult population in Malawi had hypertension, and the prevalence is estimated to continue increasing to nearly 30% by 2025. Of the patients with hypertension in Malawi, over 90% of the patients fail to have their blood pressure under control[181]. Thus, more studies are also required to investigate the impact of SF antihypertensive medicines on the clinical outcomes.

5.2.1 Methods applied for quality screening

We firstly used simple and less expensive methods for to screen for SF medicines. Visual inspection is the first step to screen for SF medicines. Under strict good manufacturing

practices, pharmaceutical dosage units achieve precise uniformity in physical parameters such as colour, weight, printing, and imprinting. Though visual inspection alone cannot be used to conclude that a medicine is of poor quality, non-uniformity of visual physical characteristics may be an indicator for gross physical or chemical defects of medicines. Visual inspection was complemented by more informative screening methods: thin layer chromatography (GPHF Minilab®) and disintegration.

5.2.1.1 Strength and limitations of methods applied to detect SF medicines

High performance liquid chromatography (HPLC) and dissolution testing are the gold standard for testing the quantity and release of API respectively in pharmaceutical dosage forms. HPLC has very high sensitivity and is characterized by very low limits of detection and quantification (LOD and LOQ). It performs absolute quantification of API and ably separates the API from other pharmaceutical excipients and impurities with high resolution power. We used the Agilent® 1120 HPLC coupled with UV/Vis detector. UV/Vis detectors are very sensitive and provide precise (Relative standard deviation < 2%) measurements over a wide range of concentrations of pharmaceutical compounds.

In dissolution testing, appropriate solvents and temperature conditions were controlled to mimic gastric conditions. Samples were collected from the dissolution apparatus for quantification of actual amount of dissolved API using pharmaceutical assay. Furthermore, triplicate sampling was done to ensure accuracy and precision.

Thin layer chromatography (TLC) has been widely used to detect substandard and falsified medicines in African and Asian countries including DR Congo, Cameroon, Nigeria, Kenya, Uganda, and India [182]. TLC is easy, cost-effective and offers great reproducibility. Separation of various compounds is detected visually by either using UV light or various

stains such as iodine vapour. Therefore, qualitative evaluation of medicine quality using TLC is objective and highly reliable. TLC, however, has low resolution power and therefore makes quantitative analysis challenging. The technique only offers relative quantification but may not be applied for absolute quantification of API. Thus, only extreme deviations (<80% or >120% of API content) can be detected using TLC.

Disintegration is the first process that solid dosage forms undergo prior to dissolution. It offers a good prediction of the ability of material to dissolve as well as the ability to achieve the intended bioavailability. However, disintegration test has limitations, as on its own does not guarantee total dissolution of all particles. Disintegration is even more challenging for falsified medicines as the breakdown of the misrepresented ingredients may not achieve any intended effect, even if they may be completely dissolved.

The major limitation of this study was that only 21.8% (64/293) samples were subjected to pharmacopeial assay and dissolution. This was due to limited reagents and standards which are relatively expensive. In addition, most of the work was done during Covid-19 pandemic which disrupted the importation of goods into Malawi. Thus, based on the above strength and limitations of the screening methods which were mainly applied in the study (TLC and disintegration), the burden of SF medicines may be over/underestimated in Malawi. As presented in the results, we found some samples that passed during screening but failed upon subjecting them to pharmacopeial test. On the other hand, all samples that were suspected to be SF medicines during screening, were confirmed as such by pharmacopeial analysis.

5.3 Challenges of medicine availability

The WHO Health International Action (HIA) recommends a minimum of five facilities for assessing the availability of medicines. This is useful for generalization of medicine availability data in a country or province. As discussed in the methods section, only the district or central hospitals provides in-patient health care services. Thus, for the objectives of this study, we collected data from only three facilities (Zomba central, Machinga and Nsanje district hospitals). However, we did not only collect point availability data but also longitudinal availability by quantifying the number of stock-out days for a six-month period. This allowed us to further evaluate the stability of antibiotic medicines supply and hence, able to assess the impact on the prescribing pattern of antibiotic medicines.

Poor availability of essential medicines is not uncommon in LMICs. Among the reasons for poor availability of medicines include poor quantification or inventory management as a result of inadequate trained pharmacy personnel, lack of funds, infrastructure and technology, poor transportation networks and regulatory constraints [183]. The WHO recommends that at least 80% of essential medicines should be available in health facilities but the availability in most of facilities in LMICs is below 65% [184]. This is a big challenge as adherence to treatment guidelines requires constant availability, especially for first line therapy.

5.4 Detection of suspected ADRs

Spontaneous reporting is the pillar of pharmacovigilance as it seeks to provide data from real life clinical practice as opposed to clinical trial safety monitoring where the population is homogenous and subjects are closely monitored [28,91]. It is a relatively cheap, and flexible method where health care workers or patients relate observed signs and symptoms

and voluntarily reports as a suspected adverse drug reaction. The major challenge with spontaneous reporting remains under-reporting [185–187]. Due to limited knowledge and skills among health care professionals and the similarities in presentation of ADRs and other diseases, detection of adverse drug reactions may sometime be a challenging task [188–190].

In the study, we applied the global trigger tool which is a standardized approach for measuring medicine related harm among hospitalized patients. The clues provided in the tool helps to achieve a faster and more efficient way of systematically detecting ADEs [191]. Further, the global trigger tool offers an advantage for low resource setting as it does not require computerized record linkage [192].

Studies have shown that the global trigger tool achieves over 10-fold improvement in ADE detection rate as compared to voluntary reporting and other active chart review methods which does not use reference clues [78]. Reported ADR prevalence in studies which applied the global trigger tool ranges from 10.6 – 28% with positive predictive values of up to 48% for the triggers [193–197]. This tool is therefore appealing for not only research applications but also for clinical leadership at hospital level, where data for medicine related harm can be used to inform preventive measures at the facility.

Challenges associated with the global trigger tool include the requirement for trained personnel. Further it faces limitations when there is missing information in case management charts as it involves retrospective review of charts [78]. In our study, most of the laboratory-based clues such as partial thromboplastin time (M2) and abnormal blood urea nitrogen (BUN) or serum creatinine (M5) were not used as there was no information

due to limited laboratory capacities in the facilities. Thus, lack of such information may also limit the detection of ADEs in resource limited settings.

5.5.1 Use of ADR patterns to detect SF medicines

As presented in our results, SF medicines impact on the clinical outcomes of patients. Thus, the pattern of ADRs can be used for systematic detection of possible SF medicines. This can be done through observation of repeated cases (clusters) of loss of efficacy or unexpected adverse drug reactions [198]. Algorithms have been applied on larger databases such as the vigibase® to provide linkage between clinical outcomes and medicine information to predict the quality of the medicines [199].

5.6. Study Limitations

Firstly, the study was conducted only districts located in the southern region of Malawi. The region was selected based on the proximity to the Kamuzu University of Health Sciences, where the laboratory analysis of samples was conducted. However, the geographical distribution of storage facilities is an important factor for substandard medicines that deteriorate on storage due to the differences in atmospheric temperatures and humidity [200]. Therefore, this may have an impact on the results by under- or over-estimating the prevalence of substandard medicines in Malawi. On the other hand, the source of medicines for the formal market (mainly public and CHAM facilities) may have not been affected as most of the facilities across the country source the medicines mainly through one supplier, CMST [201].

Another limitation is that in this study, we only collected samples from the formal outlets (registered hospitals and pharmacies). Studies have shown that the prevalence of SF medicines is higher in the informal market than the formal markets [37,202–204].

Therefore, our findings may under-estimate the burden of SF medicines by excluding the formal markets which usually stock unlicensed products and where the compliance to good pharmaceutical storage practices is very poor.

In objective 2, we only included 16 antibiotic medicines to assess for the overall antibiotic availability without considering other possible alternative antibiotic medicines. This bias may have affected the findings for the antibiotic medicine availability. Further, we excluded 5.6% (18/322) records from our analysis which affected the results. It is also important to note that the medicine selection by clinicians may also be influenced by other factors apart from the availability of the recommended first line medicines. Therefore, our results may be affected by failure to examine the prescriber level factors such as the level of training, experience and personal preference [205–207].

In the study, we did not adequately investigate other possible contributors to the poor clinical outcomes and thus, the results may be biased and affected by other confounding factors. Furthermore, the use of retrospective and routinely collected data poses a challenge of missing out important information due to possible insufficient documentation and lack of verification or direct follow up with the patients. Due to the type of study design, there was a limited number of participants who were exposed to substandard antibiotics and therefore the study power was inadequate to accurately detect statistically significant effects. Thus, the findings of this study cannot be generalized to a larger population.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

We assessed the quality, availability and use of antibiotic medicines and the associated clinical outcomes in Southern Malawi. Our findings reveal high prevalence of SF antibiotic medicines which is associated with local manufacturing and bulk plastic packaging; poor availability of antibiotics that directly impacts on adherence to treatment guidelines; and occurrence of serious ADRs as some of the major challenges encountered during antibiotic therapy. These problems may significantly affect the effectiveness of antibiotic therapy and therefore lead to poor patient outcomes and exacerbate the risk of antibiotic resistance.

We therefore recommend to the Ministry of Health (MoH) to increase awareness and allocation of resources for strengthening pharmaceutical quality assurance systems at the Pharmacy and Medicines Regulatory Authority (PMRA), Central Medicine Stores Trust (CMST) and all health facilities. The National PV centre at PMRA needs to be adequately capacitated in terms of well-qualified staff to improve on the post marketing surveillance through routine collection and testing of medicine samples rather than mostly relying on spontaneous reporting. The centre should also improve the coverage and quality of pharmacovigilance training with much focus on equipping healthcare workers with practical skills in the detection and reporting of suspected medicinal product quality defects and adverse drug reactions. Furthermore, they should ensure that accessible and convenient reporting tools for both suspected SF medicines and adverse drug reactions are available in all health facilities in Malawi. Although the prevalence of SF medicines in Malawi is within the WHO estimates for LMICs, efforts have to be intensified to further reduce the burden to at least below 5% as strategized by other African countries such as Nigeria [208].

The CMST also needs to conduct comprehensive pharmacoeconomic analysis (such as the cost-benefit and cost-consequences analyses) to evaluate the rationale for purchasing bulk plastic-packaged medicines which are associated with poor pharmaceutical quality. This is because, much as the plastic-packaged medicines are cheaper than blister-packaged medicines, the former requires additional pharmacy staff for re-packaging the medicines in pill bags. Further, the pill bags are also costly to purchase which has led to some of the facilities using unacceptable materials such as paper for dispensing which raises more safety and quality concerns for the patients.

The MoH should also intensify policy measures to improve rational prescribing of medicines and the adherence to STGs. In particular, there is a need to enforce the WHO recommendation that states that at least 60% of antibiotic prescriptions being from the 'Access' list to control the spread of antibacterial resistance.

REFERENCES

1. Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny MP, Sheikh A. Medication without harm: WHO's third global patient safety challenge. Lancet. 2017;389(10080):1680–1.

2. World Health Organization. Reporting and learning systems for medication errors: the role of pharmacovigilance centres. Geneva: World Health Organization; 2014. 110 p.

3. Lewis TP, McConnell M, Aryal A, Irimu G, Mehata S, Mrisho M, et al. Health service quality in 2929 facilities in six low-income and middle-income countries: a positive deviance analysis. Lancet Glob Heal. 2023;11(6):e862–70.

4. Hamid H, Abid Z, Amir A, Rehman TU, Akram W, Mehboob T. Current burden on healthcare systems in low- and middle-income countries: recommendations for emergency care of COVID-19. Drugs Ther Perspect. 2020;36(10):466–8.

5. Langlois E V, Mckenzie A, Mecaskey JW. Measures to strengthen primary health-care systems in low- and middle-income countries. Policy Pract. 2020;98(11):781–91.

6. Witter S, Sheikh K, Schleiff M. Learning health systems in low-income and middle-income countries: exploring evidence and expert insights. BMJ Glob Heal. 2022;7:1–11.

7. World Health Organization. Medication without harm. Geneva: World Health Organization; 2023. 16 p.

8. Sheikh A, Dhingra-Kumar N, Kelley E, Kieny MP, Donaldson LJ. The third global patient safety challenge: tackling medication-related harm. Bull World Health Organ. 2017;95(8):546.

9. Khan MAA, Hamid S, Babar Z-U-D. Pharmacovigilance in high-income countries: current developments and a review of literature. Pharmacy. 2023;11(1):10.

10. World Health Organization. Pharmacovigilance: ensuring the safe use of medicines. Geneva: World Health Organization; 2004. 6 p.

11. Dimopoulos MA, Kastritis E. Thalidomide for myeloma: still here? Lancet Haematol. 2018;5(10):e439–40.

12. Andrews PLR, Williams RSB, Sanger GJ. Anti-emetic effects of thalidomide: evidence, mechanism of action, and future directions. Curr Res Pharmacol Drug Discov. 2022;3(June):100138.

13. Rehman W, Arfons LM, Lazarus HM. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. Ther Adv Hematol. 2011;2(5):291–308.

14. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease. Toxicol Sci. 2011;122(1):1–6.

15. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res Part C - Embryo Today Rev. 2015;105(2):140–56.

16. Letourneau M, Wells G, Walop W, Duclos P. Improving global monitoring of vaccine safety: a survey of national centres participating in the WHO Programme

for International Drug Monitoring. Drug Saf. 2008;31(5):389–98.

17. Letourneau M, Wells G, Walop W, Duclos P. Improving global monitoring of vaccine safety: A quantitative analysis of adverse event reports in the WHO Adverse Reactions Database. Vaccine. 2008;26(9):1185–94.

18. Ampadu HH, Hoekman J, de Bruin ML, Pal SN, Olsson S, Sartori D, et al. Adverse drug reaction reporting in Africa and a comparison of individual case safety report characteristics between Africa and the rest of the world: analyses of spontaneous reports in VigiBase®. Drug Saf. 2016;39(4):335–45.

19. World Health Organization. WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) [Internet]. 2023 [cited 2024 Feb 15]. Available from: https://www.who.int/groups/ACSoMP

20. Khalid Abbood M, Alaa Aldeen Khalaf H, H. Abudlqader E, Sagban Taghi H, Alaa Al-Temimi A. Scope of pharmacovigilance: comprehensive review. Chem Sci Int J. 2022;31(5):29–39.

21. Buckley GJ, Gostin LO. Countering the problem of falsified and substandard drugs. Wahington, D.C: National Academies Press; 2013. 351 p.

22. World Health Organization. The WHO Member State mechanism on substandard and falsified medical products. Who. 2019;19(April):1–12.

23. Pisani E, Hasnida A, Rahmi M, Kok MO, Harsono S, Anggriani Y. Substandard and falsified medicines: proposed methods for case finding and sentinel surveillance. JMIR Public Heal Surveill. 2021;7(8):e29309.

24. World Health Organization. Global surveillance and monitoring system for substandard and falsified medical products. World Health Organization. Geneva: World Health Organization; 2017. 73 p.

25. Dal Pan GJ. Ongoing challenges in pharmacovigilance. Drug Saf. 2014;37(1):1–8.

26. Kiguba R, Olsson S, Waitt C. Pharmacovigilance in low- and middle-income countries: a review with particular focus on Africa. Br J Clin Pharmacol. 2021;89(2):491–509.

27. Kiguba R, Olsson S, Waitt C. Pharmacovigilance in low- and middle-income countries: a review with particular focus on Africa. Br J Clin Pharmacol. 2023;89(2):491–509.

28. Asiamah M, Akuffo KO, Nortey P, Donkor N, Danso-Appiah A. Spontaneous reporting of adverse drug reaction among health professionals in Ghana. Arch Public Heal. 2022;80(1):1–11.

29. Jusot V, Chimimba F, Dzabala N, Menang O, Cole J, Gardiner G, et al. Enhancing pharmacovigilance in sub-Saharan Africa through training and mentoring: a GSK pilot initiative in Malawi. Drug Saf. 2020;43(6):583–93.

30. Kumwenda P, Adukwu EC, Tabe ES, Ujor VC, Kamudumuli PS, Ngwira M, et al. Prevalence, distribution and antimicrobial susceptibility pattern of bacterial isolates from a tertiary hospital in Malawi. BMC Infect Dis. 2021;21(1):1–10.

31. Musicha P, Cornick JE, Bar-zeev N, French N, Masesa C, Denis B, et al. Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in

Malawi (1998 – 2016): a surveillance study. Lancet Infect Dis. 2017;17(10):1042–52.

32. Makoka MH, Miller WC, Hoffman IF, Cholera R, Gilligan PH, Kamwendo D, et al. Bacterial infections in Lilongwe, Malawi: aetiology and antibiotic resistance. BMC Infect Dis. 2012;12:6–8.

33. Khuluza F, Kigera S, Heide L. Low prevalence of substandard and falsified antimalarial and antibiotic medicines in public and faith-based health facilities of southern Malawi. Am J Trop Med Hyg. 2017;96(5):1124–35.

34. Khuluza F. In-vitro evaluation of the quality of paracetamol and co-trimoxazole tablets used in Malawi based on pharmacopoeial standards. Malawi Med J. 2014;26(2):38–41.

35. Hagen N, Khuluza F, Heide L. Quality, availability and storage conditions of oxytocin and misoprostol in Malawi. BMC Pregnancy Childbirth. 2020;20(1):1–18.

36. Khuluza F, Kigera S, Jähnke RWO, Heide L. Use of thin-layer chromatography to detect counterfeit sulfadoxine/pyrimethamine tablets with the wrong active ingredient in Malawi. Malar J. 2016;15(1):1–7.

37. Chikowe I, Osei-Safo D, Harrison JJEK, Konadu DY, Addae-Mensah I. Post-marketing surveillance of anti-malarial medicines used in Malawi. Malar J. 2015;14(1):1–11.

38. McManus D, Naughton BD. A systematic review of substandard, falsified, unlicensed and unregistered medicine sampling studies: a focus on context,

prevalence, and quality. BMJ Glob Heal. 2020;5(8):1–9.

39. Rolfe R, Kwobah C, Muro F, Ruwanpathirana A, Lyamuya F, Bodinayake C, et al. Barriers to implementing antimicrobial stewardship programs in three low- and middle-income country tertiary care settings: findings from a multi-site qualitative study. Antimicrob Resist Infect Control. 2021;10(1):1–11.

40. Kimbowa IM, Ocan M, Eriksen J, Nakafeero M, Obua C, Lundborg CS, et al. Characteristics of antimicrobial stewardship programmes in hospitals of Uganda. PLoS One. 2022;17(5):1–14.

41. Cox JA, Vlieghe E, Mendelson M, Wertheim H, Ndegwa L, Villegas M V., et al. Antibiotic stewardship in low- and middle-income countries: the same but different? Clin Microbiol Infect. 2017;23(11):812–8.

42. Kamere N, Rutter V, Munkombwe D, Aywak A, Muro P, Kaminyoghe F, et al. Supply-chain factors and antimicrobial stewardship. Policy Pract. 2023;101(6):403.

43. Khuluza F, Heide L. Availability and affordability of antimalarial and antibiotic medicines in Malawi. PLoS One. 2017;12(4):1–15.

44. Khuluza F, Haefele-Abah C. The availability, prices and affordability of essential medicines in Malawi: a cross-sectional study. PLoS One. 2019;14(2):1–22.

45. Bhattarai S, Sharma BK, Subedi N, Ranabhat S, Baral MP. Burden of serious bacterial infections and multidrug-resistant organisms in an adult population of Nepal: a comparative analysis of minimally invasive tissue sampling informed mortality surveillance of community and hospital deaths. Clin Infect Dis.

2021;73(Suppl_5):S415–21.

46. Ikuta KS, Swetschinski LR, Robles Aguilar G, Sharara F, Mestrovic T, Gray AP, et al. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2022;400(10369):2221–48.

47. Coates MM, Ezzati M, Aguilar GR, Kwan GF, Vigo D, Mocumbi AO, et al. Burden of disease among the world's poorest billion people: an expert-informed secondary analysis of global burden of disease estimates. PLoS One. 2021;16(8):1–21.

48. Kiguba R, Karamagi C, Bird SM. Antibiotic-associated suspected adverse drug reactions among hospitalized patients in Uganda: a prospective cohort study. Pharmacol Res Perspect. 2017;5(2):1–16.

49. Blaser MJ, Melby MK, Lock M, Nichter M. Accounting for variation in and overuse of antibiotics among humans. BioEssays. 2021;43(2).

50. Balasubramanian R, Van Boeckel TP, Carmeli Y, Cosgrove S, Laxminarayan R. Global incidence in hospital-associated infections resistant to antibiotics: an analysis of point prevalence surveys from 99 countries. PLoS Med. 2023;20(6):e1004178.

51. Sharma A, Singh A, Dar MA, Kaur RJ, Charan J, Iskandar K, et al. Menace of antimicrobial resistance in LMICs: current surveillance practices and control measures to tackle hostility. J Infect Public Health. 2022;15(2):172–81.

52. Mallah N, Orsini N, Figueiras A, Takkouche B. Income level and antibiotic misuse: a systematic review and dose–response meta-analysis. Eur J Heal Econ.

2022;23(6):1015–35.

53. Bui DS, Nguyen T. A real challenge to tackle the overuse of antibiotics in LMIC: a case from Vietnam. Lancet Reg Heal - West Pacific. 2023;30:100650.

54. Knowles R, Sharland M, Hsia Y, Magrini N, Moja L, Siyam A, et al. Measuring antibiotic availability and use in 20 low-and middle-income countries. Bull World Health Organ. 2020;98(3):177–87.

55. Siachalinga L, Godman B, Mwita JC, Sefah IA, Ogunleye OO, Massele A, et al. Current Antibiotic Use Among Hospitals in the sub-Saharan Africa Region; Findings and Implications. Infect Drug Resist. 2023;16(April):2179–90.

56. Hossain S, Islam F, Arka B, Rohman M, Ahmed S, Ahammed T. Articles Antibiotic prescription from quali fi ed sources for children with fever / cough : cross-sectional study from 59 low- and middle- income countries. eClinicalMedicine. 2023;61(December):102055.

57. Hughes G, Li D, Kerrigan R, Gupta I, Wilkinson S. Antibiotic prescribing practices in primary healthcare in sub-Saharan Africa: a systematic review and our experience on the use of telemedicine in Zambia. JAC- Antimicrob Resist. 2022;1–2.

58. Klein EY, Van Boeckel TP, Martinez EM, Pant S, Gandra S, Levin SA, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. Proc Natl Acad Sci U S A. 2018;115(15):E3463–70.

59. Abubakar U. Antibiotic use among hospitalized patients in northern Nigeria: a multicenter point-prevalence survey. BMC Infect Dis. 2020;20(1):1–9.

60. Ozawa S, Chen HH, Lee YF, Higgins CR, Yemeke TT. Characterizing medicine quality by active pharmaceutical ingredient levels: a systematic review and meta-analysis across low-and middle-income countries. Am J Trop Med Hyg. 2022;106(6):1778–90.

61. Pisani E. Antimicrobial resistance: what does medicine quality have to do with it? London: King's College London; 2015. 45 p.

62. Bowie C. The burden of disease in Malawi. Malawi Med J. 2007;18(3).

63. Gowshall M, Taylor-Robinson SD. The increasing prevalence of non-communicable diseases in low-middle income countries: the view from Malawi. Int J Gen Med. 2018;255–64.

64. Barbosa TM, Levy SB. The impact of antibiotic use on resistance development and persistence. Drug Resist Updat. 2000;3(5):303–11.

65. Klein EY, Boeckel TP Van, Martinez EM, Pant S, Gandra S, Levin SA. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. PNAS. 2018;115(15):3463–70.

66. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. Lancet. 2022;399(10325):629–55.

67. Sartelli M, Hardcastle TC, Catena F, Chichom-Mefire A, Coccolini F, Dhingra S, et al. Antibiotic use in low and middle-income countries and the challenges of antimicrobial resistance in surgery. Antibiotics. 2020;9(8):1–12.

68. C Reygaert W. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018;4(3):482–501.

69. Ayukekbong JA, Ntemgwa M, Atabe AN. The threat of antimicrobial resistance in developing countries: causes and control strategies. Antimicrob Resist Infect Control. 2017;6(1):1–8.

70. Desai M. Pharmacovigilance and spontaneous adverse drug reaction reporting: challenges and opportunities. Perspect Clin Res. 2022;13(4):177–9.

71. Hauben M, Aronson JK. Defining "signal" and its subtypes in pharmacovigilance based on a systematic review of previous definitions. Drug Saf. 2009;32(2):99–110.

72. European Medicines Agency. Note for guidance on planning pharmacovigilance activites. London: European Medicines Agency; 2005. 16 p.

73. Pal SN, Duncombe C, Falzon D, Olsson S. WHO strategy for collecting safety data in public health programmes: complementing spontaneous reporting systems. Drug Saf. 2013;36(2):75–81.

74. Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: two "challenging" case reports. J Pharmacol Pharmacother. 2013;4(Suppl_1):S66-72.

75. Härmark L, Van Grootheest AC. Pharmacovigilance: methods, recent developments and future perspectives. Eur J Clin Pharmacol. 2008;64(8):743–52.

76. Shrestha RT, Malabanan A, Haugen BR, Levy EG, Hennessey J V. Adverse event reporting in patients treated with thyroid hormone extract. Endocr Pract.

2017;23(5):566–75.

77. Wang J, Yu LC, Zhang X. Explainable detection of adverse drug reaction with imbalanced data distribution. PLoS Comput Biol. 2022;18(6):1–17.

78. Sharek PJ. The emergence of the trigger tool as the premier measurement strategy for patient safety. AHRQ WebM&M Morb Mortal rounds Web. 2012;2012(5):1–5.

79. Institute_for_Healthcare_Improvement. IHI Global Trigger Tool for Measuring Adverse Events. 2023.

80. Griffin F, Resar R. IHI Global Trigger Tool for measuring adverse events. Cambridge, MA: Institute for Healthcare Improvement; 2009.

81. Montané E, Santesmases J. Adverse drug reactions. Med Clin (Barc). 2020;154(5):178–84.

82. Mirosevic Skvrce N, Galic I, Pacadi C, Kandzija N, Mucalo I. Adverse drug reactions that arise from the use of medicinal products outside the terms of the marketing authorisation. Res Soc Adm Pharm. 2020;16(7):928–34.

83. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. Lancet. 2000;356(9237):1255–9.

84. Walter SR, Day RO, Gallego B, Westbrook JI. The impact of serious adverse drug reactions: a population-based study of a decade of hospital admissions in New South Wales, Australia. Br J Clin Pharmacol. 2017;83(2):416–26.

85. Yadesa TM, Kitutu FE, Deyno S, Ogwang PE, Tamukong R, Alele PE. Prevalence, characteristics and predicting risk factors of adverse drug reactions among

hospitalized older adults: a systematic review and meta-analysis. Vol. 9, SAGE Open Medicine. 2021. p. 205031212110390.

86. Insani WN, Whittlesea C, Alwafi H, Man KKC, Chapman S, Wei L. Prevalence of adverse drug reactions in the primary care setting: A systematic review and meta-analysis. PLoS One. 2021;16(5 May):1–24.

87. Fattinger K, Roos M, Vergères P, Holenstein C, Kind B, Masche U, et al. Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine. Br J Clin Pharmacol. 2000;49(2):158–67.

88. Montastruc JL, Lafaurie M, de Canecaude C, Durrieu G, Sommet A, Montastruc F, et al. Fatal adverse drug reactions: a worldwide perspective in the World Health Organization pharmacovigilance database. Br J Clin Pharmacol. 2021;87(11):4334–40.

89. Qing-Ping S, Xiao-Dong J, Feng D, Yan L, Mei-Ling Y, Jin-Xiu Z, et al. Consequences, measurement, and evaluation of the costs associated with adverse drug reactions among hospitalized patients in China. BMC Health Serv Res. 2014;14:1–9.

90. Ribeiro MR, Motta AA, Fonseca LAM, Kalil-Filho J, Giavina-Bianchi P. Increase of 10% in the rate of adverse drug reactions for each drug administered in hospitalized patients. Clinics. 2018;73(8):1–6.

91. Sultana J, Cutroneo P, Trifirò G. Clinical and economic burden of adverse drug reactions. J Pharmacol Pharmacother. 2013;4(Suppl_1):73–7.

92. Osanlou R, Walker L, Hughes DA, Burnside G, Pirmohamed M. Adverse drug reactions, multimorbidity and polypharmacy: a prospective analysis of 1 month of medical admissions. BMJ Open. 2022;12(7):1–7.

93. Weiss ME, Bernstein DI, Blessing-moore J, Cox L, Lang DM, Nicklas RA, et al. Drug allergy: An updated practice parameter. Ann Allergy, Asthma Immunol. 2010;105(4):259-273.e78.

94. Wilke RA, Lin DW, Roden DM, Watkins PB, Flockhart D, Zineh I, et al. Identifying genetic risk factors for serious adverse drug reactions: current progress and challenges. Nat Rev Drug Discov. 2007;6(11):904–16.

95. Putriana NA, Rusdiana T, Rostinawati T, Akbar MR, Destiani DP. Evaluation of adverse drug reaction in patients warfarin therapy. J Adv Pharm Technol Res. 2022;13(4):291–5.

96. Iasella CJ, Johnson HJ, Dunn MA. Adverse drug reactions: Type A (Intrinsic) or Type B (Idiosyncratic). Clin Liver Dis. 2017;21(1):73–87.

97. Böhm R, Proksch E, Schwarz T, Cascorbi I. Drug hypersensitivity. Medicine (Baltimore). 2018;115(29–30):501–12.

98. Costa MJ, Herdeiro MT, Polónia JJ, Ribeiro-Vaz I, Botelho C, Castro E, et al. Type B adverse drug reactions reported by an immunoallergology department. Pharm Pract (Granada). 2018;16(1):1–6.

99. Akpobolokemi T, Martinez-Nunez RT, Raimi-Abraham BT. Tackling the global impact of substandard and falsified and unregistered/unlicensed anti-tuberculosis

medicines. J Med Access. 2022;6:239920262110704.

100. World Health Organization. Report of the fourth meeting of the Member State mechanism on substandard/spurious/falsely - labelled/falsified/counterfeit medical products. Geneva: World Health Organization; 2015. 10 p.

101. Hauk C, Hagen N, Heide L. Identification of substandard and falsified medicines: Influence of different tolerance limits and use of authenticity inquiries. Am J Trop Med Hyg. 2021;104(5):1936–45.

102. Johnston A, Holt DW. Substandard drugs: a potential crisis for public health. Br J Clin Pharmacol. 2014;78(2):218–43.

103. Schiavetti B, Wynendaele E, Melotte V, Van Der Elst J, De Spiegeleer B, Ravinetto R. A simplified checklist for the visual inspection of finished pharmaceutical products: a way to empower frontline health workers in the fight against poor-quality medicines. J Pharm Policy Pract. 2020;13(1):1–7.

104. Suchatanugal N, Chedthanorrakul P, Thaveesangsakulthai I, Nhujak T, Kulsing C. Thin layer chromatography based extraction approaches for improved analysis of volatile compounds with gas chromatography–mass spectrometry and direct analysis with gas analyzer. J Sep Sci. 2021;44(2):666–75.

105. Touchstone JC. Instrumentation for thin-layer chromatography: a review. J Chromatogr Sci. 1988;26(12):645–9.

106. Chemistry Hall. Thin layer chromatography: a complete guide to TLC [Internet]. Chemistry Hall. 2020 [cited 2023 Aug 20]. Available from:

https://chemistryhall.com/thin-layer-chromatography/

107. Gupta A, Hunt RL, Shah RB, Sayeed VA, Khan MA. Disintegration of highly soluble immediate release tablets: a surrogate for dissolution. AAPS PharmSciTech. 2009;10(2):495–9.

108. Grube A, Gerlitzki C, Brendel M. Dissolution or disintegration–substitution of dissolution by disintegration testing for a fixed dose combination product. Drug Dev Ind Pharm. 2019;45(1):130–8.

109. Pharmaguideline. Disintegration test and apparatus [Internet]. Pharmaguideline. 2023 [cited 2023 Oct 12]. Available from: https://www.pharmaguideline.com/2011/06/disintegration-test-and-apparatus.html

110. Ho NT, Desai D, Zaman MH. Rapid and specific drug quality testing assay for artemisinin and its derivatives using a luminescent reaction and novel microfluidic technology. Am J Trop Med Hyg. 2015;92(6):24–30.

111. Kumar BR. Application of HPLC and ESI-MS techniques in the analysis of phenolic acids and flavonoids from green leafy vegetables (GLVs). J Pharm Anal. 2017;7(6):349–64.

112. Pharmaguideline. Principle of HPLC (liquid Chromatography. 2023.

113. Pharma_Specialist. USP dissolution apparatus: Types and principles. 2023.

114. Al-Worafi YM, editor. Medication errors. In: Drug Safety in Developing Countries: Achievements and Challenges. Academic Press; 2020. p. 59–71.

115. Hodkinson A, Tyler N, Ashcroft DM, Keers RN, Khan K, Phipps D, et al.

Preventable medication harm across health care settings: a systematic review and meta-analysis. BMC Med. 2020;18(1):1–13.

116. WHO. Key facts about medication errors (MEs) in the WHO European Region. Geneva: World Health Organization; 2022. 3 p.

117. World Health Organization. WHO launches global effort to halve medication-related errors in 5 years [Internet]. Geneva: World Health Organization; 2017. Available from: https://www.who.int/news/item/29-03-2017-who-launches-global-effort-to-halve-medication-related-errors-in-5-years

118. Rasool MF, Rehman A ur, Imran I, Abbas S, Shah S, Abbas G, et al. Risk factors associated with medication errors among patients suffering from chronic disorders. Front Public Heal. 2020;8:531038.

119. Savva G, Papastavrou E, Charalambous A, Vryonides S, Merkouris A. Exploring nurses' perceptions of medication error risk factors: findings from a sequential qualitative study. Glob Qual Nurs Res. 2022;9:23333936221094856.

120. Hammoudi BM, Ismaile S, Abu Yahya O. Factors associated with medication administration errors and why nurses fail to report them. Scand J Caring Sci. 2018;32(3):1038–46.

121. Gopalakrishnan S, Udayshankar P, Rama R. Standard treatment guidelines in primary healthcare practice. J Fam Med Prim Care. 2014;3(4):424.

122. Govender T, Suleman F, Perumal-Pillay VA. Evaluating the implementation of the standard treatment guidelines (STGs) and essential medicines list (EML) at a public

South African tertiary institution and its associated primary health care (PHC) facilities. J Pharm Policy Pract. 2021;14(1):1–14.

123. Steinhardt LC, Chinkhumba J, Wolkon A, Luka M, Luhanga M, Sande J, et al. Quality of malaria case management in Malawi: results from a nationally representative health facility survey. PLoS One. 2014;9(2).

124. Ministry of Health. Malawi standard treatment guidelines: incorporating Malawi essential medicines list. 5th ed. Lilongwe: Ministry of Health; 2015. 559 p.

125. Ministry-of-Health-National-Malaria-Programme. Guidelines for the treatment of malaria in Malawi. Lilongwe; 2013.

126. Sendekie AK, Netere AK, Tesfaye S, Dagnew EM, Belachew EA. Incidence and patterns of adverse drug reactions among adult patients hospitalized in the University of Gondar comprehensive specialized hospital: a prospective observational follow-up study. PLoS One. 2023;18(2):1–20.

127. Jung IY, Kim JJ, Lee SJ, Kim J, Seong H, Jeong W, et al. Antibiotic-related adverse drug reactions at a tertiary care hospital in South Korea. Biomed Res Int. 2017;2017(1):4304973.

128. Lewis JM, Lester R, Mphasa M, Banda R, Thomson NR, Feasey N. Emergence of carbapenemase producing Enterobacteriaceae, Malawi. J Antimicrob Resist. 2020;225–7.

129. GPHF-Minilab^{TM}. Protection against counterfeit medicines [Internet]. GPHF-Minilab. 2016 [cited 2023 Jun 12]. Available from:

https://www.gphf.org/en/minilab/index.htm

130. British Pharmacoeia Commission. British Pharmacopoeia. London: TSO information and publishing solutions; 2013.

131. The-Indian-Pharmacopoeia-Commission. Indian Pharmacopoeia. Vol. 2, Indian Pharmacopoeia. GHAZIABAD; 2007. p. 225.

132. Tran C Van, Vargas JR. Determination of specific absorbance (A^{1}_{1}) for six psychoactive drugs encountered in forensic toxicology. J Anal Toxicol. 2021;44(6):531–40.

133. Prinja S, Bahuguna P, Tripathy JP, Kumar R. Availability of medicines in public sector health facilities of two North Indian States. BMC Pharmacol Toxicol. 2015;16(1):1–11.

134. Tefera BB, Tafere C, Yehualaw A, Mebratu E, Chanie Y, Ayele S, et al. Availability and stock-out duration of essential medicines in Shegaw Motta general hospital and Motta Health Centre, North West Ethiopia. PLoS One. 2022;17(9):1–10.

135. Yadesa TM, Kitutu FE, Deyno S, Ogwang PE, Tamukong R, Alele PE. Prevalence, characteristics and predicting risk factors of adverse drug reactions among hospitalized older adults: a systematic review and meta-analysis. SAGE Open Med. 2021;9:20503121211039100.

136. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30(2):239–45.

137. Bethesda(MD). Adverse Drug Reaction Probability Scale (Naranjo) in Drug Induced Liver Injury. Natl Institutes Heal US Dept Heal Hum Serv. 2019;1–5.

138. Nowinski CJ, Bureau SC, Buckland ME, Curtis MA, Daneshvar DH, Faull RLM, et al. Applying the Bradford Hill criteria for causation to repetitive head impacts and chronic traumatic encephalopathy. Front Neurol. 2022;13:938163.

139. Murali M, Suppes SL, Feldman K, Goldman JL. Utilization of the Naranjo scale to evaluate adverse drug reactions at a free-standing children's hospital. PLoS One. 2021;16(1):e0245368.

140. Arulappen AL, Danial M, Sulaiman SAS. Evaluation of reported adverse drug reactions in antibiotic usage: a retrospective study from a tertiary care hospital, Malaysia. Front Pharmacol. 2018;9:809.

141. Saqib A, Sarwar MR, Sarfraz M, Iftikhar S. Causality and preventability assessment of adverse drug events of antibiotics among inpatients having different lengths of hospital stay: a multicenter, cross-sectional study in Lahore, Pakistan. BMC Pharmacol Toxicol. 2018;19(1):1–14.

142. Hewawasam L, Wijesinghe MSD, Nazeer I, Amarathunga DM, Jayawardena P. Causality, severity, and preventability of adverse drug reactions due to multi-drug therapy in leprosy: evidence from a national level institution in Sri Lanka. Lepr Rev. 2023;94(2):124–34.

143. Comfort S, Dorrell D, Meireis S, Fine J. MOdified NARanjo causality scale for ICSRs (MONARCSi): a decision support tool for safety scientists. Drug Saf. 2018;41(11):1073–85.

144. Khan LM, Al-Harthi SE, Osman AMM, Sattar MAAA, Ali AS. Dilemmas of the causality assessment tools in the diagnosis of adverse drug reactions. Saudi Pharm J. 2016;24(4):485–93.

145. World Health Organization. Safety of medicines: a guide to detecting and reporting adverse drug reactions. Geneva: World Health Organization; 2022. 20 p.

146. Du Y, Lin J, Shen J, Ding S, Ye M, Wang L, et al. Adverse drug reactions associated with six commonly used antiepileptic drugs in southern China from 2003 to 2015. BMC Pharmacol Toxicol. 2019;20(1):1–8.

147. Keche Y, Gaikwad N, Dhaneria S. Preventability, predictability, severity and causality assessment of adverse drug reactions reported from a teaching hospital in chhattisgarh: a retrospective analysis. J Fam Med Prim Care. 2021;6(2):169–70.

148. Anthony L, P P. Patterns, causality, severity, and preventability of adverse drug reactions: an observational study at a tertiary health-care center. Natl J Physiol Pharm Pharmacol. 2022;12(12):1.

149. Schumock GT, Thornton JP. Focusing on the preventability of adverse drug reactions. Hosp Pharm. 1992;27(6):538.

150. Rohilla A, Singh N. Pharmacovigilance: needs and objectives. J Adv Pharm Edu Res. 2012;2(4).

151. Ozawa S, Higgins CR, Nwokike JI, Phanouvong S. Modeling the health and economic impact of substandard and falsified medicines: a review of existing models and approaches. Am J Trop Med Hyg. 2022;107(1):14–20.

152. Wang M, Ye X, Ruan Y, Xu J, Guo X, Dong D, et al. Detection of cluster adverse drug events in the spontaneous reporting system of China using a disproportionality filter algorithm. J Clin Pharm Ther. 2019;44(6):952–7.

153. Strauss J, Greeff OBW. Excipient-related adverse drug reactions: a clinical approach. Curr Allergy Clin Immunol. 2015;28(1):24–7.

154. World-Health-Organization(WHO). Model list of essential medicines. Vol. 21. Geneva; 2019.

155. UNDP. Review of the Buy Malawi Campaign in Malawi [Internet]. United Nations Development Programme. 2015. Available from: https://jobs.undp.org/cj_view_job.cfm?cur_job_id=58285

156. Bakker-'t Hart IME, Ohana D, Venhuis BJ. Current challenges in the detection and analysis of falsified medicines. J Pharm Biomed Anal. 2021;197:113948.

157. Yaren Çapkın İ, Gökelma M. A review on characterization and recyclability of pharmaceutical blisters. Clean Waste Syst. 2023;4:100082.

158. WHO. The WHO AWaRe (access, watch, reserve) antibiotic book. World Health Organization. Geneva: World Health Organization; 2022. 697 p.

159. Electronic-medicines-compendium. Summary of product characteristics. 2023.

160. The Centers for Disease Control and Prevention (CDC). At A Glance: CDC Campaign to Prevent Antimicrobial Resistance in Healthcare Settings 12 Steps to Prevent Antimicrobial Resistance Among At A Glance CDC Campaign to Prevent Antimicrobial Resistance in Healthcare Settings. Pharmacia. 2004;5–6.

161. Uchil RR, Kohli GS, Katekhaye VM, Swami OC. Strategies to combat antimicrobial resistance. J Clin Diagnostic Res. 2014;8(7):8–11.

162. The United States Pharmacopeial Convention. How medicine quality affects antimicrobial resistance and the medicines supply chain [Internet]. Quality Matters. 2022 [cited 2023 Oct 12]. Available from: https://qualitymatters.usp.org/how-medicine-quality-affects-antimicrobial-resistance-and-medicines-supply-chain

163. Iskandar K, Molinier L, Hallit S, Sartelli M, Catena F, Coccolini F, et al. Drivers of antibiotic resistance transmission in low-and middle-income countries from a "one health" perspective—a review. Antibiotics. 2020;9(7):1–23.

164. Simmons B, Ariyoshi K, Ohmagari N, Pulcini C, Huttner B, Gandra S, et al. Progress towards antibiotic use targets in eight high-income countries. Bull World Health Organ. 2021;99(8):550–61.

165. Lester R, Musicha P, Kawaza K, Langton J, Mango J, Mangochi H, et al. Effect of resistance to third-generation cephalosporins on morbidity and mortality from bloodstream infections in Blantyre, Malawi: a prospective cohort study. The Lancet Microbe. 2022;3(12):e922–30.

166. Haigh K, Dube Q, Kasambara W, Feasey NA, Lester R. Cephalosporin resistance in Malawi. Lancet Infect Dis. 2020;20(3):285–6.

167. Drugs.com. Comparing Ceftriaxone vs Meropenem [Internet]. 2023 [cited 2024 May 22]. Available from: https://www.drugs.com/compare/ceftriaxone-vs-meropenem

168. Ferreira CM, Ferreira WA, Almeida NCO da S, Naveca FG, das Graças Vale Barbosa Barbosa M. Extended-spectrum beta-lactamase-producing bacteria isolated from hematologic patients in manaus, state of Amazonas, Brazil. Brazilian J Microbiol. 2011;42(3):1076–84.

169. Sabur NF, Brar MS, Wu L, Brode SK. Low-dose amikacin in the treatment of multidrug-resistant tuberculosis (MDR-TB). BMC Infect Dis. 2021;21(1):1–8.

170. Pokharel S, Shrestha P, Adhikari B. Antimicrobial use in food animals and human health: time to implement 'One Health' approach. Antimicrob Resist Infect Control. 2020;9(1):1–5.

171. Martin MJ, Thottathil SE, Newman TB. Antibiotics overuse in animal agriculture: a call to action for health care providers. Am J Public Health. 2015;105(12):2409–10.

172. Gebretekle GB, Serbessa MK. Exploration of over the counter sales of antibiotics in community pharmacies of Addis Ababa, Ethiopia: pharmacy professionals' perspective. Antimicrob Resist Infect Control. 2016;5(1):1–7.

173. Pokharel S, Adhikari B. Antimicrobial resistance and over the counter use of drugs in Nepal. J Glob Health. 2020;10(1):1–4.

174. Tarrant C, Colman AM, Jenkins DR, Chattoe-Brown E, Perera N, Mehtar S, et al. Drivers of broad-spectrum antibiotic overuse across diverse hospital contexts: a qualitative study of prescribers in the UK, Sri Lanka and South Africa. Antibiotics. 2021;10(1):1–14.

175. Tadesse WT, Mekonnen AB, Tesfaye WH, Tadesse YT. Self-reported adverse drug

reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study. BMC Pharmacol Toxicol. 2014;15(1).

176. Leporini C, De Sarro G, Russo E. Adherence to therapy and adverse drug reactions: is there a link? Expert Opin Drug Saf. 2014;13(Suppl_1):41–55.

177. Wiedenmayer K, Ombaka E, Kabudi B, Canavan R, Rajkumar S, Chilunda F, et al. Adherence to standard treatment guidelines among prescribers in primary healthcare facilities in the Dodoma region of Tanzania. BMC Health Serv Res. 2021;21(1):1–10.

178. Ravinetto R, Pinxten W, Rägo L. Quality of medicines in resource-limited settings: need for ethical guidance. Glob Bioeth. 2018;29(1):81–94.

179. Vickers S, Bernier M, Zambrzycki S, Fernandez FM, Newton PN, Caillet C. Field detection devices for screening the quality of medicines: a systematic review. BMJ Glob Heal. 2018;3:e000725.

180. Caillet C, Vickers S, Vidhamaly V, Boutsamay K, Boupha P, Zambrzycki S, et al. Evaluation of portable devices for medicine quality screening: lessons learnt, recommendations for implementation, and future priorities. PLoS Med. 2021;18(9):1–12.

181. World Health Organization. Hypertension fact sheet. Hypertension [Internet]. 2011;1–2. Available from: https://cdn.who.int/media/docs/default-source/country-profiles/hypertension/npl_en.pdf?sfvrsn=2c2ad0ce_9&download=true

182. Petersen A, Held N, Heide L. Surveillance for falsified and substandard medicines

in Africa and Asia by local organizations using the low-cost GPHF Minilab. PLoS One. 2017;12(9):1–22.

183. Modisakeng C, Matlala M, Godman B, Meyer JC. Medicine shortages and challenges with the procurement process among public sector. BMC Health Serv Res. 2020;20(1):1–10.

184. Yenet A, Nibret G, Tegegne BA. Challenges to the Availability and Affordability of Essential Medicines in African Countries: A Scoping Review. Clin Outcomes Res. 2023;15:443–58.

185. Ribeiro-Vaz I, Silva AM, Costa Santos C, Cruz-Correia R. How to promote adverse drug reaction reports using information systems: a systematic review and meta-analysis. BMC Med Inform Decis Mak. 2016;16(1):1–10.

186. Tabali M, Jeschke E, Bockelbrink A, Witt CM, Willich SN, Ostermann T, et al. Educational intervention to improve physician reporting of adverse drug reactions (ADRs) in a primary care setting in complementary and alternative medicine. BMC Public Health. 2009;9:1–11.

187. Vallano A, Cereza G, Pedròs C, Agustí A, Danés I, Aguilera C, et al. Obstacles and solutions for spontaneous reporting of adverse drug reactions in the hospital. Br J Clin Pharmacol. 2005;60(6):653–8.

188. Alsaleh FM, Alzaid SW, Abahussain EA, Bayoud T, Lemay J. Knowledge, attitude and practices of pharmacovigilance and adverse drug reaction reporting among pharmacists working in secondary and tertiary governmental hospitals in Kuwait. Saudi Pharm J. 2017;25(6):830–7.

189. Gurmesa LT, Dedefo MG. Factors affecting adverse drug reaction reporting of healthcare professionals and their knowledge, attitude, and practice towards ADR reporting in Nekemte Town, West Ethiopia. Biomed Res Int. 2016;2016:5–8.

190. Hussain R, Hassali MA, Hashmi F, Akram T. Exploring healthcare professionals' knowledge, attitude, and practices towards pharmacovigilance: a cross-sectional survey. J Pharm Policy Pract. 2021;14(1):1–13.

191. Pérez Zapata AI, Rodríguez Cuéllar E, de la Fuente Bartolomé M, Martín-Arriscado Arroba C, García Morales MT, Loinaz Segurola C, et al. Predictive Power of the "Trigger Tool" for the detection of adverse events in general surgery: a multicenter observational validation study. Patient Saf Surg. 2022;16(1):1–10.

192. Health Quality & Safety Commission of New Zealand. The global trigger tool: a review of the evidence. Wellington: Health Quality & Safety Commission; 2016. 67 p.

193. Pandya AD, Patel K, Rana D, Gupta SD, Malhotra SD, Patel P. Global trigger tool: proficient adverse drug reaction autodetection method in critical care patient units. Indian J Crit Care Med. 2020;24(3):172–8.

194. Noorda NMF, Sallevelt BTGM, Langendijk WL, Egberts TCG, van Puijenbroek EP, Wilting I, et al. Performance of a trigger tool for detecting adverse drug reactions in patients with polypharmacy acutely admitted to the geriatric ward. Eur Geriatr Med. 2022;13(4):837–47.

195. Ji HH, Song L, Xiao JW, Guo YX, Wei P, Tang TT, et al. Adverse drug events in Chinese pediatric inpatients and associated risk factors: a retrospective review using

the Global Trigger Tool. Sci Rep. 2018;8(1):1–7.

196. Yu N, Wu L, Yin Q, Du S, Liu X, Wu S, et al. Adverse drug events in Chinese elder inpatients: a retrospective review for evaluating the efficiency of the Global Trigger Tool. Front Med. 2023;10:1–11.

197. Sam A, Lian Jessica L, Parasuraman S. A retrospective study on the incidences of adverse drug events and analysis of the contributing trigger factors. J Basic Clin Pharm. 2015;6(2):64.

198. Pozsgai K, Szűcs G, Kőnig-Péter A, Balázs O, Vajda P, Botz L, et al. Analysis of pharmacovigilance databases for spontaneous reports of adverse drug reactions related to substandard and falsified medical products: a descriptive study. Front Pharmacol. 2022;13:1–13.

199. Juhlin K, Karimi G, Andér M, Camilli S, Dheda M, Har TS, et al. Using VigiBase to identify substandard medicines: detection capacity and key prerequisites. Drug Saf. 2015;38(4):373–82.

200. Wotring VE. Chemical potency and degradation products of medications stored over 550 earth days at the international space station. AAPS J. 2016;18(1):210–6.

201. Mohan S, Mangal TD, Colbourn T, Chalkley M, Chimwaza C, Collins JH, et al. Factors associated with medical consumable availability in level 1 facilities in Malawi: a secondary analysis of a facility census. Lancet Glob Heal. 2024;12(6):e1027–37.

202. Gnegel G, Häfele-Abah C, Neci R, Difäm-EPN Minilab Network, Heide L.

Surveillance for substandard and falsified medicines by local faith-based organizations in 13 low- and middle-income countries using the GPHF Minilab. Sci Rep. 2022;12(1):13095.

203. Schäfermann S, Hauk C, Wemakor E, Neci R, Mutombo G, Ndze EN, et al. Substandard and falsified antibiotics and medicines against noncommunicable diseases in western Cameroon and northeastern Democratic Republic of Congo. Am J Trop Med Hyg. 2020;103(2):894–908.

204. Dégardin K, Roggo Y, Margot P. Understanding and fighting the medicine counterfeit market. J Pharm Biomed Anal. 2014;87:167–75.

205. Yassini SM, Harrazi MA, Askari J. The study of most important factors influencing physician choice. Procedia - Soc Behav Sci. 2010;5:1945–9.

206. Chen X, Zhang T, Wang H, Feng Z, Jin G, Shao S, et al. Factors influencing the prescription pattern of essential medicines from the perspectives of general practitioners and patients: a qualitative study in China. BMJ Open. 2022;12(5):e055091.

207. Davari M, Khorasani E, Tigabu BM. Factors influencing prescribing decisions of physicians: a review. Ethiop J Health Sci. 2018;28(6):795–804.

208. NAFDAC. Curbing substandard, falsified (SFS) and counterfeit medicines [Internet]. NAFDAC. 2019 [cited 2023 Jun 10]. Available from: https://nafdac.gov.ng/curbing-substandard-falsified-sfs-and-counterfeit-medicines/

APPENDICES

Appendix I: IHI Global Trigger Tool

List of triggers

Adopted from the IHI innovation series 2009 (second edition)

A. Care Module Triggers

C1–Transfusion of Blood or Use of Blood Products

C2–Code, Cardiac or Pulmonary Arrest, or Rapid Response Team Activation

C3–Acute Dialysis

C4–Positive Blood Culture

C5–X-Ray or Doppler Studies for Emboli or Deep Vein Thrombosis

C6–Decrease in Hemoglobin or Hematocrit of 25% or Greater

C7–Patient Fall

C8–Pressure Ulcers

C9–Readmission within 30 Days

C10–Restraint Use

C11–Healthcare-Associated Infections

C12–In-Hospital Stroke

C13–Transfer to Higher Level of Care

C14–Any Procedure Complication

C15–Other

B. Medication Module Triggers

M1–Clostridium difficile

Positive

M2–Partial Thromboplastin Time (PTT) Greater than 100 Seconds

M3–International Normalized Ratio (INR) Greater than 6.

M4–Glucose Less than 50 mg/dl

M5–Rising BUN or Serum Creatinine Two Times (2x) over Baseline

M6–Vitamin K Administration

M7–Diphenhydramine (Benadryl) Administration

M8–Romazicon (Flumazenil) Administration

M9–Naloxone (Narcan) Administration

M10–Anti-Emetic Administration

M11–Over-Sedation/Hypotension

M12–Abrupt Medication Stop

M13–Other

c. Surgical Module Triggers

S1–Return to Surgery

S2–Change in Procedure

S3–Admission to Intensive Care Post-Operatively

S4–Intubation or Reintubation or Use of BiPap in Post Anesthesia Care Unit (PACU)

S5–X-Ray Intra-Operatively or in Post Anesthesia Care Unit

S6–Intra- or Post-Operative Death

S7–Mechanical Ventilation Greater than 24 Hours Post-Operatively

S8–Intra-Operative Administration of Epinephrine, Norepinephrine, Naloxone, or Romazicon

S9–Post-Operative Increase in Troponin Levels Greater than 1.5 Nanogram/ml

S10–Injury, Repair, or Removal of Organ During Operative Procedure

S11–Occurrence of Any Operative Complication

D. **Intensive Care Module**

Triggers

I1-Pneumonia Onset

I2–Readmission to the Intensive Care Unit

I3–In-Unit Procedure

I4–Intubation/Reintubation

E. **Perinatal Module Triggers**

P1–Terbutaline Use

P2–3rd- or 4th-Degree Lacerations

P3–Platelet Count Less than 50,000

P4–Estimated Blood Loss Greater than 500 ml for Vaginal Delivery, or Greater than 1,000 ml for Cesarean Delivery

P5–Specialty Consult

P6–Administration of Oxytocic Agents (such as oxytocin, methylergonovine, and 15-methyl-prostaglandin in the post-partum period)

P7–Instrumented Delivery

P8–Administration of General Anesthesia

F. **Emergency Department (ED) Module**

Triggers

E1–Readmission to the ED within 48 Hours

E2–Time in ED Greater than 6 Hours

Appendix II: Adverse Drug Reaction Probability Scale

Naranjo Algorithm

Question	Yes	No	Do Not Know	Score
1 Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3 Did the adverse event improve when the drug was discontinued, or a specific antagonist was administered?	+1	0	0	
4. Did the adverse event reappear when the drug was readministered?	+2	-1	0	
5. Are there alternative causes that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7 Was the drug detected in blood or other fluids in concentrations known to be toxic?	+1	0	0	
8 Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	
9 Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
	Total Score:			

Naranjo Algorithm - ADR Probability Scale

Score	Interpretation of Scores
Total Score ≥9	**Definite**. The reaction (1) followed a reasonable temporal sequence after a drug or in which a toxic drug level had been established in body fluids or tissues, (2) followed a recognized response to the suspected drug, and (3) was confirmed by improvement on withdrawing the drug and reappeared on re-exposure.
Total Score 5 to 8	**Probable**. The reaction (1) followed a reasonable temporal sequence after a drug, (2) followed a recognized response to the suspected drug, (3) was confirmed by withdrawal but not by exposure to the drug, and (4) could not be reasonably explained by the known characteristics of the patient's clinical state.
Total Score 1 to 4	**Possible**. The reaction (1) followed a temporal sequence after a drug, (2) possibly followed a recognized pattern to the suspected drug, and (3) could be explained by characteristics of the patient's disease.
Total Score ≤0	**Doubtful**. The reaction was likely related to factors other than a drug.

Appendix III: Criteria for seriousness of suspected adverse drug reactions (sADRs)

1. Did the patient die?

   Yes ☐ No ☐

2. Was the event life threatening?

   Yes ☐ No ☐

3. Did the event cause any permanent or significant disability?

   Yes ☐ No ☐

4. Did the event cause or prolonged hospitalization?

   Yes ☐ No ☐

5. Did the event cause congenital anomaly?

   Yes ☐ No ☐

6. Did the event require any intervention to prevent further or permanent damage?

   Yes ☐ No ☐

7. Were there any clinically significant issues caused by the event? Please indicate

   _____

Note: The event was not serious if all the above are nullified

Remark

The event was Serious Yes ☐ No ☐

Appendix IV: ADR Preventability Assessment

(Shumock and Thornton Scale)

1. Was the drug involved in the ADR ***not*** appropriate for the patient's condition?

   Yes ☐ No ☐

2. Were the dose, route, and frequency of administration ***not*** appropriate for the patient's age, weight, organ function and disease state?

   Yes ☐ No ☐

3. If the reaction was due to allergy, was this allergy previously ***not*** documented?

   A. In the admitting orders?

      Yes ☐ No ☐

   B. In the patient's profile?

      Yes ☐ No ☐

4. Were appropriate therapeutic drug monitoring or other laboratory tests which may have predicted this reaction ***not*** performed?

   Yes ☐ No ☐

5. Was a drug interaction involved in the reaction?

   Yes ☐ No ☐

6. Was a toxic serum drug concentration recorded?

   Yes ☐ No ☐

7. Was poor compliance observed in the reaction?

   Yes ☐ No ☐

Note: If any of the above is yes, the ADR was preventable

Remark

Preventable ☐ Not Preventable ☐

Appendix V: Charlson Co-morbidity Index (CCI)
Adapted from: https://www.mdcalc.com/calc/3917/charlson-comorbidity-index-cci

ID number :

1. Age

<50 years 0	50-59 years +1	60-69 years _+2	70-79 years +3	≥ 80 years +4

2. Myocardial infarction
   Definition: History of definite or probable MI (EKG changes and/or enzyme changes)

No 0	Yes +1

3. CHF
   Definition: Exertional or paroxysmal nocturnal dyspnea and has responded to digitalis, diuretics, or afterload reducing agents

No 0	Yes +1

4. Peripheral vascular disease
   Definition: Intermittent claudication or past bypass for chronic arterial insufficiency, history of gangrene or acute arterial insufficiency, or untreated thoracic or abdominal aneurysm (≥6cm)

No 0	Yes +1

5. Cerebral vascular accident (CVA) or transient ischemic attack (TIA)
   Definition: History of a cerebrovascular accident with minor or no residua and transient ischemic attacks

No 0	Yes +1

6. Dementia
   Definition: Chronic cognitive deficit

No 0	Yes +1

7. Chronic Obstructive pulmonary diseases (COPD)

No 0	Yes +1

8. Connective tissue disease

No 0	Yes +1

9. Peptic ulcer disease

Definition: Any history of treatment for ulcer disease or history of ulcer bleeding

No 0	Yes +1

10. Liver disease

Definitions: Severe = cirrhosis and portal hypertension with variceal bleeding history, moderate = cirrhosis and portal hypertension but no variceal bleeding history, mild = chronic hepatitis (or cirrhosis without portal hypertension)

None 0	Mild +1	Moderate to severe +3

11. Diabetes mellitus

None or diet-controlled 0	Uncomplicated +1	End organ damage +2

12. Hemiplegia

No 0	Yes +2

13. Moderate to severe CKD

Severe = on dialysis, status post kidney transplant, uremia, moderate = creatinine >3 mg/dL (0.27 mmol/L)

No 0	Yes +2

14. Solid tumor

None 0	Localized +2	Metastatic +6

15. Leukemia

No 0	Yes +2

16. Lymphoma

No 0	Yes +2

17. HIV/ AIDS

No 0	Yes +6

Total Score: _____

Appendix VI: List of all medicines collected for the objective I

Sample ID	Generic name	Strength	MEML category[a]	Stated Country of origin	Expiry date	Storage	Primary Pack	Visual	Disintegration	Dissolution	TLC	Assay
NS TRI 285	Amoxicillin	250mg	HVA	Kenya	Mar-24	SIAB	Bottle	Pass	Pass		Pass	
MG DHO 142	Amoxicillin	250mg	HVA	Malawi	Feb-24	Ordinary	Bottle	Pass	Pass		Pass	
MG NAY 52	Amoxicillin	250mg	HVA	Malawi	Dec-23	SIAB	Bottle	Pass	Fail	Fail	Fail	Fail
MG MPI 68	Amoxicillin	250mg	HVA	India	Apr-22	Ordinary	Bottle	Pass	Fail	Fail	Fail	Fail
MG NAM 59	Amoxicillin	250mg	HVA	Malawi	Oct-23	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass
ZA MAC 181	Amoxicillin	250mg	HVA	Malawi	Jan-24	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass
MG MPO 108	Amoxicillin	250mg	HVA	Kenya	Jun-22	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
NS SAN 255	Amoxicillin	250mg	HVA	Malawi	Nov-23	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass
NS TRI 244	Amoxicillin	250mg	HVA	Kenya	Jun-22	SIAB	Bottle	Pass	Fail	Fail	Fail	Fail
ZA NKA 01	Amoxicillin	250mg	HVA	Kenya	Jun-22	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
ZA DHO 22	Amoxicillin	250mg	HVA	Malawi	Dec-23	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
ZA STL 117	Amoxicillin	25mg	HVA	India	Jul-22	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass
ZA STL 118	Amoxicillin	250mg	HVA	Kenya	Jun-22	SIAB	Bottle	Pass	Fail	Fail	Fail	Fail
NS KAL 237	Amoxicillin	250mg	HVA	India	May-22	SIAB	Bottle	Pass	Pass		Pass	

ZA CTL 032	Amoxicillin	250mg	HVA	Austria	Feb-22	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
MG MED 094	Amoxicillin	625mg	HVA	India	Feb-23	Ordinary	Bottle	Pass	Pass		Pass	
NS DHO 196	Amoxicillin	250mg	HVA	Malawi	Oct-23	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
ZA CTL 031	Amoxicillin	250mg	HVA	Malawi	Aug-23	Ordinary	Bottle	Pass	Pass		Pass	
ZA CTL 033	Amoxicillin	625mg	HVA	India	Jul-22	Ordinary	Bottle	Pass	Pass		Pass	
MG NAM 85	Amoxicillin	250mg	HVA	Kenya	Jun-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA NKA 02	Amoxicillin	250mg	HVA	India	Aug-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA THO 09	Amoxicillin	250mg	HVA	Malawi	Oct-23	SIAB	Bottle	Pass	Fail		Fail	
ZA MAT 171	Amoxicillin	250mg	HVA	India	Aug-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA CHA 174	Amoxicillin	250mg	HVA	Malawi	Nov-23	SIAB	Bottle	Pass	Pass		Pass	
ZA MAY 152	Amoxicillin	625mg	HVA	India	May-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA CHA 293	Amoxicillin	250mg	HVA	Malawi	Jan-24	SIAB	Bottle	Pass	Pass		Pass	
ZA MAT 162	Azithromycin	500mg	DEA	Kenya	Oct-22	Ordinary	Strips	Pass	Pass			
MG NAM 60	Azithromycin	500mg	DEA	India	Nov-22	SIAB	Strips	Pass	Pass			
NS PHO 220	Azithromycin	500mg	DEA	Austria	Oct-22	SIAB	Strips	Pass	Pass			
NS PHO 221	Azithromycin	500mg	DEA	India	Nov-22	SIAB	Strips	Pass	Pass			

MG CHI 076	Azithromycin	500mg	DEA	India	Nov-22	SIAB	Strips	Pass	Pass			
MG MED 096	Azithromycin	500mg	DEA	India	Mar-22	Ordinary	Strips	Pass	Pass			
ZA MAY 154	Azithromycin	500mg	DEA	India	Feb-22	Ordinary	Strips	Pass	Pass			
ZA GHE 45	Azithromycin	500mg	DEA	Kenya	Oct-24	Ordinary	Strips	Pass	Pass			
MG NAY 283	Azithromycin	500mg	DEA	India	Dec-23	SIAB	Strips	Pass	Pass			
MG GAW 284	Azithromycin	500mg	DEA	India	Dec-23	Ordinary	Strips	Pass	Pass			
ZA THO 265	Azithromycin	250mg	DEA	India	Apr-24	SIAB	Strips	Pass	Pass			
MG MED 097	Cefuroxime	500mg	N/A	India	Oct-23	Ordinary	Strips	Pass	Pass			
ZA CHA 294	Ciprofloxacin	250mg	DVA	Malawi	Jan-24	SIAB	Bottle	Pass	Fail		Fail	
ZA MAT 163	Ciprofloxacin	500mg	DVA	India	Nov-22	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
ZA THO 12	Ciprofloxacin	500mg	DVA	India	Jun-24	SIAB	Strips	Pass	Pass	Pass	Pass	Pass
MG DHO 144	Ciprofloxacin	500mg	DVA	India	Jun-24	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
MG GAW 135	Ciprofloxacin	500mg	DVA	India	Jun-24	Ordinary	Strips	Pass	Pass		Pass	
ZA CHA 176	Ciprofloxacin	250mg	DVA	Malawi	Oct-23	SIAB	Bottle	Pass	Pass		Pass	
MG NAM 86	Ciprofloxacin	250mg	DVA	India	Aug-23	Ordinary	Strips	Pass	Pass		Pass	
MG NAY 53	Ciprofloxacin	250mg	DVA	Kenya	Aug-23	SIAB	Strips	Pass	Pass		Pass	

MG MPI 69	Ciprofloxacin	500mg	DVA	Kenya	Sep-22	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
MG NAM 61	Ciprofloxacin	250mg	DVA	India	Jul-23	SIAB	Strips	Pass	Pass		Pass	
MG MPO 109	Ciprofloxacin	500mg	DVA	India	Jul-23	Ordinary	Strips	Pass	Pass		Pass	
MG MGH 128	Ciprofloxacin	250mg	DVA	India	Aug-23	SIAB	Strips	Pass	Pass		Pass	
NS SAN 256	Ciprofloxacin	250mg	DVA	Malawi	Oct-23	SIAB	Bottle	Pass	Pass		Pass	
NS CHI 213	Ciprofloxacin	500mg	DVA	India	Jun-24	Ordinary	Strips	Pass	Pass		Pass	
NS TRI 246	Ciprofloxacin	500mg	DVA	India	May-23	SIAB	Strips	Pass	Pass		Pass	
ZA NKA 04	Ciprofloxacin	500mg	DVA	Netherlands	Feb-22	Ordinary	Strips	Pass	Pass		Pass	
NS MBE 205	Ciprofloxacin	500mg	DVA	India	Jun-24	SIAB	Strips	Pass	Pass	Pass	Pass	Pass
ZA DHO 24	Ciprofloxacin	250mg	DVA	Malawi	Oct-23	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
ZA STL 120	Ciprofloxacin	500mg	DVA	India	Jul-23	SIAB	Strips	Pass	Pass	Pass	Pass	Pass
ZA CTL 035	Ciprofloxacin	250mg	DVA	Malawi	Oct-23	Ordinary	Bottle	Pass	Pass		Pass	
MG CHI 077	Ciprofloxacin	250mg	DVA	India	Aug-23	SIAB	Strips	Pass	Pass		Pass	
MG MED 098	Ciprofloxacin	500mg	DVA	India	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
ZA THO 11	Ciprofloxacin	250mg	DVA	Malawi	Oct-23	SIAB	Bottle	Pass	Pass		Pass	
ZA GHE 46	Ciprofloxacin	500mg	DVA	India	Feb-23	Ordinary	Strips	Pass	Pass		Pass	

MG NAY 282	Ciprofloxacin	500mg	DVA	India	Jun-24	SIAB	Strips	Pass	Pass		Pass	
NS MBE 288	Ciprofloxacin	250mg	DVA	Malawi	Sep-24	SIAB	Bottle	Pass	Fail	Fail	Fail	Fail
NS MBE 289	Ciprofloxacin	500mg	DVA	India	Jun-24	SIAB	Strips	Pass	Pass	Pass	Fail	Fail
NS PHO 290	Ciprofloxacin	250mg	DVA	Malawi	Sep-24	SIAB	Bottle	Pass	Fail	Fail	Fail	Fail
NS TRI 286	Ciprofloxacin	500mg	DVA	India	Jun-24	SIAB	Strips	Pass	Pass	Pass	Fail	Fail
NS MBE 301	Ciprofloxacin	250mg	DVA	Malawi	Sep-24	SIAB	Bottle	Pass	Pass	Pass	Fail	Fail
ZA THO 266	Ciprofloxacin	250mg	DVA	India	Sep-24	SIAB	Strips	Pass	Pass		Pass	
ZA MAT 164	Flucloxacillin	250mg	DVA	Kenya	Dec-22	Ordinary	Strips	Pass	Fail		Fail	
ZA GHE 47	Flucloxacillin	250mg	DVA	Kenya	Jul-23	Ordinary	Strips	Pass	Fail		Fail	
ZA MAC 182	Flucloxacillin	250mg	DVA	India	Aug-22	SIAB	Strips	Pass	Fail		Fail	
ZA DHO 25	Flucloxacillin	250mg	DVA	India	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
ZA CTL 036	Flucloxacillin	250mg	DVA	India	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
MG MED 100	Flucloxacillin	250mg	DVA	England	Sep-22	Ordinary	Strips	Pass	Fail		Fail	
ZA MAK 277	Flucloxacillin	250mg	DVA	India	Aug-22	SIAB	Strips	Pass	Pass		Pass	
ZA CTL 268	Flucloxacillin	250mg	DVA	India	Mar-23	Ordinary	Strips	Pass	Pass		Pass	
ZA DHO 267	Flucloxacillin	250mg	DVA	India	Aug-22	Ordinary	Strips	Pass	Pass		Pass	

ZA MAK 189	Ciprofloxacin	250mg	DVA	Malawi		SIAB	Bottle	Pass	Pass		Pass	
NS DHO 257	Ciprofloxacin	250mg	DVA	Malawi		Ordinary	Bottle	Pass	Fail	Fail	Pass	Pass
ZA MAT 160	Amlodipine	10mg	DVA	India	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
ZA GHE 44	Amlodipine	5mg	DVA	India	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
MG MPO 107	Amlodipine	5mg	DVA	India	Apr-22	Ordinary	Strips	Pass	Pass		Pass	
ZA STL 116	Amlodipine	5mg	DVA	India	Apr-22	SIAB	Strips	Pass	Pass		Pass	
NS PHO 219	Amlodipine	5mg	DVA	India	Sep-21	SIAB	Strips	Pass	Pass		Pass	
NS KAL 236	Amlodipine	10mg	DVA	India	Aug-23	SIAB	Strips	Pass	Pass		Fail	
MG MED 093	Amlodipine	10mg	DVA	India	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
ZA MAK 188	Amlodipine	5mg	DVA	India		SIAB	Strips	Pass	Pass		Pass	
ZA MAT 161	Atenolol	50mg	DVA	Malawi	Sep-22	Ordinary	Bottle	Pass	Pass	Pass	Fail	Fail
MG DHO 143	Atenolol	50mg	DVA	India	Sep-22	Ordinary	Strips	Pass	Pass	Pass	Fail	Fail
ZA CHA 175	Atenolol	50mg	DVA	Malawi	Mar-23	SIAB	Bottle	Fail	Pass	Pass	Fail	Fail
ZA DHO23	Atenolol	50mg	DVA	Malawi	Feb-23	Ordinary	Bottle	Fail	Fail	Fail	Fail	Fail
ZA STL 119	Atenolol	50mg	DVA	Malawi	Oct-21	SIAB	Bottle	Fail	Fail	Fail	Pass	Pass
ZA CTL 034	Atenolol	50mg	DVA	Malawi	Oct-22	Ordinary	Bottle	Fail	Fail	Fail	Pass	Pass

MG MED 095	Atenolol	100mg	DVA	India	Aug-22	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
NS DHO 201	Atenolol	50mg	DVA	Malawi	Oct-22	Ordinary	Bottle	Fail	Fail	Fail	Pass	Pass
ZA NKA 03	Atenolol	50mg	DVA	Malawi	Oct-21	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
ZA MAY 153	Atenolol	50mg	DVA	India	Sep-22	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
ZA THO 10	Atenolol	50mg	DVA	Malawi	Mar-23	SIAB	Bottle	Fail	Fail	Fail	Pass	Pass
ZA MAT 170	Enalapril	10mg	DVA	India	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
ZA STL 121	Enalapril	5mg	DVA	India	Jun-23	SIAB	Strips	Pass	Pass		Pass	
NS PHO 222	Enalapril	5mg	DVA	India	Apr-22	SIAB	Strips	Pass	Pass		Fail	
MG MED 099	Enalapril	10mg	DVA	India	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
ZA THO 13	Enalapril	10mg	DVA	India	Dec-21	SIAB	Strips	Pass	Pass		Pass	
ZA GHE 51	Enalapril	10mg	DVA	Tanzania	Mar-22	Ordinary	Strips	Pass	Pass		Pass	
NS DHO 197	Enalapril	10mg	DVA	India	Dec-21	Ordinary	Strips	Pass	Pass		Pass	
ZA MAT 165	Glibenclamide	5mg	DVA	Malawi	Feb-23	Ordinary	Bottle	Pass	Pass		Pass	
ZA THO 14	Glibenclamide	5mg	DVA	Malawi	Oct-22	SIAB	Bottle	Pass	Pass		Pass	
MG DHO 145	Glibenclamide	5mg	DVA	Malawi	Oct-22	Ordinary	Bottle	Pass	Pass		Pass	
MG NAY 54	Glibenclamide	5mg	DVA	India	Mar-22	Ordinary	Bottle	Pass	Pass		Pass	

MG NAM 62	Glibenclamide	5mg	DVA	Malawi	Oct-22	Ordinary		Pass	Pass		Pass	
MG MPO 110	Glibenclamide	5mg	DVA	India	Jun-22	Ordinary	Strips	Pass	Pass		Pass	
MG MGH 129	Glibenclamide	5mg	DVA	India	Mar-22	SIAB	Strips	Pass	Pass		Pass	
NS SAN 257	Glibenclamide	5mg	DVA	Malawi	Oct-22	SIAB	Bottle	Pass	Pass		Pass	
NS TRI 247	Glibenclamide	5mg	DVA	Malawi	Feb-23	SIAB	Bottle	Pass	Pass		Pass	
ZA DHO 26	Glibenclamide	5mg	DVA	Malawi	Oct-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA STL 122	Glibenclamide	5mg	DVA	India	Jun-22	SIAB	Strips	Pass	Pass		Pass	
NS KAL 238	Glibenclamide	5mg	DVA	India	Jul-23	SIAB	Strips	Pass	Pass		Pass	
ZA CTL 037	Glibenclamide	5mg	DVA	Malawi	Oct-23	Ordinary	Bottle	Pass	Pass		Pass	
MG CHI 078	Glibenclamide	5mg	DVA	Malawi	Oct-22	SIAB	Bottle	Pass	Pass		Pass	
MG MED 101	Glibenclamide	5mg	DVA	Malawi	Feb-23	Ordinary	Bottle	Pass	Pass		Pass	
NS PHO 223	Glibenclamide	5mg	DVA	Malawi	Oct-22	SIAB	Bottle	Pass	Pass		Pass	
NS DHO 199	Glibenclamide	5mg	DVA	Malawi	Oct-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA MAT 166	Hydrochlorothiazide	25mg	DVA	Kenya	Feb-24	Ordinary	Bottle	Pass	Pass		Pass	
MG GAW 136	Hydrochlorothiazide	250mg	DVA	India	Feb-24	Ordinary	Bottle	Pass	Pass		Pass	
MG NAM 87	Hydrochlorothiazide	25mg	DVA	Kenya	Oct-22	Ordinary	Bottle	Pass	Pass		Pass	

MG MPI 70	Hydrochlorothiazide	50mg	DVA	Kenya	Oct-21	Ordinary	Bottle	Pass	Pass		Pass	
MG MPO 111	Hydrochlorothiazide	25mg	DVA	Kenya	Feb-24	Ordinary	Bottle	Pass	Pass		Pass	
NS CHI 214	Hydrochlorothiazide	25mg	DVA	China	Nov-22	Ordinary	Bottle	Pass	Pass		Pass	
NS TRI 248	Hydrochlorothiazide	25mg	DVA	India	Feb-24	SIAB	Bottle	Pass	Pass		Pass	
ZA NKA 05	Hydrochlorothiazide	25mg	DVA	Netherlands	NOT INDICATED	Ordinary	Bottle	Pass	Pass		Pass	
NS MBE 206	Hydrochlorothiazide	25mg	DVA	India	Jan-22	SIAB	Bottle	Pass	Pass		Pass	
NS TEN 231	Hydrochlorothiazide	25mg	DVA	India	Jan-22	SIAB	Bottle	Pass	Pass		Pass	
ZA STL 127	Hydrochlorothiazide	25mg	DVA	India	Feb-24	SIAB	Bottle	Pass	Pass		Pass	
NS PHO 225	Hydrochlorothiazide	25mg	DVA	India	Jan-22	SIAB	Bottle	Pass	Pass		Pass	
MG MED 102	Hydrochlorothiazide	25mg	DVA	India	Feb-24	Ordinary	Bottle	Pass	Pass		Pass	
NS DHO 198	Hydrochlorothiazide	25mg	DVA	India	Jan-22	Ordinary	Bottle	Pass	Pass		Pass	
MG CHI 084	Metform	850mg	DVA	India		SIAB	Strips	Pass	Pass	Pass	Pass	Pass
ZA MAT 167	Metform	500mg	DVA	Malawi	Dec-23	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
MG DHO 146	Metform	500mg	DVA	Malawi	Jul-22	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass

NS SAN 258	Metform	500mg	DVA	Malawi	Dec-21	Ordinary	Bottle	Pass	Pass	Pass	Pass	Pass
NS TRI 249	Metform	500mg	DVA	India	May-23	SIAB	Strips	Pass	Pass	Pass	Pass	Pass
NS PHO 224	Metform	500mg	DVA	Malawi	Dec-21	SIAB	Bottle	Fail	Pass	Pass	Fail	Fail
NS KAL 239	Metform	500mg	DVA	India	Aug-22	SIAB	Strips	Pass	Pass	Pass	Pass	Pass
ZA CTL 038	Metform	850mg	DVA	India	Dec-21	Ordinary	Strips	Pass	Pass	Pass	Fail	Fail
MG CHI 079	Metform	500mg	DVA	Malawi	Mar-22	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass
MG MED 103	Metform	500mg	DVA	India	Oct-23	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
NS DHO 200	Metform	850mg	DVA	India	Feb-23	Ordinary	Strips	Pass	Pass	Pass	Pass	Pass
ZA MAK 191	Metform	500mg	DVA	Malawi	Dec-21	SIAB	Bottle	Pass	Pass	Pass	Pass	Pass
ZA GHE 48	Metform	500mg	DVA	Malawi	Nov-23	Ordinary	Bottle	Pass	Pass		Pass	
ZA THO 15	Metform	500mg	DVA	India	Oct-24	SIAB	Strips	Pass	Pass		Pass	
ZA THO 16	Metform	850mg	DVA	India	Feb-23	SIAB	Strips	Pass	Pass		Pass	
ZA GHE 272	Metform	500mg	DVA	Malawi	May-24	Ordinary	Bottle	Pass	Pass		Pass	
ZA DHO 27	Metform	500mg	DVA	India	Dec-23	Ordinary	Strips	Pass	Pass		Pass	
ZA GHE 49	Metform	500mg	DVA	Kenya	Mar-24	Ordinary	Bottle	Pass	Pass		Pass	
ZA MAT 168	Methyldopa	250mg	DEA	Kenya	Jan-22	Ordinary	Strips	Pass	Pass			

MG DHO 147	Methyldopa	250mg	DEA	Malawi	Feb-24	Ordinary	Strips	Pass	Pass			
MG GAW 137	Methyldopa	250mg	DEA	Kenya	Oct-22	Ordinary	Strips	Pass	Pass			
NS TRI 250	Methyldopa	250mg	DEA	Kenya	Jan-22	SIAB	Strips	Pass	Pass			
ZA MAY 155	Methyldopa	250mg	DEA	Malawi	Apr-22	Ordinary	Bottle	Pass	Pass			
ZA DHO 28	Methyldopa	250mg	DEA	Malawi	Aug-22	Ordinary	Bottle	Pass	Pass			
MG MED 104	Methyldopa	250mg	DEA	Kenya	Jan-22	Ordinary	Strips	Pass	Pass			
ZA NKA 06	Methyldopa	25mg	DEA	India	Oct-22	Ordinary	Strips	Pass	Pass			
ZA CTL 039	Methyldopa	250mg	DEA	Malawi	Apr-22	Ordinary	Bottle	Pass	Pass			
NS TRI 245	Artesunate/Amodiaquine	185mg	DVA	Morocco	Feb-23	SIAB	Strips	Pass	Pass			
ZA CHA 296	Lumefantrine Artemether	140mg	HVA	India	Oct-22	SIAB	Strips	Pass	Pass		Pass	
ZA CHA 297	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	SIAB	Strips	Pass	Pass		Pass	
MG GAW 299	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
MG GAW 300	Lumefantrine Artemether	140mg	HVA	India	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
ZA MAY 275	Lumefantrine Artemether	140mg	HVA	India	Apr-24	Ordinary	Strips	Pass	Pass		Pass	
ZA MAY 276	Lumefantrine Artemether	140mg	HVA	India	Oct-22	Ordinary	Strips	Pass	Pass		Pass	

ZA MAK 278	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	SIAB	Strips	Pass	Pass		Pass	
ZA MAK 279	Lumefantrine Artemether	140mg	HVA	India	Nov-23	SIAB	Strips	Pass	Pass		Pass	
ZA MAC 280	Lumefantrine Artemether	140mg	HVA	India	Nov-23	SIAB	Strips	Pass	Pass		Pass	
ZA MAC 281	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	SIAB	Strips	Pass	Pass		Pass	
ZA GHE 270	Lumefantrine Artemether	140mg	HVA	India	Mar-24	Ordinary	Strips	Pass	Pass		Pass	
NS KAL 287	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	
NS SAN 291	Lumefantrine Artemether	140ng	HVA	India	Oct-23	SIAB	Strips	Pass	Pass		Pass	
NS SAN 292	Lumefantrine Artemether	140ng	HVA	India	Dec-23	SIAB	Strips	Pass	Pass		Pass	
ZA CHA 298	Lumefantrine Artemether	140mg	HVA	India	Nov-23	SIAB	Strips	Pass	Pass		Pass	
NS DHO 203	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	Ordinary	Strips	Pass	Pass		Pass	
MG MPI 75	Lumefantrine Artemether	140mg	HVA	India	Aug-21	Ordinary	Strips	Pass	Pass		Pass	
NS CHI 218	Lumefantrine Artemether	140mg	HVA	India	Sep-21	Ordinary	Strips	Pass	Pass		Pass	
ZA MAY 157	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
ZA MAY 158	Lumefantrine Artemether	140mg	HVA	India	Oct-23	Ordinary	Strips	Pass	Pass		Pass	

ZA MAY 159	Lumefantrine Artemether	140mg	HVA	Uganda	Dec-23	Ordinary	Strips	Pass	Pass		Pass	
MG NAY 57	Lumefantrine Artemether	140mg	HVA	India	Jan-23	SIAB	Strips	Pass	Pass		Pass	
MG MPI 73	Lumefantrine Artemether	140mg	HVA	India	Jul-22	Ordinary	Strips	Pass	Pass		Pass	
NS SAN 260	Lumefantrine Artemether	140mg	HVA	India	Jan-23	SIAB	Strips	Pass	Pass		Pass	
NS DHO 204	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	Ordinary	Strips	Pass	Pass		Pass	
MG NAY 58	Lumefantrine Artemether	140mg	HVA	Switzerland	Jun-20	SIAB	Strips	Pass	Pass		Pass	
ZA MAC 184	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	SIAB	Strips	Pass	Pass		Pass	
ZA MAC 185	Lumefantrine Artemether	140mg	HVA	Switzerland	Jul-22	SIAB	Strips	Pass	Pass		Pass	
MG MPO 114	Lumefantrine Artemether	140mg	HVA	Switzerland	Jul-22	Ordinary	Strips	Pass	Pass		Pass	
MG MGH 132	Lumefantrine Artemether	140mg	HVA	Switzerland	Jul-23	Ordinary	Strips	Pass	Pass		Pass	
NS TRI 252	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	SIAB	Strips	Pass	Pass		Pass	
NS MBE 209	Lumefantrine Artemether	140mg	HVA	Switzerland	Mar-22	SIAB	Strips	Pass	Pass		Pass	
ZA STL 124	Lumefantrine Artemether	140mg	HVA	Switzerland	Jul-22	SIAB	Strips	Pass	Pass		Pass	
MG CHI 083	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	SIAB	Strips	Pass	Pass		Pass	

NS PHO 228	Lumefantrine Artemether	140mg	HVA	Turkey	Mar-22	SIAB	Strips	Pass	Pass		Pass	
MG NAM 66	Lumefantrine Artemether	140mg	HVA	India	Oct-22	SIAB	Strips	Pass	Pass		Pass	
ZA CTL 042	Lumefantrine Artemether	140mg	HVA	India	Oct-22	Ordinary	Strips	Pass	Pass		Pass	
ZA NKA 08	Lumefantrine Artemether	140mg	HVA	India	Oct-22	Ordinary	Strips	Pass	Pass		Pass	
MG MPI 72	Lumefantrine Artemether	140mg	HVA	Switzerland	Jul-22	Ordinary	Strips	Pass	Pass		Pass	
MG NAM 67	Lumefantrine Artemether	140mg	HVA	Switzerland	Mar-22	SIAB	Strips	Pass	Pass		Pass	
NS CHI 216	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	Ordinary	Strips	Pass	Pass		Pass	
NS KAL 241	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	SIAB	Strips	Pass	Pass		Pass	
MG MPI 74	Lumefantrine Artemether	140mg	HVA	India	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
ZA MAC 187	Lumefantrine Artemether	140mg	HVA	India	Aug-22	SIAB	Strips	Pass	Pass		Pass	
NS CHI 217	Lumefantrine Artemether	140mg	HVA	India	Jul-22	Ordinary	Strips	Pass	Pass		Pass	
ZA STL 125	Lumefantrine Artemether	140mg	HVA	India	Jun-23	SIAB	Strips	Pass	Pass		Pass	
ZA MAT 172	Lumefantrine Artemether	140mg	HVA	India	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
MG NAY 56	Lumefantrine Artemether	140mg	HVA	Uganda	Dec-23	SIAB	Strips	Pass	Pass		Pass	

ZA CHA 178	Lumefantrine Artemether	140mg	HVA	Uganda	Jun-23	SIAB	Strips	Pass	Pass		Pass	
NS DHO 211	Lumefantrine Artemether	140mg	HVA	Uganda	Jun-23	Ordinary	Strips	Pass	Pass		Pass	
NS PHO 229	Lumefantrine Artemether	140mg	HVA	Uganda	Jun-23	SIAB	Strips	Pass	Pass		Pass	
NS PHO 230	Lumefantrine Artemether	140mg	HVA	Uganda	Feb-23	SIAB	Strips	Pass	Pass		Pass	
ZA THO 18	Lumefantrine Artemether	240mg	HVA	India	Mar-23	SIAB	Strips	Pass	Pass		Pass	
MG DHO 150	Lumefantrine Artemether	140mg	HVA	India	Oct-23	Ordinary	Strips	Pass	Pass		Pass	
ZA CHA 180	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	
MG MPO 113	Lumefantrine Artemether	140mg	HVA	India	Apr-23	Ordinary	Strips	Pass	Pass		Pass	
MG MGH 131	Lumefantrine Artemether	140mg	HVA	India	Sep-23	Ordinary	Strips	Pass	Pass		Pass	
NS SAN 261	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	
NS SAN 262	Lumefantrine Artemether	140mg	HVA	Uganda	May-23	SIAB	Strips	Pass	Pass		Pass	
NS MBE 208	Lumefantrine Artemether	140mg	HVA	India	Apr-23	SIAB	Strips	Pass	Pass		Pass	
ZA DHO 30	Lumefantrine Artemether	140mg	HVA	China	Oct-23	Ordinary	Strips	Pass	Pass		Pass	
NS KAL 243	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	

MG CHI 081	Lumefantrine Artemether	140mg	HVA	India	Apr-23	SIAB	Strips	Pass	Pass		Pass	
ZA MAT 173	Lumefantrine Artemether	140mg	HVA	Uganda	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
MG MPO 115	Lumefantrine Artemether	140mg	HVA	Uganda	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
ZA THO 20	Lumefantrine Artemether	240mg	HVA	Uganda	Dec-23	SIAB	Strips	Pass	Pass		Pass	
ZA MAC 186	Lumefantrine Artemether	140mg	HVA	Uganda	Jun-23	SIAB	Strips	Pass	Pass		Pass	
NS TRI 253	Lumefantrine Artemether	140mg	HVA	Uganda	Dec-23	SIAB	Strips	Pass	Pass		Pass	
NS KAL 242	Lumefantrine Artemether	140mg	HVA	Uganda	May-23	SIAB	Strips	Pass	Pass		Pass	
NS PHO 227	Lumefantrine Artemether	140mg	HVA	India	Mar-23	SIAB	Strips	Pass	Pass		Pass	
MG NAM 90	Lumefantrine Artemether	140mg	HVA	India	Dec-23	Ordinary	Strips	Pass	Pass		Pass	
NS MBE 210	Lumefantrine Artemether	140mg	HVA	Uganda	Jun-23	SIAB	Strips	Pass	Pass		Pass	
NS TEN 235	Lumefantrine Artemether	140mg	HVA	Uganda	Dec-23	SIAB	Strips	Pass	Pass		Pass	
MG MED 106	Lumefantrine Artemether	560mg	HVA	India	Apr-23	Ordinary	Strips	Pass	Pass		Pass	
ZA CTL 043	Lumefantrine Artemether	140mg	HVA	Uganda	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
NS DHO 212	Lumefantrine Artemether	140mg	HVA	Uganda	May-23	Ordinary	Strips	Pass	Pass		Pass	

MG DHO 149	Lumefantrine Artemether	140mg	HVA	India	Sep-23	Ordinary	Strips	Pass	Pass		Pass	
MG NAM 65	Lumefantrine Artemether	140mg	HVA	India	Nov-23	SIAB	Strips	Pass	Pass		Pass	
ZA CTL 041	Lumefantrine Artemether	140mg	HVA	India	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
MG CHI 082	Lumefantrine Artemether	140mg	HVA	India	Nov-23	SIAB	Strips	Pass	Pass		Pass	
MG NAM 89	Lumefantrine Artemether	140mg	HVA	India	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
MG NAM 91	Lumefantrine Artemether	140mg	HVA	India	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
MG NAM 64	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	
MG MGH 133	Lumefantrine Artemether	140mg	HVA	India	Nov-23	Ordinary	Strips	Pass	Pass		Pass	
NS TRI 254	Lumefantrine Artemether	140mg	HVA	India	Nov-23	SIAB	Strips	Pass	Pass		Pass	
NS TEN 233	Lumefantrine Artemether	140mg	HVA	India	Oct-23	SIAB	Strips	Pass	Pass		Pass	
NS TEN 234	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	
ZA STL 126	Lumefantrine Artemether	140mg	HVA	India	Sep-23	SIAB	Strips	Pass	Pass		Pass	
ZA NKA 07	Lumefantrine Artemether	140mg	HVA	Switzerland		Ordinary	Strips	Pass	Pass		Pass	
ZA THO 19	Lumefantrine Artemether	240mg	HVA	Switzerland	Aug-22	SIAB	Strips	Pass	Pass		Pass	

MG GAW 141	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	Ordinary	Strips	Pass	Pass		Pass	
MG MGH 134	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	SIAB	Strips	Pass	Pass		Pass	
MG NAM 92	Lumefantrine Artemether	140mg	HVA	India	Oct-22	Ordinary	Strips	Pass	Pass		Pass	
MG GAW 139	Lumefantrine Artemether	140mg	HVA	India	Oct-22	Ordinary	Strips	Pass	Pass		Pass	
MG DHO 151	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	Ordinary	Strips	Pass	Pass		Pass	
ZA CHA 179	Lumefantrine Artemether	140mg	HVA	Switzerland	Aug-22	SIAB	Strips	Pass	Pass		Pass	
NS TEN 232	Lumefantrine Artemether	140mg	HVA	Switzerland	May-22	SIAB	Strips	Pass	Pass		Pass	
MG GAW 140	Lumefantrine Artemether	140mg	HVA	India	Oct-23	Ordinary	Strips	Pass	Pass		Pass	
ZA THO 21	Lumefantrine Artemether	240mg	HVA	India	Dec-20	SIAB	Strips	Pass	Pass		Pass	
MG MED 105	Quinine sulfate	300mg	DVA	India	Jul-22	SIAB	Bottle	Pass	Pass		Pass	
ZA MAY 273	Sulfadoxine pyrimethamine	525mg	HVA	China	May-23	Ordinary	Bottle	Pass	Fail		Pass	Fail
ZA MAY 274	Sulfadoxine pyrimethamine	525mg	HVA	China	Mar-24	Ordinary	Bottle	Pass	Pass		Pass	
ZA GHE 271	Sulfadoxine pyrimethamine	525mg	HVA	Tanzania	Jun-25	Ordinary	Bottle	Pass	Pass		Pass	

ZA MAT 169	Sulfadoxine pyrimethamine	325mg	HVA	China	May-22	Ordinary	Bottle	Pass	Pass		Pass	Fail
ZA THO 17	Sulfadoxine pyrimethamine	525mg	HVA	China	May-22	SIAB	Bottle	Pass	Pass		Pass	Fail
MG DHO 148	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	Ordinary	Bottle	Pass	Pass		Pass	Fail
MG GAW 138	Sulfadoxine pyrimethamine	525mg	HVA	China	Oct-23	Ordinary	Bottle	Pass	Pass		Pass	Fail
ZA GHE 50	Sulfadoxine pyrimethamine	525mg	HVA	Tanzania	Aug-22	Ordinary	Bottle	Pass	Pass		Pass	Fail
ZA CHA 177	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-21	SIAB	Bottle	Pass	Pass		Pass	Fail
MG NAM 88	Sulfadoxine pyrimethamine	525mg	HVA	China	May-23	Ordinary	Bottle	Pass	Pass		Pass	
MG NAY 55	Sulfadoxine pyrimethamine	525mg	HVA	India	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
MG MPI 71	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	Ordinary	Bottle	Pass	Pass		Pass	
MG NAM 63	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
ZA MAC 183	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	

MG MPO 112	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-21	Ordinary	Bottle	Pass	Pass		Pass	
MG MGH 130	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-21	Ordinary	Bottle	Pass	Pass		Pass	Fail
NS SAN 259	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
NS CHI 215	Sulfadoxine pyrimethamine	525mg	HVA	China	May-22	Ordinary	Bottle	Pass	Fail		Pas	Fail
NS TRI 251	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
NS MBE 207	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
ZA DHO 29	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA STL 123	Sulfadoxine pyrimethamine	525mg	HVA	China	May-23	SIAB	Bottle	Pass	Pass		Pass	
NS PHO 226	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
NS KAL 240	Sulfadoxine pyrimethamine	525mg	HVA	China	May-22	SIAB	Bottle	Pass	Pass		Pass	
ZA CTL 040	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	Ordinary	Bottle	Pass	Pass		Pass	

MG CHI 080	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Pass		Pass	
ZA MAY 156	Sulfadoxine pyrimethamine	525mg	HVA	China	Apr-22	Ordinary	Bottle	Pass	Pass		Pass	
ZA CHA 295	Sulfadoxine pyrimethamine	525mg	HVA	China	Dec-22	SIAB	Bottle	Pass	Fail		Pass	Fail

[a] The Malawi Essential Medicines List (MEML) of 2015 specifies the level of health institution at which the medicine is normally permitted for use: H = at health centre, district hospital and central hospital levels; D = at district hospital and central hospital levels only; C = at central hospital level only. N = level of use not specified. The 'therapeutical priority' code categorizes medicines based on therapeutic importance of each medicine by the use of: V = vital medicines which are potentially life-saving, of major public health relevance and having significant withdraw side-effects, E = essential medicines which are effective against less severe, but nonetheless significant forms of illness; N = non-essential medicines which are used for minor self-limiting illness and are often of questionable efficacy. The third categorization of 'procurement system' has two codes: 'A'= medicines required by a large number of patients as such to be routinely procured and stocked by CMST; and 'B'= medicines required for a limited number of patients and not routinely stocked by CMST).

Appendix VII: List and description of results that failed under various quality tests

Medicine (INN)	Sample ID	Type of Sampling Site	Stated Country of origin	Primary packaging	Visual Inspection	TLC	Disintegration	Dissolution	Assay (HPLC/UV-Vis)	Reason for non-compliance (reference)
SF medicines with assay deviations not less than 80%(non- extreme deviations)										
Atenolol	NS-DHO 201	Public	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	56.9%	89.9% (UV/Vis)	Low API content and dissolution (USP-38 NF 33)
Atenolol	ZA CHA 175	Public	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	80.0%	83.9% (UV/Vis)	Low API content (USP-38 NF 33)
Atenolol	ZA CTL 034	Public	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	51.2%	94.8% (UV/Vis)	Low dissolution (USP-38 NF 33)
Atenolol	ZA STL 119	Faith-based	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	53.0%	90.6% (UV/Vis)	Low dissolution (USP-38 NF 33)
Atenolol	ZA DHO 23	Public	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	26.8%	87.7% (UV/Vis)	Low API content and dissolution (USP-38 NF 33)
Atenolol	ZA THO 10	Public	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	31.4%	89.9% (UV/Vis)	Low API content and dissolution (USP-38 NF 33)
Atenolol	ZA MAT 161	Public	Malawi	Bottle	Compliant	Compliant	Compliant	72.5%	81.6% (UV/Vis)	Low API content (USP-38 NF 33)
Atenolol	MG DHO 143	Public	India	Strips	Compliant	Compliant	Compliant	77.8%	88.8% (UV/Vis)	Low API content (USP-38 NF 33)
Metformin	NS PHO 224	Public	Malawi	Bottle	Tablet discoloration	Compliant	Compliant	77.1%	87.7% (UV/Vis)	Low API content (USP-38 NF 33)
Metformin	ZA CTL 038	Public	India	Strips	Compliant	Compliant	Compliant	71.7%	84.1% (UV/Vis)	Low API content (USP-38 NF 33)
Amoxicillin	ZA THO 09	Public	Malawi	Bottle	Compliant	Compliant	Compliant	65.0%	87.9% (HPLC)	Low API content (USP-38 NF 33)
Amoxicillin	MG NAY 52	Public	Malawi	Bottle	Compliant	Compliant	Non-compliant	59.3%	86.6% (UV/Vis)	Low API content and dissolution (USP-38 NF 33)

Medicine (INN)	Sample ID	Type of Sampling Site	Stated Country of origin	Primary packaging	Visual Inspection	TLC	Disintegration	Dissolution	Assay (HPLC/UV-Vis)	Reason for non-compliance (reference)
Amoxicillin	MG MPI 68	Public	India	Bottle	Compliant	Compliant	Non-compliant	57.3%	84.9% (HPLC)	Low API content and dissolution (USP-38 NF 33)
Amoxicillin	ZA STI 118	Faith-based	Kenya	Bottle	Compliant	Compliant	Non-compliant	52.5%	82.9% (HPLC)	Low API content and dissolution (USP-38 NF 33)
Amoxicillin	NS SAN 244	Public	Kenya	Bottle	Compliant	Compliant	Non-compliant	66.3%	84.7% (HPLC)	Low API content and dissolution (USP-38 NF 33)
Ciprofloxacin	ZA CHA 294	Public	Malawi	Bottle	Compliant	Non-compliant	Non-compliant	50.6%	83.5% (HPLC)	Low API content and dissolution (USP-38 NF 33)
Ciprofloxacin	NS MBE 288	Public	Malawi	Bottle	Compliant	Non-compliant	Non-compliant	64.8%	86.0% (HPLC)	Low API content and dissolution (USP-38 NF 33)
Ciprofloxacin	NS PHO 290	Public	Malawi	Bottle	Compliant	Non-compliant	Non-compliant	56.6%	74.3% (HPLC)	Low API content and dissolution (USP-38 NF 33)
Ciprofloxacin	NS MBE 289	Public	India	Strips	Compliant	Compliant	Compliant	72.3%	88.2% (HPLC)	Low API content (USP-38 NF 33)
Ciprofloxacin	NS TRI 286	Faith-based	India	Strips	Compliant	Compliant	Compliant	73.7%	81.8% (HPLC)	Low API content (USP-38 NF 33)
Ciprofloxacin	NS MBE 301	Public	Malawi	Bottle	Compliant	Compliant	Compliant	70.1%	77.5% (HPLC)	Low API content (USP-38 NF 33)
Ciprofloxacin	NS DHO 257	Public	Malawi	Bottle	Compliant	Non-compliant	Non-compliant	57.6%	91.5% (HPLC)	Low dissolution (USP-38 NF 33)
SF medicines assay deviations below 80% or above 120% (extreme deviations)										
SP (pyrimethamine (1) and Sulfadoxine (2)	MG MGH 130 (1)	Public	China	Bottle	Compliant	Non-compliant	Compliant	NA	191.2% (HPLC)	High API content (USP-38 NF 33)
	MG MGH 130 (2)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	58.1% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimetha	ZA MAK 169 (1)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	175.3 (HPLC)	High API content (USP-38 NF 33)

Medicine (INN)	Sample ID	Type of Sampling Site	Stated Country of origin	Primary packaging	Visual Inspection	TLC	Disintegration	Dissolution	Assay (HPLC/UV-Vis)	Reason for non-compliance (reference)
mine (1) and Sulfadoxine (2)	ZA MAK 169 (2)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	57.1% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	ZA MAY 273 (1)	Faith-based	China	Bottle	Compliant	Compliant	Compliant	NA	197.2% (HPLC)	High API content (USP-38 NF 33)
	ZA MAY 273 (2)	Faith-based	China	Bottle	Compliant	Compliant	Compliant	NA	57.3% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	ZA CHI 215 (1)	Public	China	Bottle	Compliant	Compliant	Non-compliant	NA	166.9% (HPLC)	High API content (USP-38 NF 33)
	ZA CHI 215 (2)	Public	China	Bottle	Compliant	Compliant	Non-compliant	NA	63.0% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	ZA CHA 295 (1)	Public	China	Bottle	Compliant	Compliant	Non-compliant	NA	168.5% (HPLC)	High API content (USP-38 NF 33)
	ZA CHA 295 (2)	Public	China	Bottle	Compliant	Compliant	Non-compliant	NA	55.3% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	ZA THO 17 (1)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	165.3% (HPLC)	High API content (USP-38 NF 33)
	ZA THO 17 (2)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	77.2% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	MG DHO 148 (1)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	166.9% (HPLC)	High API content (USP-38 NF 33)
	MG DHO 148 (2)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	67.5% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimetha	MG GAW 138 (1)	Faith-based	China	Bottle	Compliant	Compliant	Compliant	NA	150.2% (HPLC)	High API content (USP-38 NF 33)

Medicine (INN)	Sample ID	Type of Sampling Site	Stated Country of origin	Primary packaging	Visual Inspection	TLC	Disintegration	Dissolution	Assay (HPLC/UV-Vis)	Reason for non-compliance (reference)
mine (1) and Sulfadoxine (2)	MG GAW 138 (2)	Faith-based	China	Bottle	Compliant	Compliant	Compliant	NA	77.1% (HPLC)	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	MG NAM 88 (1)	Faith-based	China	Bottle	Compliant	Compliant	Compliant	NA	171.8% (HPLC)	High API content (USP-38 NF 33)
	MG NAM 89 (2)	Faith-based	China	Bottle	Compliant	Compliant	Compliant	NA	66.3%	Low API content (USP-38 NF 33)
SP (pyrimethamine (1) and Sulfadoxine (2)	ZA CHA 177 (1)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	153.3%	High API content (USP-38 NF 33)
	ZA CHA 177 (2)	Public	China	Bottle	Compliant	Compliant	Compliant	NA	67.6%	Low API content (USP-38 NF 33)
SF not confirmed by pharmacopeial analysis										
Flucloxacillin	ZA MAT 164	Public	Kenya	Strips	Compliant	NA	Non-compliant	NA	NA	Capsule disintergration time >30 min (Mini lab)
Flucloxacillin	ZA GHE 47	Private	Kenya	Strips	Compliant	NA	Non-compliant	NA	NA	Capsule disintegration time >30 min (Mini lab)
Flucloxacillin	ZA MAC 182	Public	India	Strips	Compliant	NA	Non-compliant	NA	NA	Capsule disintegration time >30 min (Mini lab)
Flucloxacillin	MG MED 100	Private	England	Strips	Compliant	NA	Non-compliant	NA	NA	Capsule disintegration time >30 min (Mini lab)
Amlodipine	NS KAL 236	Faith-based	India	Strips	Compliant	Non-compliant	Compliant	NA	NA	Low API content observed by spot size (Mini lab)
Enalapril	NS PHO 222	Public	India	Strips	Compliant	Non-compliant	Compliant	NA	NA	Low API content observed by spot size (Mini lab)

Appendix VII: Summary of MSTG treatment protocols for common bacterial infections

Table summarizing antibiotic treatment protocols for common bacterial infections as stated in Malawi Standard Treatment Guidelines (2015)

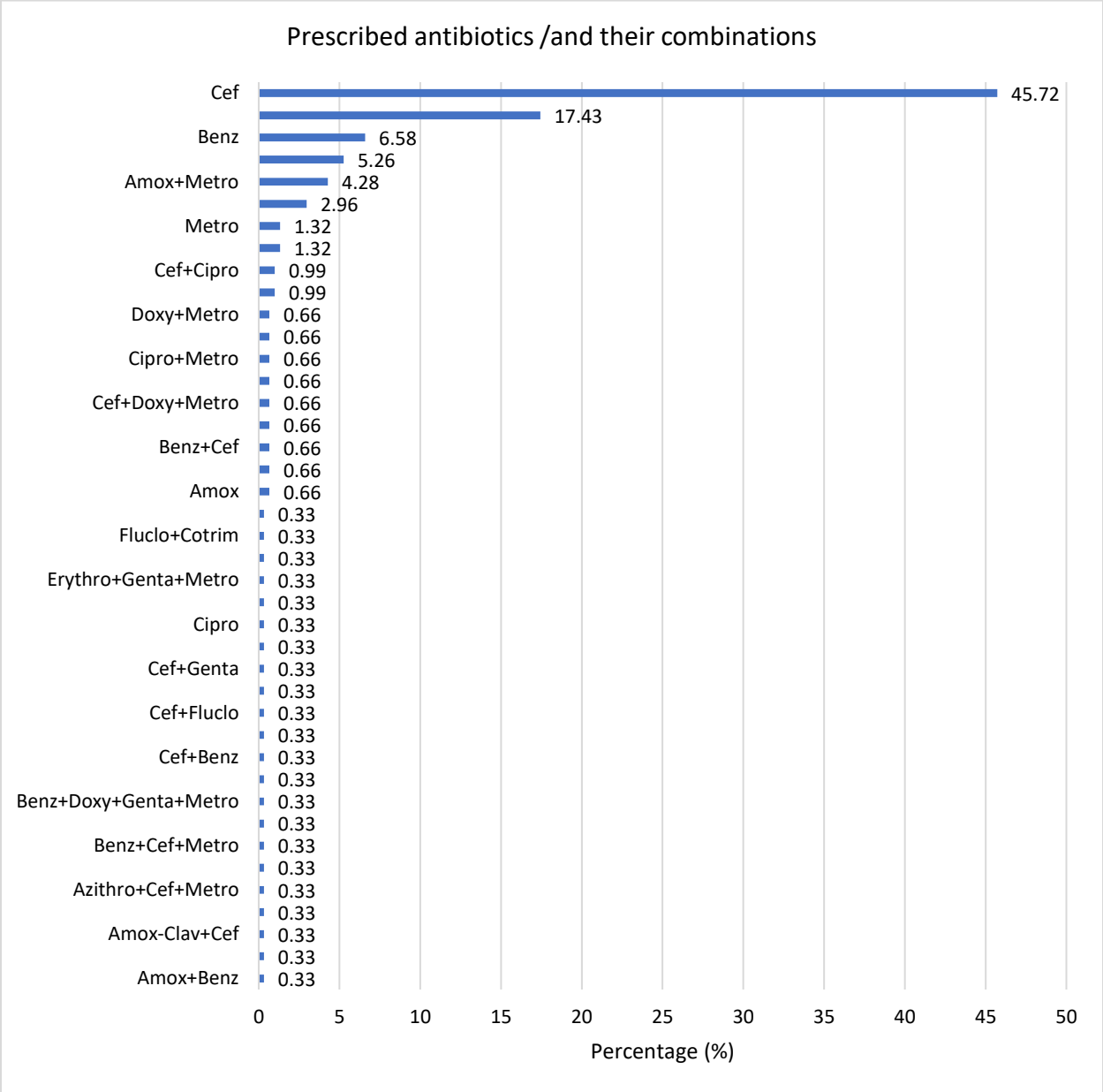
Disease condition	Description/sub-type if applicable	First line treatment according to MSTG	Secondline/ alternative treatment
Sepsis		Ceftriaxone 2g IV q24h for 10 days	Ciprofloxacilin 400 mg IV every q12h or 500 mg orally bd plus Benzylpenicillin 2MU IV q6h. Switch to oral Ciprofloxacin 500 mg bd plus Amoxycillin 500 mg tds, or oral Co-amoxiclav 625 mg tds, when improved. If intraabdominal source, add Metronidazole 500 mg IV or 400 mg orally tds.
Meningitis	Suspected cases	Benzyl Penicillin 5MU IV or IM stat	
	Confirmed bacterial meningitis	Ceftriaxone 2g IV q12h	Chloromphenical 1g IV q6h or Benzyl penicillin 5MU IV q6h
	Meningococcal Meningitis (Prophylaxis)	Ciprofloxacin 500mg stat.	Give Doxycycline 300mg stat
Pneumonia	Community acquired Pneumonia	Amoxycillin 500mg tds for 5-7 days	Erythromicin 500mg qid for 5-7 days or Doxycycline 100mg bd for 5 - 7 days
	Atypical Pneumonia	Erythromycin 500mg qid for 5 days	
	Nosocomial Pneumonias	Ceftriaxone 2g IV q24h or oral Co-amoxiclav 625mg tds for 7 days	
	Severe Pneumonia	Give Ceftriaxone 2g IV q12h plus Azithromycin or Erythromycin 500mg qid	Give Co-amoxiclav 1.2g IV q8h or Erythromycin 500mg qid for 7 days Or Doxycycline 100mg od for 7 days. If aspirating Add Clindamycin 600mg qid or Metronidazole 400mg tds 1.2g IV q8h

Other respiratory infections	Bacterial Sinusitis	Amoxycillin 500mg tds for 7 days	Erythromycin 500 mg qid for 7 days
	Acute bronchitis	Amoxycillin 500mg tds for 5 days	Doxycycline 200mg on first day
	Bronchiectasis	Co-amoxiclav 625mg tds	Doxycycline 200mg stat then Doxycycline. If sputum is smelling, add metronidazole 400mg tds
	Pharyngitis, Tonsillitis and its complications	Benzathine Penicillin 1.2 MU single dose	Amoxycillin 500mg tds for 7 days or Erythromycin 500mg qid for 7 days
	Peritonsillar Abscess	Amoxycillin 500mg tds and Metronidazole 400mg tds	Benzylpenicillin 2 MU IV q6h. Switch when possible (usually after 48-72 hours) to oral Amoxycillin 500mg tds or if penicillin allergic Give Erythromycin 500mg qid
	Retropharyngeal Abscess	Give Co-amoxiclav 625mg tds (or Co-Amoxclav 375mg plus Amoxicillin 240mg for 14 days)	Chloramphenicol 25 mg/kg tds, initially IM or IV. later orally for
Urinary tract infections	Cystitis/Urethritis	Ciprofloxacin	Give Nitrofurantoin 100mg qid with food for 7 days
	Complicated Urinary Tract Infections	Give Ciprofloxacin 500mg orally bd for 5 days	Give Co-amoxiclav 375mg tds or 625mg bd for 5 days
Sexually transmitted diseases	Genital ulcer disease (GUD)	Ciprofloxacin 500mg orally stat and Benzathine penicillin 2.4 MU IM stat plus Acyclovir 800mg bd for 7 days	Give Erythromycin 500mg qid for 15 days plus Acyclovir 800mg bd for 7 days
	Early Syphillis in adults	Benzathine Penicillin one dose of 2.4 MU IM	Doxycycline 100mg bd for 15 days or Erythromycin 500mg qid for 15 days
	Late syphilis in adults	Benzathine Penicillin 3 doses of 2.4 MU IM at weekly intervals	Doxycline 100mg orally every 12 hours for 30 days

	Neurosyphilis	Give Benzylpenicillin 4MU IV q6h for 14 days then Give Benzathine Penicillin 2.4 MU IM once weekly for 3 consecutive weeks	Doxycycline 200mg every 12 hours for 30 days
	Trichomoniasis, vaginal	Give Metronidazole 5 mg/kg every 8 hours for 5 days	
	Urethral Discharge/Urethritis	Gentamycin 240mg IM stat plus Doxycycline 100mg bd with food for 7 days	Erythromycin 500mg qid for 7 days
	Abnormal Vaginal Discharge in Women	Gentamycin 240mg IM stat plus Doxycycline 100mg bd with food for 7 days, plus metronidazole 2g orally single dose	
	Lower abdominal pain in women (LAP syndrome)	Gentamycin 240mg IM stat plus Doxycycline 100mg bd with food for 7 days, plus metronidazole 400mg tds for 7 days	
	Acute scrotal swelling or pain	Give Gentamycin 240mg IM stat and Doxcycline 100mg bd for 7 days.	
Skin infections	Cellulitis	Give Flucloxacillin 125 -500mg qid for 7 -10 days	Erythromycin 500mg qid for 7 -10 days
	Staphylococcal Scalding Skin Syndrome	Cloxacillin 250 - 500 qid for 5 days	
Gastrointestinal	Peptic Ulcer Disease/Gastritis	Metronidazole 400mg every 8 hours for 7-10 days ,plus Amoxycillin 1g every twelve hours for 7 - 10days, plus Omeprazole 40mg once daily for 2 weeks	Metronidazole 400mg every eight hours plus, Clarithromycin 500mg twice daily for 7-10 days, plus Omeprazole 40mg once daily for 2 weeks

Appendix VIII: Antibiotic combinations or monotherapies prescribed among patients

Figure showing prescribed antibiotic therapies of combinations



Amox= Amoxicillin; Benz = Benzylpenicillin; Azithro = Azithromycin; Genta= Gentamicin; Metro= Metronidazole; Doxy= Doxycyline; Fluclo= Flucloxacillin; Cef= Ceftriaxone; Cipro= Ciprofloxacin

Appendix IX: Medicine sample collection

MEDICINE SAMPLE COLLECTION RECORD

Name of District: _____Date of visit: _____/_____/_____

Name of facility: _____Govt ☐ CHAM ☐ Pvt ☐

	Drug samples collected	Dosage form and strength	Manufacturer and country	Batch number	Expiry Date	PMPB registration	Reference number	Number of sampling for the batch
1	Gentamycin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
2	Ceftriaxone					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
3	Erythromycin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
4	Azithromycin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
5	Clarithromycin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
6	Metronidazole					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
7	Amoxicillin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
8	Cloxacillin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
9	Flucloxacillin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
10	Benzyl penicillin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
11	Benzathine penicillin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
12	Ciprofloxacin					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
13	Nalidixic acid					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
14	Cotrimoxazole					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐
15	Doxycycline					Yes ☐ No ☐		1st ☐ 2nd ☐ 3rd ☐ 4th ☐

Appendix X: Data collection form on availability of antibiotic medicines

ASSESSMENT OF AVAILABILITY OF ANTIBIOTIC MEDICINES

Name of District: _____Date of visit: _____/_____/_____

Name of facility: _____Govt ☐ CHAM ☐ Pvt ☐

Main Storage type: ORDINARY ☐ PREFABRICATED SIaB ☐

	Name of antibiotic Medicine	**Procurement type**	**Appropriate level of facility (according to the MEML)**	**Stock at Hand**	**NUMBER OF STOCK OUT DAYS (last six month)**	Monthly consumption (in tabs/vials, based on last six months)	Stockout time in last 6 months (= total number of days when this medicine was not available)	**Comments**
						Take picture for stock card for reference		
1	Gentamycin	CMST☐ PVT ☐	YES☐ NO ☐					
2	Ceftriaxone	CMST☐ PVT ☐	YES☐ NO ☐					
3	Erythromycin	CMST☐ PVT ☐	YES☐ NO ☐					
4	Azithromycin	CMST☐ PVT ☐	YES☐ NO ☐					
5	Clarithromycin	CMST☐ PVT ☐	YES☐ NO ☐					
6	Metronidazole	CMST☐ PVT ☐	YES☐ NO ☐					
7	Amoxicillin	CMST☐ PVT ☐	YES☐ NO ☐					

8	Cloxacillin	CMST☐ PVT ☐	YES☐ NO ☐					
9	Flucloxacillin	CMST☐ PVT ☐	YES☐ NO ☐					
10	Benzyl penicillin	CMST☐ PVT ☐	YES☐ NO ☐					
11	Benzathine penicillin	CMST☐ PVT ☐	YES☐ NO ☐					
12	Ciprofloxacin	CMST☐ PVT ☐	YES☐ NO ☐					
13	Nalidixic acid	CMST☐ PVT ☐	YES☐ NO ☐					
14	Cotrimoxazole	CMST☐ PVT ☐	YES☐ NO ☐					
15	Doxycycline	CMST☐ PVT ☐	YES☐ NO ☐					
16	Meropenem	CMST☐ PVT ☐	YES☐ NO ☐					

Appendix XI: Recording sheet for medicine quality tests

Laboratory test result record

LABELING		
Item	Information available	Comment
Product Name	YES ☐ NO ☐	
INN	YES ☐ NO ☐	
Batch Number	YES ☐ NO ☐	
PMPB reg number	YES ☐ NO ☐	
Storage conditions	YES ☐ NO ☐	
Leaflet (In English)	YES ☐ NO ☐	

APPEARANCE		
Uniformity of color	OK ☐ NOT OK ☐	
Uniformity of shape	OK ☐ NOT OK ☐	
Absence of physical damage e.g., Cracks, breaks, abrasion, sticky etc.	OK ☐ NOT OK ☐	
Absence of foreign contaminants or dirty marks	OK ☐ NOT OK ☐	

DISINTEGRATION TEST

Pass ☐ Fail ☐

TLC RESULTS

Pass ☐ Fail ☐

DISSOLUTION TEST

Pass ☐ Fail ☐

ASSAY

Titration ☐ UV/Vis ☐ HPLC ☐

Pass ☐ Fail ☐

Appendix XII: Form for clinical data collection

APPROPRIATENESS OF ANTIBIOTIC USE AND THE PATIENT OUTCOMES

1. PATIENT INFORMATION								
Patient's study ID:		Age:		Gender: ☐Male ☐Female			Weight (kg): Height (cm):	
2. TREATMENT (indicate if there was switching of antibiotics) Number of antibiotics prescribed: ☐								
Antibiotic name (And indication)	Dose, frequency and duration	Recommended dose range	Culture done	Sensitivity test	No. of days taken before antibiotic was administered	Batch Number administered	Batch sampled for test	Comment(s)
			YES☐ NO ☐	+ve☐-ve ☐ Not done ☐			YES☐ NO ☐	
			YES☐ NO ☐	+ve☐-ve ☐ Not done ☐			YES☐ NO ☐	
			YES☐ NO ☐	+ve☐-ve ☐ Not done ☐			YES☐ NO ☐	
			YES☐ NO ☐	+ve☐-ve ☐ Not done ☐			YES☐ NO ☐	
CONCOMITANT DRUGS								

Drug name	Indication	Dose, frequency and duration	Recommended dose range	Known Interactions with antibiotics prescribed	Comment

3. CLINICAL OUTCOMES

☐Recovered or recovering ☐Not recovered or not recovering ☐ Adverse event detected ☐ No adverse event detected ☐ Death

LENGTH OF HOSPITAL STAY (D

DESCRIPTION OF ADVERSE DRUG EVENTS (INCLUDING TREATMENT FAILURE) IF DETECTED:

RELEVANT MEDICAL HISTORY OF PATIENT: including pre-existing medical conditions (allergies, previous exposure, alcohol use etc.)

Appendix XIII: COMREC certificate of study approval

CERTIFICATE OF ETHICS APPROVAL

This is to certify that the College of Medicine Research and Ethics Committee (COMREC) has reviewed and approved a study entitled:

P.10/21/3447 - Assessing the quality and use of antibiotics and associated clinical outcomes in southern Malawi by Francis Chiumia

On 10-Dec- 21

As you proceed with the implementation of your study, we would like you to adhere to international ethical guidelines, national guidelines and all requirements by COMREC some of which are indicated on the next page for your study

10-Dec-21

Prof. E. Umar -Chairperson (COMREC)

Date

Approved by College of Medicine

10-Dec-2021

(COMREC) Research and Ethics Committee

Appendix XIV: Informed consent form (English)

Study title

Assessing the quality and use of antibiotics and associated clinical outcomes in southern Malawi

Investigator

Mr Francis Chiumia, PhD Student, Department of Pharmacy, Kamuzu University of Health Sciences

Supervisors

Dr Felix Khuluza, Pharmacy Department, Kamuzu University of Health Sciences

Dr Elizabeth Kampira, Medical Laboratory Sciences Department, Kamuzu University of Health Sciences

Prof Adamson Muula, School of Public Health and Family Medicine, Kamuzu University of Health Sciences

Introduction

I am PhD student at the Kamuzu University of Health Sciences. I am conducting a research on the quality and use of antibiotics and associated clinical outcomes. This study focuses on a crucial topic which concerns the life and safety of patients. It will therefore not just help in fulfilling the requirements for my study but also be of benefit to the nation at large. This sheet provides the information about the study and also invites you to participate in this study. You are therefore requested to go through it and ask any question that you need me to clarify.

What we want to do in the study

In this study, we will investigate the appropriateness of the use of antibiotic medicines, the quality of the formulation, associated storage factors and clinical outcomes. We will do this by reviewing your medical records and ask you or your healthcare provider for any information we need. The information will include your demographics, diagnosis, drugs prescribed and how you are responding to the medicines provided. We will also take samples of the medicine batch you are taking and subject it to laboratory analysis to see if thy meet quality standards or not whilst simultaneously assessing the factors that affect the quality of the medicines.

How you will participate in the study

You participation in the study will barely involve physical interaction with the investigator. The investigator will only use your patient file to extract the information that is necessary

for the study. However, where necessary the investigator may need to get missing information from the files, for example age from either your health care provider or yourself.

Volunteerism in the Study

Your participation in this study will be very essential to us to get the required data for our study. Moreover, we expect that very few patients will be able to meet the criteria for enrolment in the study. However, we would like you to know that your participation is voluntary. You have the right to decline enrolling in our study if you feel not comfortable to do so or lack adequate information to make a decision. Even if you choose to participate in the study, we will still give you the freedom to withdraw at any stage if you feel so for any reasons that you feel is sound to you.

Confidentiality

The information provided to us will be treated with utmost confidentiality and will not be shared with anyone except members of this research team. We will use identification numbers on our forms instead of your real name so that no one will be able to know who was prescribed which medicine or who was suffering from which condition.

Sharing of study findings

The findings of our study will be shared to key stakeholders such as PMRA, Ministry of Health, Pharmaceutical Society of Malawi (PHASOM), Medical Council of Malawi, members of the academia and general public through publication and meetings. These are key institution for policy making in the country and beyond. In whatever circumstances, no identity of any of our participants will be mentioned when sharing our findings.

Agreement to participate

I have read and understood the information about this study and the clarification from the researchers have given me adequate knowledge of the study. I therefore voluntarily consent to participate in this study.

Place: _____

Participant's ID: _____

Signature of Participant: _____

Date: _____/_____/_____

Declaration by researcher

I_____ declare that I have offered adequate information about this study to _____(Participant ID) and that upon his/her satisfaction, they have agreed to voluntarily participate in the study.

Signature of researcher: _____

Date: _____/_____/_____

Appendix XV: Informed consent form (Chichewa)

Mutu wa kafukufuku

Assessing the quality and use of antibiotics and associated clinical outcomes in southern Malawi

Wochita kafukufuku

Mr Francis Chiumia, PhD Student, Department of Pharmacy, Kamuzu University of Health Sciences

Aphunzitsi akulu omutsogozela amene akuchita kafukufuku

Dr Felix Khuluza, Pharmacy Department, Kamuzu University of Health Sciences

Dr Elizabeth Kampira, Medical Laboratory Sciences Department, Kamuzu University of Health Sciences

Prof Adamson Muula, School of Public Health and Family Medicine, Kamuzu University of Health Sciences

Chiyambi

Ine ndine wophunzira wochita za degree ya udotolo ku sukulu ya Kamuzu University of Health Sciences. Ndikuchita kafukufuku oyang'ana ngati makhwala ali abwino komanso kunikila zotsatila zake kwa odwala. Izi zikuunikila pa mutu ofunikila kwambiri umene ukukhudzana ndi miyoyo ya anthu komanso kuonetsetsa kuti anthu onse Sali pa chiophyezo Kamba kokumwa mankhwala. Kotero kafukufuku ameneyi sikuti ndiongothazila pa maphunziro anga komanso ndiothanziza dziko lonse la Malawi.Tsambali likufotokoza mwachindunji zomwe tikuchita mu kafukufuku ameneyi ndiponso kupempha kuti ngati muli odzipereka mukhale nawo mu kafukufuku ameneyi. Inu mukuphemphedwa kuti muwerenge ndikumvetsetsa tsambali komanso kufunsa pomwe simunamve.

Zomwe tikuchita

Mu kafukufuku ameneyi, tikuyanga ngati mankhwala opha tizilombo ta bacteria akugwiritidwa bwino ntchito, ndi osaonongeka komanso mmene izi zikukhuzila ngati odwala athu akuthandizika ndi mankhwalawa. Pochita kafukufuku ameneyi, tizaona mma failo anu akuno kuchipatala komanso kukufunsani inu kapena ogwira mu chipatala muno uthenga ulionse omwe tikuyangana. Ife tizatengaso nawo mankhwala omweinu mukumwa kuti akayezedwe uku tikuyang'ana zomwe zimachititsa kuti mankhwalawa asakhale abwino.

Mmene mungatengere mbali

Kukhala nawo mukafukufuku ameneyi sikofunikila kuti inu muzikhala nafe. Ochita kafukufuku ndi amene atazatenge failo yanu nkuunikila zomwe akufunika kutengamo. Pokhapokha pemene akufuna uthenga omwe mu failo mulibe mwachitsanzo ngati zaka zanu zakubadwa mulibemo ndipamene muzafunidwe,

Kuzipereka

Inu kukhala nawo mu kafukufuku ameneyi ndi chinthu cha mtengo wapatali kwambiri chifukwa uthenga wanuwo ndi omwe ungathanzize kuchita kafukufuku ndipo kupeza odwala oti akhale nawo mu kafukufuku ndi chinthu chosowa. Ngakhale zili choncho, inu sindinu okakamizidwa mwanjira iliyonse kukhala nafe. Mukuyenela kupanga chitsankhochi mwakuzipereka kwanu panokha ngati mukuona kuti palibe vuto lililonse komanso mwakhutidwa ndi uthenga umene mwapatsidwawu. Komanso ngakhale mutavomela kukhala nafe, muliso ndi uflu osinthamaganzio nthawi iliyonse.

Chinsinsi

Uthenga onse otengedwa mu kafukufuku amakhala wachinsisi ndipo sugawidwa kwa anthu Wamba koma okhawo amene akuchita nawo kafukufuku. Sitizagwiritsa ntchito dzino lanu koma ma nambala chabe oimila dzina lanu ndipo palibe angadziwe kuti ndi ndani amadwala matenda wo ndikulandila mankhwala wo.

Zotsatila za kafukufuku

Zotsatila zake zizaperekedwa kwa mabungwe oyanganila za mankhwala, unduna wa umoyo komanso mabungwe a anthu ogwira ntchito za umoyo monga ma dokotola, akatsiwi a zamankhwala ndi ena komanso ophunzitsa sukulu za ukachenjede. Awa ndi amene amapanga ziganizo zokhuzana ndi umoyo mu dziko lino.

Kugwirizana nazo zokhala mu kafukufuku

Ine ndawerenga ndikumvetsetsa za uthenga wa kafukufuku ameneyi. Komanso ndinapatsidwa mwayi ofunsa pomwe sindikumvetsetsa. Kotero ndikugwirizana nazo ndikulowa mu kafukufuku ameneyi mozipereka ndekha.

Malo: _____

Numbala ya ochita nawo kafukufuku: _____

Kusayina : _____

Tsiku: _____/_____/_____

Ochita kafukufuku

I_____ ndikuvomeleza kuti ndapereka uthenga onse kwa _____amene akulowa atakhutitsidwa ndi uthenga waperekedwa mozipereka yekha

Kusayinila: _____

Tsiku: _____/_____/_____

Appendix XVI: Addendum to the thesis

1. Correction on the number of facilities in abstract of chapter 5.1

The correct number of facilities is 29 as indicated in the methods section of the manuscript. This error has been reported to the journal through a letter attached as appendix XVII.

2. Addendum to Figure 3 of chapter 5.1 Factors associated with SF medicines in Southern Malawi

We provide additional analysis to assess if type of facility (primary, secondary or tertiary) is a potential factor associated with SF medicines

Figure 3 (chapter 5.1) *Crude analyses of the association between facility type and compliance to quality*

		Compliance to Quality		
Variable	**Characteristic**	**OR**	**95% Confidence interval**	**P value**
Facility Type	Primary	Reference	Reference	
	Secondary	0.60	0.26 - 1.39	0.234
	Tertiary	0.47	0.12 - 1.84	0.281

We found no significant difference in medicine quality among primary, secondary and tertiary level facilities. The non-significant findings may however have been affected by the small sample size.

3. Addendum to Chapter 5.3 Revised table for multivariate logistic regression analysis for factors associated with occurrence of adverse drug reactions

Table 4 Factors associated with occurrence of adverse drug reactions

Variable	Characteristic	OR	95% CI	P value	aOR	95% CI	P value
Age	< 65	1			1		
	≥ 65	2.65	1.46 – 4.80	0.001	4.53	2.21 – 9.28	<0.001
Sex	Female	1					
	Male	1.11	0.65 - 1.88	0.705			
HIV status	Non-reactive	1					
	Reactive	1.16	0.59 - 2.29	0.661			
Co-morbidities	Non-hypertensive	1					
	Hypertensive	0.43	0.17 - 1.05	0.065	0.19	0.07 - 0.54	0.002
	Non-diabetic	1			1		
	Diabetic	1.23	0.42 - 3.58	0.7			
Number of antibiotics prescribed	1	1			1		
	>1	1.74	1.02 - 2.96	0.041	2.14	1.18 - 3.9	0.012
Number of concomitant medicines	≤ 1	1					
	>1	3.94	0.91 - 17.15	0.067	2.82	1.39 – 5.74	0.004
Length of stay (days)	≤ 3	1					
	>3	4.3	2.20 - 8.43	<0.001	5.11	2.47 – 10.55	<0.001

OD = Odds ratio

aOR = adjusted odds ratio

CI = confidence interval

P value ≤0.05 was considered statistically significant

4. Addendum to Chapter 5.4

Supplementary Table 1 Factors affecting patient recovery (Logistic regression results)

Variable	Characteristics	Odds Ratio (95% CI)	P value	Adjusted Odds Ratio (95% CI)	P value
Age		0.97 (0.96 - 0.99)	0.013	0.98 (0.95 - 1.00)	0.122
Sex	Female	1			
	Male	1.22 (0.52 - 2.86)	0.799	0.92 (0.35 - 2.41)	0.873
Diagnosis	Sepsis	1			
	Pneumonia	0.61 (0.17 - 2.11)	0.428	0.6 (0.1 - 2.3)	0.477
	Meningitis	1.48 (0.16 -13.6)	0.728	1.2 (0.1 - 12.46)	0.827
	Cellulitis	0.64 (0.06 - 6.38)	0.71	0.5 (0.04 - 6.4)	0.625
	Peptic ulcers	0.23 (0.04 - 1.51)	0.127	0.15 (0.01 - 1.24)	0.079
	Others	0.59 (0.19 -1.76)	0.342	0.97 (0.28 - 3.2)	0.969
Charlson Score		0.83 (0.72 - 0.97)	0.015	0.89 (0.73 - 1.1)	0.304
Quality	Low API	1			
	Optimal API	1.29 (0.27 - 6.18)	0.747	1.56 (0.28 - 8.67)	0.606

5. Notification letter to PlosOne on the error in Chapter 5.1

Vice Chancellor

Prof. M. Mallewa (BMedSc, MBBS, MRCP, MRCPCH, DTM&H, PhD)

Our Ref:

Your Ref:

21 September 2024

The Editor

PLOS ONE

Dear Editor,

NOTIFICATION OF MANUSCRIPT ERROR

I write to inform you that we have noticed an error in the paper which was published in 2022 entitled "**Burden of and factors associated with poor quality antibiotics, antimalarials, antihypertensive and antidiabetic medicines in Malawi"** by authors: Francis Kachidza Chiumia, Happy Magwaza Nyirongo, Elizabeth Kapira, Adamson Sinjani Muula and Felix Khuluza.

In the abstract section, we mention that the study was conducted in 23 healthcare facilities. However, the correct number of facilities was 29 as indicated in the methodology section. This mistake was due to a typing error, and we apologize to our readers and editorial team for this oversight.

Yours sincerely

Felix Khuluza, PhD

Asscociate Professor of Pharmacy