Monitoring Safety of Medicines in Uganda: Strategies for better Pharmacovigilance Systems in Settings with Limited Resources

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Candidate: Helen Byomire Ndagije

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Institut de recherche santé et société, Université Catholique de Louvain

Promotor: Professor Niko Speybroeck

MEMBERS OF THE JURY

Professor D'HOORE William, President
Faculté de santé publique (FSP)
Institut de Recherche Santé et Société (IRSS)
Université catholique de Louvain
Brussels, Belgium

SPINEWINE Anne, MPharm, MSc, PhD
Professor in Clinical Pharmacy
Louvain Drug Research Institute, et Faculté de Pharmacie et Sciences Biomédicales
Clinical Pharmacy Research Group (LDRI/CLIP)
Université catholique de Louvain
Brussels, Belgium

Professor SPEYBROECK Niko, Promotor
Institut de Recherche Santé et Société
Université catholique de Louvain
Brussels, Belgium

OLSSON Sten
Immediate Past President
International Society of Pharmacovigilance, (ISoP)
ISoP Secretariat Ltd,
London, United Kingdom

Professor KIRAKOYA, Fati, Msc, MPH, PhD
Centre de Recherche en Epidemiologie, Biostatistique et Recherche Clinique
Université libre de Bruxelles (ULB)
Brussels, Belgium

Professor RAVINETTO Raffaella, PharmD, PhD
Department of Public Health
Institute of Tropical Medicine
Antwerp, Belgium

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"Give thanks to him who led his people through the wilderness.
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List of Abbreviations

AAT	Amodiaquine/Artesunate tablets
ACT	Artemisinin-based Combination Therapy
ADE	Adverse Drug Event
ADR	Adverse Drug Reactions
AL	Artemether/Lumefantrine
ALT	Artemether/Lumefantrine tablets
AMRH	African Medicines Regulatory Harmonization
API	Active Pharmaceutical Ingredient,
AS/AQ	Artesunate/Amodiaquine
CDS	Community Dialogue and Sensitization
CHEWs	Community Health extension workers
DHP	Dihydroartemisinin/Piperaquine
DPT	Dihydroartemisinin/Piperaquine
EPI	Expanded Program on Immunization
EAC	East African Community
EMA	European Medicines Agency
FGD	Focus group Discussion
FPP	Finished Pharmaceutical product,
GMP	Good Manufacturing Practice
GPHF	Global Pharma Health Fund
HC	Health Centre
HCP	Healthcare Professional
HSDP	Health Sector Development Plan
ICSR	Individual Case Safety Report
IMHDSS	Iganga/Mayuge Health Demographic Surveillance Site
KAP	Knowledge Attitudes and Practice
LC	Local Council
LMIC	Low- and Middle- Income Countries
MedDRA	Medical Dictionary for Regulatory Authorities
MTC	Medicine and Therapeutic Committee
MUCHAP	Makerere University Centre for Health and Population Research
NDA	National Drug Authority
NMS	National Medical Stores
NPC	National Pharmacovigilance Centre
NPSSP	National Pharmaceutical Sector Strategic Plan
ODK	Open Data Kit
PFP	Private -for-profit
PHP	Public Health Program
PIDM	Program on international Drug Monitoring
PMS	Post-marketing Surveillance
PNFP	Private-not-for-profit
RDT	Rapid Diagnostic Test-kit
REC	Research Ethics Committee

RPC	Regional Pharmacovigilance Centre
SOC	System Organ Class
SSA	Sub-Saharan Africa
TLC	Thin-Layer Chromatography
UMC	Uppsala Monitoring Centre
USAID	United States Aid for International Development
WHO	World Health Organization

PART 1: INTRODUCTION

1.2 Motivation for this Study

As more and newer medical products hit the market, regulatory authorities should monitor their use in daily practice. Through pharmacovigilance, the authorities systematically collect and analyze empirical data on drug usage and take corrective action to improve patient safety. This generates new information that should subsequently informs practice. The envisioned drug safety monitoring system is one that learns from previous experience and creates order in health service delivery in Uganda by prioritizing safety of patients. The NDA has made considerable progress towards monitoring safety of medicines after their approval for more than twelve years now, however more needs to be done.

This research project was motivated by the achievements of the Uganda National Pharmacovigilance Centre. It has trained health workers on monitoring safety of medicines in its network of 14 regions pharmacovigilance centres countrywide. With limited resources, Uganda, through the pharmacovigilance centre,implemented a new method of targeted spontaneous reporting of Tenofovir-related adverse drug reactions in collaboration with the World Health Organization as part of the European Union funded Monitoring Medicines Project. In 2010, the assessment of the safety of medicines in sub-Saharan Africa by the USAID Strengthening Pharmaceutical Systems Program recognized Uganda as one of the countries with operational pharmacovigilance systems that effectively detects, evaluates and addresses medicine safety issues. However, one of the areas for improvement raised in that report for low-resource countries was the limited expertise to assess drug safety issues. Medicine safety issues bring an additional strain to a healthcare system that is already struggling to contain the killer diseases such as HIV/AIDS, tuberculosis, and malaria common in sub-Saharan Africa Looking back at the remarkable progress that has been made in the past decade, the enhanced local capacity to assess and use drug safety evidence will inform Uganda's pharmacovigilance policy and for low-resource countries in general.

One writer once said that the difference between stumbling blocks and stepping-stones is how you use them. My hope is that this thesis provides a stepping-stone towards building a modern reliable pharmacovigilance system providing safer patient care in my country and other countries with limited resources.

1.2 The Uniqueness of Pharmacovigilance as a Scientific Discipline

Pharmacovigilance is the science and activities relating to detection, assessment, understanding and prevention of adverse effects or any other possible drug-related

problems[1, 2]. It is rapidly evolving and widening in scope and nature. Up until about 2007, pharmacovigilance was mainly about the detection of new drug safety signals to medicines[3]. More recently the scope of drug regulation, and thus the range of safety concerns, has expanded to include herbal medicines, medical devices, vaccines and biologicals, and blood and blood products[4]. Activities related to the identification, management and prevention of sub-standard medicines, medication errors, lack of therapeutic efficacy, and abuse and misuse of medicines are relevant to pharmacovigilance[5]. As a scientific discipline, it is fundamentalto effective clinical practice and to overall improved public health. In turn, many other scientific and non-scientific disciplines are relevant to an effective pharmacovigilance system.

On 5 April 2018, a magistrates' court in Uganda, convicted a man over possession and vending of restricted cancer drugs to patients in and around Mulago National Referral Hospital[6]. The man was hawking Bevacizumab (Avastin®) tablets, which is ordinarily a solution for intravenous infusion. What he was vending was allegedly a product that was re-formulated and packaged in 60 tablets plastic containers. A month's supply of this vendor's drug was worth three million Uganda shillings (about USD 800 equivalent). This is more expensive than a four- milliliter vial or a monthly injection dose of two million four hundred thousand (about USD 640). The counterfeit bluish-grey "Avastin" tablets were reported to be manufactured in Sweden; however, the genuine Avastin is registered and manufactured by La Roche Company in Germany. Following a tip-off by a concerned clinician from the Uganda Cancer Institute, about the hawker, the National Drug Authority arrested the imposter and took nine months to secure his conviction in court.

This case, the first of its kind in Uganda, demonstrated the holistic approach to drug safety that the science and practice of pharmacovigilance encompasses. The initial suspicion was raised by a clinician who noticed the change in Avastin presentation. He wondered how an infusion drug for cold storage, could now be freely handled at room temperatures as tablets. His main concern was whether it would still be effective in a tablet form. Upon hearing this, the drug authority swung into action and arrested the "anti-cancer medicine" hawker. The media worked with the drug authority to alert the unsuspecting public about this counterfeit medicine, calling for vigilance by providing information about suspicious cases of pharmaceutical products suppliers and sounding a warning about purchasing drugs from unlicensed suppliers.

The pharmaceutical manufacturers, on their part, quickly contacted the Authority to provide information on genuine products and, especially, clarifications regarding the counterfeit Avastin case under investigation. The World Health Organization Rapid Alert System also sent an alert to other drug regulatory agencies concerning the counterfeit medicine found in Uganda. The Uganda police Criminal Investigation Department worked with the National Drug Authority enforcement unit to elucidate the supply chain of this counterfeit medicine and gathered evidence for

law courts. Within a record nine months, the case was concluded with the conviction of this unscrupulous man. Clinicians, pharmaceutical manufacturers, judicial system officials, police, media, scientists, drug regulators, patients and the general public, all performed their complementary roles in achieving the common goal: improving patient safety.

The uniqueness of the pharmacovigilance discipline resides in how its activities are carried out. It frequently starts with collection of suspicions or observations regarding individual cases from healthcare professionals, patients and consumers[7]. Public health monitoring, however, requires pharmaco-epidemiological statistical skills to achieve effectively systematic monitoring of populations. The review of health statistics and of drug utilization are relevant to pharmacovigilance towards improving patient care[4]. Pharmacovigilance also involves effective analysis of health data as well as dissemination of this data to concerned stakeholders[5], a process that benefits from input from social scientists. As the safety data accumulates, the pharmacovigilance professionals recruit additional engineers to support the development of improved digital technologies and artificial intelligence models to search and identify drug-related issues.

Pharmacovigilance continues to evolve and to draw its relevance from interaction with different scientific disciplines. It plays a pivotal and specialized role in keeping the medical products on the market safe, providing confidence to patients towards the medicines they take to save their lives and towards the healthcare systems that supply them.

A more comprehensive surveillance system, for Uganda and the rest of Africa, would lead to a deeper understanding of medicine-related problems, especially the burden of preventable medication errors as well as problems related to drugs quality[8].

1.3 The Landscape of Drug Safety in Africa

Post-marketing surveillance of medicines in Africa is important and is one of the quickest ways through which public confidence in the medicines and healthcare system can be significantly increased[9, 10]. Pharmaceuticals are becoming increasingly prominent in the health budget of many countries[11], and the reliance of public health systems on pharmacovigilance, especially through drug utilization and cost studies, will support decision-making regarding expenditure on health. Medicines constitute the largest portion of household health budgets and they are easily accessed in the community in order to quickly treat the common childhood killer diseases in settings with limited resources settings[12]. The high disease burden in many African countries has encouraged the casual use of prescription drugs that would normally be given under the supervision of a health professional

to a home caregiver. This may result in the use of new medicines whose safety profiles have not been fully characterized, or older medicines with a toxic profile[5]. The pharmacovigilance system is important mainly because it promotes safe use of such medicines, thereby safeguarding the health of the population.

The majority of medicines registered in Uganda are usually in their later stages of development. However, several new potential medicines (especially for treating HIV/AIDS, Malaria, Tuberculosis and the neglected tropical diseases) that are still in the development pipeline or are almost exclusively destined to the African market were recently reported[13-15]. Due to the urgent need for access, these drugs go through an accelerated or conditional approval process. The aim of such procedures is to provide access to more effective treatments for vulnerable populations and to support the advancement of important innovations since the African pharmaceutical manufacturing capacity is still low. However, such situations require careful safety monitoring of these medicines to avert possible harm that could befall the patients using them[16]. The large quantities of generic medicines used in the limited safety monitoring environments provide an opportunity for development of pharmacovigilance skills that can eventually handle the newer drugs as they are introduced in developing market economies. Mature regulatory agencies have proper drug safety monitoring facilities that can restrict access to, or modify the use of drugs, according to their potential of causing harm. According to a study of drug withdrawals across the globe since the 1950s, show there were fewer withdrawals in Africa than in the other five continents and, thus, harmful drugs were likely to stay on the African market longer[17, 18].

Forty-three African countries have a pharmacovigilance centre with a clear mandate and organizational structure either as a full or associate member of the World Health Organization (WHO) Program for International Drug Monitoring[19]. Seventy-two percent of the 36 full members joined the program in the last ten years. According to WHO, less than 1 percent of individual case safety reports (ICSR) in the WHO global database come from Africa[20]. With an average yearly report of 3 adverse drug reactions (ADR) per million inhabitants, adverse drugs effects remain dramatically under-reported in low-income countries, as compared to the wealthiest countries displaying an average of 130 ADR reports per million[21, 22]. The legal framework for pharmacovigilance in many African countries has many limitations[18]. In March 2019, Uganda promulgated a new regulation guiding market-authorization holders and their agents on how to continuously monitor and report on the safety of the products on the market. The East African Community (EAC) Council of Ministers of Health has also approved a similar guideline for the region in May 2019. The African Medicines Regulatory Harmonization (AMRH) initiative, aimed at ensuring rapid access to safe, efficacious, and good quality essential medicines, currently works to improve overall pharmacovigilance capacity over the whole continent.

1.4 Outline of the Thesis

This thesis focuses on the monitoring of drug safety after deliverance of the market authorizationfrom regulatory authorities. Once the drug is on the market, patients use medicine in conditions that are different from those in clinical trials. Also, more people are exposed to the new medicines, taken sometimes in conjunction with other medicines and for longer periods than in trials. A variety of side effects and other new information about drugs emerge from routine utilization. For this reason, the safety of all medicines should remain carefully monitored throughout their use in daily healthcare practice. Pharmacovigilance is responsible for both the science and practice of monitoring and preventing adverse effects or any other drug-related problem. In the present thesis, we investigate the development of efficient pharmacovigilance and the strategies for improving monitoring systems, especially in settings with limited resources, as explained in Part 1.

Part 2 provides the global study framework. Chapters 2.1 details the status and the role of pharmacovigilance, while Chapter 2.2 describes the Ugandan context and provides a brief situational analysis of the pharmacovigilance system in this East African country. Chapter 2.3 presents several solutions and strategies for improving pharmacovigilance in Uganda and other areas with limited resources.

Part 3 presents the motivation for the current study. Chapter 3.1 summarizes the rationale of this study. Chapter 3.2 presents the overall objective of the study while Chapter 3.3 provides details concerning the specific objectives.

Part 4 focuses on what needs to be done to improve pharmacovigilance in settings with limited resources, with specific reference to the Ugandan context. Chapter 4.1 proposes a new and quick method of active follow up and evaluates the burden of adverse drug reactions due to Artemisinin-based antimalarial treatment in selected health facilities in Uganda. This method is especially relevant given that the safety information for new drugs (such as Artemisinin-based combination therapies for the treatment of uncomplicated malaria) based on their clinical usage remains scarce.

Chapter 4.2 presents the results of an uncontrolled before-and-after study held among rural communities. We adapted the community dialogue approach to stimulate reporting of adverse drug events directly from patients in the community and foster new interest in healthcare services. We show that the community has some fair knowledge that medicines have a potential to cause harmful side-effects and are willing to report the occurrence of adverse events through the preferred community channels, as well as to their healthcare providers. With minimal adaptation, the community dialogue and sensitization intervention model was found to be highly beneficial for consumer reporting in settings with limited resources. We illustrate how the pharmacovigilance systems in such settings can gather useful evidence for important health policy decisions.

Chapter 4.3 deals with another stakeholder in pharmacovigilance: the clinician. This chapter presents the results of a survey investigating the hypothesis that attitudes and perceptions of clinicians towards treatment failures would provide invaluable insights about nonperforming medicines and guide post-market surveillance sampling by National Drug Authority (NDA). Clinicians interact with both the medicines and patients and are therefore in an ideal position to suspect poor quality medicine or treatment failure.

Part 5 provides overall discussion and conclusion of this thesis,and proposes indications for future work.

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PART 2: BACKGROUND

2.1 Pharmacovigilance in Settings with Limited Resources

According to WHO, one in ten medical products in low income countries are substandard or falsified (SF) medical products[1]. These products pose a huge threat to animal and human health and monitoring the product-related health effects is now part of pharmacovigilance. The high levels of SFs on the market point to a fragmented healthcare system and weak regulatory framework[2]. With the increase of the burden of non-communicable diseases[3], more complex products are being introduced onto the market, requiring more sophisticated drug safety monitoring systems.

Many countries have public health programs (PHPs) dedicated to the prevention and treatment of diseases. In settings with limited resources, per capita government spending is low and medicines are usually the most prominent item on the health budget[4]. Medicines also consume most of the PHP budget, and for patients, they account for the lion's share in household expenditure. Access to all medicines, including SF ones[5], is on the rise, increasing the need for strong post-market surveillance systems.

Pharmacovigilance in settings with limited resourcesis characterized by a few dedicated healthcare professionals who capture a limited proportion of the medicine-related harm, mainly because of spontaneous methods of reporting drug-related problems[6]. Spontaneous reporting is preferred because it is least demanding in terms of resource in comparison to other methods such as targeted spontaneous reporting and cohort event monitoring[7].

The majority of pharmacovigilance systems in settings with limited resourcesare young and often lacks expertise, and thorough pharmacovigilance education was until recently available in developed countries only[7-9]. Some countries have started monitoring medicine safety only because of regional or sub-regional harmonization initiatives, where one country leads and the others take to mentorship and attachments as a source of capacity building. Experts have observed that, the authorities in low- and middle-income countries (LMICs) usually focus on data collection and management, at the expense of safety data analysis[7]. What further raises concern is that even the data collection to support regulatory decision making has not been efficient. For pharmacovigilance to grow in these settings, the regulatory authorities ought to influence policy through evidence. These young pharmacovigilance systems cannot rely on their own data and, consequently, few regulatory decisions have been based on local information.

Global health programs have been hiring drug manufacturers to reduce production costs for medicines used to treat the poverty related diseases. On the other hand,

development partners such as the Global Fund have recognized the need to build regulatory capacity in their quality assurance policy for pharmaceutical products. Nearly half of their investment is dedicated to health systems. Principal recipients of the Global Fund investment, for example, are required to implement pharmacovigilance mechanisms and to include the costs of these mechanisms within budgets for the relevant grants since 2010[10]. This policy contributed greatly to the increase in awareness about pharmacovigilance among public health programs and other stakeholders that participates in the implementation of Global Fund grants.

The Global Fund commits to meet the cost of quality control activities and to make the results of quality control tests of their pharmaceutical products publicly available. The WHO prequalification program can also be leveraged by low-income countries to sharpen their pharmacovigilance analytical skills and improve efficiency of data collection on pharmaceutical product safety and support regulatory decision-making right from their point of introduction on the market.

Politicians and healthcare decision-makers urgently need legal instruments to increase pharmacovigilance capability and effectively strengthen patient safety. Several assessments of such pharmacovigilance systems in Africa have revealed that the legal framework and political commitment leaves much to be desired. The regulatory basis for pharmacovigilance has been found to be weak in some countries on the continent, even where the pharmacovigilance system is relatively functional[11].

The African Medicines Regulatory Harmonization initiative developed a template law intended to guide African governments to review, enact and harmonize drug-related laws and regulations across the continent. This law, which was adopted by the African Union summit in January 2016 will help member states to fill legislative gaps that hinder effective regulation of medical products and prevent harmonization of these regulations in Africa's regional economic communities.

Pharmacovigilance systems in any setting should be designed with a sustainability mindset from the outset. Safety surveillance systems should be designed in cooperation with local regulatory authorities to incorporate as much stakeholder input as possible and to reflect local capabilities. For safety monitoring systems to flourish, governments have to dedicate appropriate funding and staff to pharmacovigilance. Funding for pharmacovigilance activities is pivotal, and some lessons can be learned from the fees-based model implemented in the European Union.

Cohort event monitoring and targeted spontaneous reporting are recent methods for collecting safety data from PHPs that have been successfully implemented in Ghana, Nigeria, Tanzania, Kenya, Uganda, and Zimbabwe[12, 13]. With the introduction of new products into the developing world, these and other forms of

active surveillance will be more relevant to assess reliablerisk profiles and better frequency estimates for new products[14-16].

Pharmacovigilance is part of the healthcare system which is currently outstretched in many settings with limited resources. Its success will depend on how the authorities in the concerned countries deal with the highlighted critical challenges to increase public confidence in the medicines they take and in the healthcare system that they regularly interact with in general.

2.2 The Uganda Context

Access to medicines and vaccines in low- and middle-income countries (LMICs) like Uganda has improved in the past two decades. However, there has not been a proportionate improvement in pharmacovigilance infrastructure and activities to monitor adverse drug events and address safety issues[17-19].

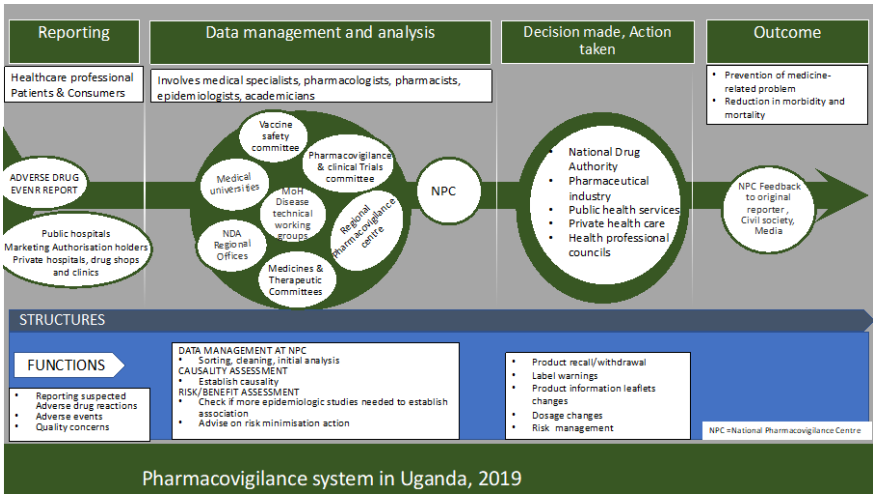
Uganda's National Drug Authority was established in 1993 by the National Drug Policy and Authority (NDP/A) Act[20]. The objective of the National Drug Policy was to ensure the availability at all times of essential, efficacious and cost-effective drugs to the Ugandan population as a means of providing satisfactory healthcare and safeguarding the use of drugs.

The Pharmacovigilance regulations (Statutory Instrument No. 37) of 2014 provides the legal basis for the establishment of drug safety and quality monitoring systems in Uganda[21]. The national policy on drug use in the National Health Sector Development Plan (HSDP) 2015-2020[22], National Medicines Policy 2015[23], and the National Pharmaceutical Sector Strategic Plan (NPSSP) 2015-2020 implements the strategy to strengthen the national pharmacovigilance system for both the public and private health sector[24]. Uganda participates actively in the East African Community, regional and continental harmonization efforts, which are expected to further improve the quality of medicines circulating in the country. The EAC partner states have begun to adapt the compendium of guidelines for strengthening pharmacovigilance systems that was approved in March 2019 by the EAC Sectoral Council of Ministers of Health.

Uganda started systematic collection of safety information in 2007 with the formation of the National Pharmacovigilance Centre (NPC), and its eventual incorporation as the 83rd member of the WHO Program of International Drug Monitoring (PIDM). Over the years, the centre promoted the development of pharmacovigilance systems in the country in healthcare facilities, public health programs, and market authorization holders, and directly engaged in active Pharmacovigilance activities as well.

Pharmacovigilance efforts rely on voluntary or mandatory spontaneous ADR reporting by healthcare professionals and patients to the country's drug regulatory agency depending on the prevailing PV system [25]. Pharmacovigilance scope has expanded to more than just adverse drug events to also include medication errors, substandard and falsified medicines, drug-drug interactions, medicine misuse and abuse and lack of efficacy of medicines [26]. The goal of pharmacovigilance is to promote patient safety. However, many countries now recognise that the views of patients are missing in matters of medicine safety and are setting up systems to reduce the burden of unsafe medication. Current estimates show that 134 million adverse events occur each year due to unsafe care in hospitals in LMICs resulting in 2.6 million deaths annually [27]. Africa contributes to less than one percent of the adverse event reports in the WHO global database. In the outpatient departments of primary health care settings, four out of every ten patients are harmed in the process of receiving care. Yet there is under-reporting of adverse events inherent in the spontaneous method of data collection that most resource-limited settings use. Furthermore, many reports received at the National Pharmacovigilance Centres are incomplete, lacking useful data for causality assessment and decision making [28]. Greater involvement of patients could reduce the burden of harm by up to 15%, saving billions of dollars each year [29] as some countries like the United States of America have demonstrated. There is a need for cost-effective sustainable solutions for LMICs that are evidence-based and strategies to address the issues of medicine safety. International efforts are already underway to support regulators in LMICs to identify, assess and adequately manage risks associated with the introduction of selected priority productions thereby building capacity for optimising post-market surveillance for all medicines across the board [30-32].

Figure 2.1: The flow of information in the pharmacovigilance system in Uganda.



Pharmacovigilance scope has expanded to include medication errors, substandard or falsified medicines, lack of efficacy, misuse and abuse of medicines [26]. When ADR reporting has happened, National Drug Authority has taken corrective action thereby potentially saving patient lives. For instance, in 2012, adverse drug event reporting of suspected lack of efficacy by several health workers led to the withdrawal of marketing authorization of 67 medicine products – manufactured by Flamingo Pharmaceuticals of India. These drugs were withdrawn from the Ugandan market thereby saving countless lives [33]. With a greater understanding of pharmacovigilance by the policy makers in Uganda, more resources have been allocated to it. In July 2017, the pharmacovigilance staff numbers doubled. Uganda has been recognised as one of those countries with progressive regulatory capacity especially in post-marketing surveillance where it has a stand-alone system. The WHO pre-qualified National Drug Quality control laboratory [34] supported the analysis of the products collected in the EAC cross-border PMS activities. The NPC piloted the new methodology of targeted spontaneous reporting of adverse drug reactions [35] in collaboration with the AIDS Control Programme. The coordination of activities countrywide is hinged onto the regional pharmacovigilance centres which are of two types: the regional and national referral hospitals and the NDA regional offices. The regional officers are important in following up mainly the issues of poor quality and lack of efficacy in the private sector as well as receive the adverse drug event reports from public health facilities. The hospital-based centres manage the adverse drug events and medication errors, conduct some preliminary assessment and submit the ADR reports through Vigiflow or manually filled report through the pharmacovigilance centre. The academia is also very active in conducting pharmacovigilance research initiated either by the regulatory authority or by themselves and guided by the numerous memoranda of understanding with the universities. The curriculum for training of various cadres of healthcare professionals has been updated with pharmacovigilance content. The health professional associations have been progressively involved in pharmacovigilance, initially at their annual meetings, more recently in the regional training activities and daily on social media platforms. Despite such efforts, under-reporting of adverse drug reactions still exists. The assessment of the health system indicates that the consumer voice is still inadequate in system strengthening. Similarly, involving patients is the next major step that could improve the quality and quantity of adverse event reports in the country and a toll-free pharmacovigilance line has been established by the Authority. More sensitization of the public needs to be done and the media will be crucial in this next step, however, they often get away with irresponsible reporting. The health journalists' trainings on risk communication should be intensified.

Uganda has a health worker to population ratio of 1:49 core health worker per 1,000 population, which is below the WHO recommended minimum of 2:3 health workers per 1,000 population[36]. In addition, the quality of health workers at the primary healthcare level leaves much to be desired as only 20 percent of them

could correctly diagnose four out of five common diseases and only 15 percent were able to correctly treat these conditions[37].

According to the 2018 Uganda national supply chain assessment conducted by the USAID and the Global Fund, quality and pharmacovigilance data collected at sub-national health facilities are hardly shared with NDA and the Ministry of Health[38]. Pharmacovigilance is a transversal specialty that can be leveraged to improve healthcare quality. However, specialized training is not readily available. The NPC has developed a pharmacovigilance training manual for routine in-service training for pharmacists, nurses and doctors. The national program also faces high turnover rate of pharmacovigilance professionals due to shift of health workers from the public sector to the higher paying jobs in the private sector or non-governmental organizations.

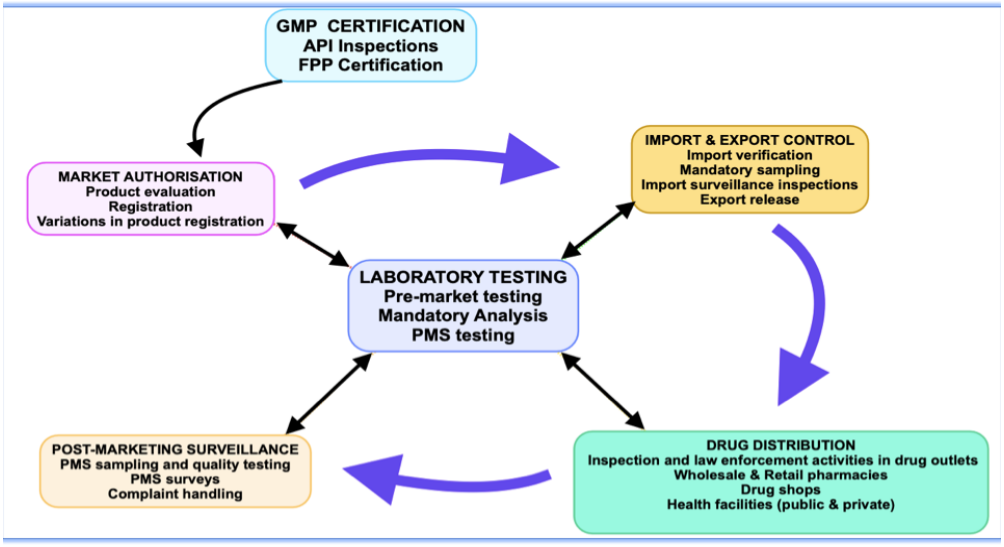
The pharmaceutical manufacturing and distribution supply chains are complex, multi-faceted and globally integrated. The ability of any regulator to assure the safety, quality and efficacy of a medicinal product domestically requires knowledge of and confidence in these supply chains and regulatory oversight at all stages[39].

The public health sector supply chain is well organized, and drugs are purchased and distributed centrally. The private health sector includes a wide range of entities: manufacturers, importers, distributors, wholesalers and retailers, including licensed drug outlets and mushrooming drug shops manned by unqualified health personnel. Medicines are also obtainedin private hospitals, private clinics, informal settings like herbal drug outlets and supermarkets.

Stock outs in the public health sector are a driver for the presence of substandard and falsified products on the market[40, 41]. During enforcement operations, the regulatory authority has confiscated medicines from hawkers. Prescription medicines are often bought without prescription, and drug information is often disseminated through social media. Misleading information promotes purchase of herbal products without scientifically proven effect. The NPC conducted recalls of 17 medical products in the last financial year. Effectiveness of recalls of defective medicines is hampered by low adherence to good distribution practices.

In line with the NDA strategic priorities, NDA committed to monitor safety of drugs post-market authorization. To achieve this objective, the NPC works with several stakeholders to ensure timely detection and mitigation of drug related risks. Figure 2.2 below represents the interplay between the different regulatory functions in an effort to assure quality and safety of medicines in the country.

Figure 2.2 Safety and quality of medicines – the relationships between different regulatory functions



GMP = Good manufacturing practice, API = Active Pharmaceutical Ingredient, FPP= Finished Pharmaceutical product,

PMS = Post-marketing Surveillance

2.3 Strategies for better Pharmacovigilance of Medical Products

The disease burden is growing and changing in nature but governments are also devising more efficient ways to prevent and treat diseases and afford their citizens more productive lives. However, many of the developing countries in which these drugs and vaccines are used don't have the capacity to effectively monitor their post-market safety[(42)].

Few LMICs have functional post-market safety systems and their contribution to global drug monitoring program is still limited. The pipeline to distribute new products to developing countries holds a lot of promise, which is unmatched, in form of advanced skill for benefit-risk assessment. Many products will be introduced exclusively or simultaneously in the low-resource countries. In such circumstances, even the unscrupulous people take advantage to grow the trade in substandard and falsified pharmaceutical products. History is likely to repeat itself as poor-quality medicines are likely to re-appear, paving the way for potentially

hazardous public health issues. Given the limited resources and expanding post-market safety needs, a new strategy is needed[43].

The strategy must leverage and complement existing efforts in the low-resource settings using best practice from regional and international pharmacovigilance initiatives. Pharmacovigilance initiatives must be designed to adapt to the limited resources and be able to address as many priority regulatory capacity gaps and health system issues as possible. The set of strategic intervention that are proposed below are not prescriptive to low-resource settings. They provide a pool of ideas that are food for thought in the struggle to implement better pharmacovigilance with very limited resources. They are based on experience and knowledge gained in service as the head of pharmacovigilance centre in Uganda, a low-income country.

One hundred and thirty-six countries, including 26 percent of low- and lower-middle income countries, are registered members of the WHO Program on International Drug Monitoring[31]. Membership to this program has enabled LMICs to access training programs, standardized adverse event definitions, and monitoring guidelines that are useful for building up their pharmacovigilance capacity.

Benchmarking practices among national regulatory authorities of regional economic communities such as the East African Community (EAC) have also provided an opportunity for regulatory capacity improvement. At the country level, cooperation among national regulatory authorities and public health programs have benefited from the pooling of scarce resources and expertise to solve medicine safety issues. However, such cooperation demands time, sustained political commitment and other resources. All the EAC partner states, for instance are not at the same level of development regarding the regulatory functions. Following an assessment of regulatory functions, some of the partner states that required capacity building have been twinned with partner states with more established regulatory capacity. However, this kind of cooperation can only be sustained if it remains relevant to the concerned parties.

Public health treatment and immunization programs in many LMICs have limited communication and collaboration with the regulatory authorities[44, 45]. The adverse events following immunization, detected and reported by the Expanded Program on Immunization, are not routinely shared with national pharmacovigilance centres. In countries where little post-market safety surveillance capacity exists, it makes sense to establish integrated drug and vaccine safety surveillance systems. In addition, each public health program, including the immunization programme, should have a pharmacovigilance focal person who would work closely with the NPC and be involved in joint studies and interpretation of data for improving patient care.

Regulators in developing countries need to use training opportunities made available in global and regional harmonization efforts. The transversal nature of pharmacovigilance deems it necessary to obtain specialized training so as to move away from data collection and management to analysis and use of the collected data.

Pharmacovigilance centres need to have a skills-mix that includes more clinical experts for differential diagnosis for disease and drug reactions. In May 2018, the ministry of education revised the health training curricula for public and general health nursing, pharmacy, Anesthesia and medical theatre techniques to make it more practical. More health training institutions will incorporate pharmacovigilance in their curricula with the guidance of the NPC and health professionals' councils. For a robust pharmacovigilance system, a training manual should be developed for in-service healthcare professionals. It is the quality of healthcare professionals that will determine the capability and performance of pharmacovigilance at the lower level health facilities. Expertise, such as is already available in public health programs, clinical trial and epidemiological sites that have trained staff, laboratory infrastructure, and, in some instances, drug utilization statistics could also be leveraged in detection and assessment of any medicine safety concerns.

The methods used for conducting pharmacovigilance for the national regulatory agencies and MAHs ought to use a mix of passive and active surveillance and some pharmaco-epidemiological methods. It is important for countries that are embarking on the process to leverage the active surveillance opportunities, which are more common now than ten years ago and to develop the spontaneous reporting system. This will generate durable and affordable systems that can address a variety of safety concerns. Working with already existing structures like the medicines and therapeutic committees (MTCs) is important for sustainability. Recent collaborative efforts with the Pharmacy Division in the Ministry of Health to revamp these committees have taught us some lessons. One lesson was that the MTC activities were not well known within the hospitals where they operated and communication of these activities to the administration and other members of staff was critical for their survival. Another lesson learnt was that more mentoring on root cause analysis, data analysis and interpretation to improve appropriate medicines use and supply chain issues was necessary. The various hospital pharmacovigilance teams that the NPC has trained and engaged over the last ten years could be transformed into sub-committees of the MTCs within their hospitals to facilitate the MTC to utilize facility level safety data for risk mitigation.

The use of information technology has become more prominent in our daily lives, in general, and in improving pharmacovigilance operations. Data collection and management, through increased use of social media and online reporting platforms, use of electronic medical records and health insurance databases will be more efficient with improved access to electronic devices. Records linkage in

support of pharmacovigilance will also be more efficient where drug, laboratory, and medical records are available in LMICs.

In the context of limited resources, risk-based pharmacovigilance should be emphasized. Submission of risk management plans by MAHs are a necessity especially for new products. However, regulatory authorities should be able to interpret and follow them up and also take care not to suffocate the generic products or the local pharmaceutical manufacturing industry.

The legal framework for pharmacovigilance in many developing countries is inadequate[46, 47]. A variety of legal instruments require MAH to report suspected ADRs and the regulatory authorities to take action. The international council on harmonization requires drug developers to submit pharmacovigilance and benefit-risk management plans about how they would assess and manage the risks of new medicines submitted for registration[48]. Regulators in developing countries should learn from such efforts so as to develop a culture of planning for post-market safety surveillance activities ahead of time. Regulations have been introduced that require a Qualified Person for Pharmacovigilance (QPPV) for drugs marketed in Uganda.

Good communication and promotion of pharmacovigilance awareness among stakeholders fosters timely identification of signals and safety concerns. The commonly used spontaneous reporting of suspected ADRs and drug-related issues is known for delivering much fewer reports than expected. It is heavily dependent on a few healthcare professionals who are passionate about preventing the recurrence of medicine-related harm. Direct patient reporting is recommended even for rural communities supported with community dialogue and sensitization on medicine safety issues[37]. For sustainability, local governments and stakeholders should be engaged in a fulltime partnership in the development and implementation of pharmacovigilance programs. Advocacy for increased funding for pharmacovigilance activities should be done because medication errors, tracking substandard and falsified products, inefficacy of medicines and inappropriate prescribing habits raise the cost of health service delivery in already constrained health system. Drug safety monitoring involves several stakeholders, including drug manufacturers, regulators, policy makers, public health programs, implementing partners and patients, each with a unique role. The NPC will harmonize stakeholder activities and harnessing synergies among the stakeholders. Additionally, the NPC will develop and implement strategies for sharing safety information, lessons and experiences among players at the national, regional and global level as means of enhancing capacity to detect and mitigate drug related problems in a timely manner.

The fees that most governments in developing countries currently charge for medicine registration are modest and insufficient to fund the range of regulatory activities needed in their conditions. Most developing countries do not charge fees for pharmacovigilance. The European Medicines Agency (EMA) has recently

proposed dedicated fees to fund its pharmacovigilance activities; low-resource countries could consider this proposal in the long term. Fees provides a sustainable source of funding for a chronically and significantly underfunded critical area of health service delivery. To address the high turnover of health personnel in the public sector, the additional fees collected could be used to increase their salaries to match those from the private sector. In addition, fees collection increases accountability of governments to the people paying such fees for the performance and improvement of pharmacovigilance systems. For similar reasons, the donor community could consider paying fees for the sustainability of a post-market safety surveillance system. The disadvantage of this is that it is the final consumer of medicines who suffers the brunt of the increase in fees especially in countries like Uganda that pay out-of-pocket for healthcare.

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PART 3: OBJECTIVES

3.1 Study Rationale

There is a need for greater access to medicines and to create a clearer monitoring of drug use patterns by generating local evidence to support public health decision making in overloaded low-resource healthcare systems, with a high disease burden. Overall, patient reporting of suspected ADRs is increasingly implemented, and recent studies have shown that more signals of drug safety issues are registered when both healthcare professionals and patients report suspected ADRs.

3.2 Overall Objective

The purpose of this study is to establish the burden of harm related to the use of antimalarial treatment and to understand the factors associated with or affecting the current ADR reporting patterns. The evidence collected should ultimately provide insights towards potential solutions to issues that Uganda faces or is likely to face in its implementation of pharmacovigilance.

3.3 Specific Objectives of the Study

Objective One

To evaluate the burden of adverse drug reactions and other problems related to the use of antimalarial medicines in Uganda. The study attempts to answer the following specific questions:

1. What is the incidence rate of adverse drug reactions related to the use of ACTs in selected health facilities in Uganda?

2. What is the proportion of reported suspected ADRs that are associated with preventable medication errors in Uganda?

Objective Two

To understand the factors associated with the current ADR reporting patterns by healthcare providers. Specifically, addressing the following two issues:

1. What is the attitude of health workers towards clinical failure of ACTs in Uganda?

2. Does suspected ADRs reporting improve confidence in treatment?

Objective Three

To investigate the benefits of patient reporting of suspected adverse drug reactions and other problems related to the use of medicines in Uganda. The following sub-objectives are to be addressed:

1. To develop, adopt and implement community dialogues and sensitization (CDS) approach for use in a patient ADR reporting context.

2. To assess whether CDS approach promotes understanding and knowledge of reporting ADRs for drug safety monitoring at the level of both communities and patients.

3. To assess whether the CDS approach promotes community participation in ADR reporting and drug safety monitoring.

4. To assess the communities' perceptions of patient ADR reporting and drug safety monitoring and the effectiveness of community participation approaches.

PART 4: PHARMACOVIGILANCE SYSTEM STRENGTHENING

4.1 The burden of adverse drug reactions due to Artemisinin-based anti-malarial treatment in selected Ugandan health facilities– an active follow-up study.

Drug Saf. 2018 Aug;41(8):753-765. doi: 10.1007/s40264-018-0659-x.

Helen Byomire Ndagije[1], Victoria Nambasa[1], Leonard Manirakiza[1], Donna Kusemererwa[1],Dan Kajungu[2], Sten Olsson[3], Niko Speybroeck[4].

[1]*National Pharmacovigilance Centre, National Drug Authority, Kampala Uganda*

[2]*Makerere University Centre for Health and Population Research, Iganga, Kampala, Uganda*

[3] *Sten Olsson Pharmacovigilance Consulting, Uppsala, Sweden*

[4]*Institute of Health and Society (IRSS), Université catholique de Louvain, Brussels Belgium*

Abstract

Background:Uganda has rapidly increased access to antimalarial medicines in an effort to address the huge malaria disease burden. Pharmacovigilance information is important to guide policy decisions.

Objectives: The purpose of this study was to establish the burden of adverse drug reactions (ADRs) and associated risk factors for developing ADRs to Artemisinin-based antimalarial treatment in Uganda.

Methods:An active follow-up study was conducted between April and July 2017 on a cohort of patients receiving treatment for uncomplicated malaria in Iganga, Mayuge and Kampala districts.

Results: A total of 782 patients were recruited with median age of 22 years, 58.6 percent were female. Majority were recruited from public health facilities (97%). Diagnostic tests before treatment were done for 76 percent of the patients and 97 percent received Artemether/Lumefantrine. The prevalence of ADRs was 22.5 percent(176/782). However, the total number of ADRs was 245 since some

patients reported more than one. The most commonly reported reactions were general body weakness (24%), headache (13%), and dizziness (11%). Women were more likely to develop an ADR (aOR=1.8; 95% CI: 1.1-2.9), urban dwellers were more likely to develop an ADR than rural residents (aOR=9.9; 95% CI: 5.4-17.9) and patients with comorbidities were more likely to develop an ADR than those without (aOR=7.4; 95% CI=4.4-12.3).

Conclusion:The burden of ADRs is high among women from urban settings and those with comorbidities. Such risk factors need to be considered in order to optimize therapy. Close monitoring of ADRs is key in implementation of malaria treatment policy.

Key Words*:*Pharmacovigilance, malaria, adverse drug reactions, community.

Key Messages

1. Active follow-up studies present a viable avenue towards establishing the burden of adverse drug reactions at community level for ADRs reported by either patients or health workers

2. It is possible with limited resources to conduct active surveillance of ADRs for malaria patients in the community with minimal loss to follow up.

3. Health service delivery in the private sector and in rural areas ought to be reviewed and improved so as to optimise therapy especially in the treatment of malaria in children.

4.1.1 Introduction

Pharmacovigilance has been defined as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug related problem[1].In Africa, about forty countries have a pharmacovigilance centre with a clear mandate and organisational structure either as a full or associate member of the World Health Organisation (WHO) programme of international drug monitoring[2]. The Uganda National Pharmacovigilance Centre (NPC) has been part of this programme for ten years now. By September 2017, all of Africa accounted for 0.9 percent of the 15.5 million individual case safety reports (ICSR) in the global database[3]. The rate of reporting suspected ADRs in Uganda is about 10 per million inhabitants annually which is below the 200 per million inhabitants, frequently used as the standard for a well performing system[4].

The change of malaria treatment policy, thrice, in six years based on evidence generated in-country that increased the accessibility of Artemisinin Based Combination therapy (ACTs) up to community level brought to the fore the need to establish the current pharmacovigilance system [(7,8)]. This system was to monitor safety of the newly introduced ACTs as well as all medicines. The suspected adverse drug reactions (ADRs) form was disseminated widely and incorporated in the national treatment guideline documents. Health workers were sensitized on the importance of pharmacovigilance of all drugs with emphasis on the new ACTs and use of rapid diagnostic test kits before treatment of malaria[(9-11)]. The current 2016 Uganda Clinical Guidelines identify the first line treatment for uncomplicated malaria as either Artemether/Lumefantrine (AL) or Artesunate/Amodiaquine (AS/AQ) and the second line medicine as Dihydroartemisinin/Piperaquine (DHP) and Quinine tablets in case the second line is not available[12].

In 2014, Uganda introduced a new pharmacovigilance regulation that makes it mandatory for health professionals to report all suspected ADRs encountered during their practice.[5] There is a network of 14 regional pharmacovigilance centres (RPCs) based in regional referral hospitals. The ADRs data are entered into VigiFlow® at RPCs or at the NPC. Vigiflow® is a web-based ICSR management tool used in the WHO Programme for International Drug Monitoring (WHO PIDM) and maintained by the Uppsala Monitoring Centre (UMC).[6] Since March 2016, healthcare professionals can enter information into the forms directly using the electronic reporting tool into Vigiflow. There is a move towards establishing direct patient reporting of adverse reactions in Uganda.

The general public seeks care and treatment from the private sector as a first point of call, but many of these outlets have limited infrastructure and skills to give good quality service including reporting adverse events[(13-15)]. How patient-reported safety information is handled, determines future performance measurements of good quality healthcare.[16] There is a growing body of evidence showing that patients who are more actuated have better health outcomes and care seeking

experiences. Policies and interventions aimed at strengthening the role of patients in managing their healthcare can contribute to improved outcomes and that patient motivation can and should be measured as an intermediate result of care that is linked to improved outcomes.[13]

There is a huge disease burden, which has led to greater medicines access in resource-limited healthcare systems that have weak regulatory systems. Therefore, the need to generate pharmacovigilance data is important to inform treatment policy decisions. The purpose of this study was to establish the burden of adverse drug reactions due to Artemisinin-based treatment of malaria in selected public and private healthcare facilities in Uganda. The study also sought to assess the proportion of suspected adverse drug reactions that could have been prevented.

4.1.2. Methodology

Design and study sites

This was an observational and active follow-up study conducted on a cohort of people taking antimalarial drugs between April and July 2017. The study was conducted in randomly selected public and private health facilities and/or drug outlets in Kampala and Iganga/Mayuge districts representing urban and rural settings respectively. The rural districts host the Iganga/Mayuge health and demographic surveillance site (IMHDSS) of Makerere University Centre for Health and Population research (MUCHAP). It is an open population-based cohort serving as a platform for research and research training that longitudinally generates population-based data. The IMHDSS comprises 65 villages, 17,000 households with a total population of 89,000 served by 17 community based public health facilities in the two districts. Over 90 percent of the population resides in the rural areas. Iganga and Mayuge share a similar malaria burden and have received similar malaria control interventions from the country's Ministry of Health.

According to the 2014 demographic health survey, Kampala is an urban district[17]. This urban population varies from communities that can afford the options of private health care to those that seek treatment from the free public health services, private drug outlets and ordinary shops for treatment[18]. Kampala has slum settlements and the swamps have been encroached on in many parts of the city which poses challenges for malaria reduction efforts and consequently high use of anti-malarial drugs in such areas.

Sampling and sample size level

Random sampling was done at health facilities or drug outlets and all public health facilities in the districts. A sample of the private sector drug outlets recognised by

local community leaders as regular sources of healthcare were randomly selected as well. The number of respondents selected from each facility or outlet catchment area was estimated using the *Scheaffer* formula of elementary survey sampling[19]. We assumed a proportion (p) with an acceptable level of 0.5, testing at the 0.05 level, and 80 percent power to detect a difference of at least 10 percent in the burden of ADRs between urban and rural settings which gave a sample size of 384 in each group (rural and urban). Considering a 5 percent anticipated loss to follow up, the final sample for the study was 806 respondents.

Patient recruitment and follow-up

Patients treated for uncomplicated malaria and consenting to participation in the study were enrolled. All patients with uncomplicated malaria confirmed by agreeing to a rapid diagnostic test, microscopy, clinical assessment basing on the presence of fever or a history of fever within the previous 24 hours were consecutively included into the study. All patients with complicated malaria were not included in this study. Data were collected using a face-to-face administered questionnaire and filled by trained research assistants.

The questionnaires (see Electronic Supplementary Material #1) were pretested prior to the main data collection. Patient phone contact details were obtained at the time of filling the pre-treatment questionnaire that was used to capture the baseline clinical, demographic and treatment data. Patients were followed-up using phone calls, health facility or home visits using a post-treatment questionnaire to capture their experience after treatment. A follow-up was made on day 3, 7, and 14. Using phone calls, patients reported whether they had developed an adverse drug event and the treatment outcome. Clinical outcome assessment was used for those visiting the facility or for those visited at home to determine whether they were cured or not and whether they had developed an adverse drug event after taking an antimalarial drug.

An adverse event is defined as any untoward medical occurence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with the treatment including worsening of the clinical condition[20].During follow up, the national form for reporting suspected ADR was filled following identification of an ADR (see Electronic Supplementary Material #2).

Outcome definition

An adverse drug reaction is defined as a response to a medicine which is noxious and unintended[20]. All adverse events reported by participants were recorded by research assistants and assessed for suspected ADRs by the trained professionals,specifically trained in pharmacovigilance. In this study, the suspected ADRs were either reported by patients or recorded by healthcare workers and were all assessed by the principal investigator. The Naranjo Algorithm (see Electronic

Supplementary Material #3)was used for causality assessment of suspected ADRs[21].

The event was classified as a suspected ADR if the two healthcare professionals agreed. In case of no consensus, an expert view was sought from a clinician with experience in malaria treatment. All suspected ADRs were also categorized according to the (MedDRA) System Organ Class (SOC) [22]. It is allowed that more than one drug be suspected of having contributed to the outcome for each ADR. The generated ADRs were compared to those in the manufacturer's product characteristics.

Method for determining preventability of ADRs

To assess the preventability of ADRs, the P-method developed by the WHO Collaborating Centre for Pharmacovigilance in Rabat, Morocco, was adapted for this study. For the identified possible or probable adverse drug reactions, a score card adapted from the P-method (see Electronic Supplementary Material #4) was used to assess those that could have been prevented[23] The score card categorized the factors associated with the ADR according to either health professional practice, quality of the drug or patient characteristics.

The factors related to professional practice investigated included incorrect dose, incorrect route of drug administration, and incorrect drug administration duration among others. Factors associated with the quality of drugs administered including poor quality and counterfeit products were assessed as part of the score card. The patient characteristics included non-compliance and self-medication with non-over the counter drugs, were also assessed in the preventability analysis.

In this study, the ICSR of patients on antimalarials were assessed using the P-method to ascertain whether they were due to medication errors and therefore preventable. The method was applied to the reported suspected adverse reactions after causality assessment using the Naranjo Algorithm. The risk factors that increased, such as likelihood of the occurrence of ADRs were assessed using the twenty criteria in the P-method. A root-cause analysis was then conducted and the details of errors tabulated.

Statistical analysis

Data were collected and reviewed daily by the investigators. Data was double entered into EPIDATA screens and checked for variations, which were cross-checked with the raw data and corrected. Data was then exported to STATA for analysis. A line list was done to check for any gaps or inconsistencies. A comparison was made between the rural and urban health facilities with respect to the variables collected in terms of demographic characteristics, ownership of the

facilities, malaria diagnostic testing and results before anti-malarial treatment, type of drugs given and comorbid disease conditions.

The outcome variable was defined as developing an adverse drug reaction or not. Univariate analysis was done to get the frequencies of the variables in each group. Bivariate analysis was used to investigate possible associations. The findings were then subjected to multinomial logistic regression to assess potential risk factors for developing ADRs. Results were presented in form using frequencies, associations, and adjusted odds ratios with confidence intervals and p-values. Those variables whose association p-value was less than 0.05 were taken to be significant.

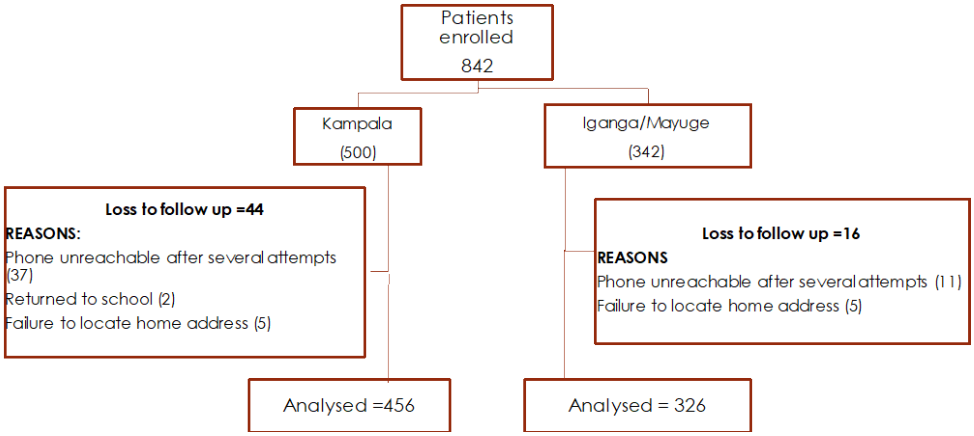
Ethical considerations

Ethical clearance was obtained from the Mildmay Uganda Research Ethics Committee (REC REF 0604-2017) and from the Uganda National Council for Science and Technology (HS 2247) which provides ethics research clearance at the national level in accordance with the World Medical Association Helsinki Declaration. Approval for the study was obtained from National Drug Authority and Makerere University Centre for Health and Population Research. Each respondent consented to participate in the study by signing the informed consent form.

4.1.3 Results

A total of 842 patients were recruited into the study from public and private health facilities. However, 60 patients (7%) did not participate in post-treatment interview to assess adverse reactions due to loss of follow-up and were not included in the final analysis data set. Of those, 44 were from Kampala while 16 were from the Iganga/Mayuge area. The reasons for loss of follow-up included phone contacts being unreachable after several trials and inability to locate their homes. The flow diagram presented in Figure 4.1 below shows patient recruitment and follow-up from the two study areas.

Figure 4.1: Flow diagram of patient recruitment and follow-up



Participants in this study were followed up either by phone (91%) or on return visit to the health facility, and home visits. Seventy nine of the patients in rural areas (Iganga/Mayuge) were followed up by making phone calls, 11percenton return visit to the health facility for follow up, and 10 percent were visited at home. All patients in Kampala were followed up by phone except 3 who visited a health facility and 1 who was visited at home.

4.1.4 Description of the study population

Overall, 782 (93%) were successfully followed up, at least, 3 days post-treatment. Analysis was conducted for those patients who completed the post-treatment questionnaire and are described in Table 4.1. There were 25 pregnancies reported and 8 were in the first trimester, 9 in the second and 8 in the third trimester.

Majority (97%) of patients were recruited from public health facilities and there were no patients from the private health facilities recruited in the rural area. Patients from urban settings (60%) were tested for malaria using microscopy or RDT and (40%) by clinical assessment before treatment was given while all the patients in Iganga/Mayuge study site were tested using microscopy or RDT. All patients in this study received antimalarial treatment irrespective of whether or not a malaria diagnostic test was done prior to treatment. The majority (97%) of the patients were prescribed Artemether/Lumefantrine. Of the 597 patients who were tested, 15 percent (40/272) were from the Kampala area compared to 0.3 percent (1/325) who received treatment despite negative malaria test results. Ninety-seven

percent of the patients received first line ACT antimalarial drugs. It was established that 57 percent (448/782) of the patients were being treated for malaria only with 64 percent from the rural area and about 53 per cent from Kampala.

More patients from the urban area reported comorbidities (64.7%) than those from the rural study area (35.3%). The comorbidities reported among the 334 patients were HIV/AIDS (35.6%), tuberculosis (31.4%), peptic ulcers (21.5%), asthma (7%), and hypertension (4.5%).

Table 4.1: Characteristics of the respondents

Variable	Kampala (Urban) n=456 (58%)	Iganga/Mayuge (Rural) n=326 (42%)	Total, N=782
Age: Median (Min-Max)	25 (1-78)	17 (1-73)	22 (1-78)
Age groups			
0-4	49 (38.0)	80 (62.0)	129
5-10	64 (56.6)	49 (43.4)	113
11-18	29 (35.4)	53 (64.6)	82
19-29	145 (63.9)	82 (36.1)	227
30-39	97 (73.5)	35 (26.5)	132
40 and above	72 (72.7)	27 (27.3)	99
Gender			
Male	223 (68.8)	101(31.2)	324
Female	233 (50.8)	225 (49.1)	458
Pregnant women	9(36.0)	16(64.0)	25
Trimester			
First	4 (50.0)	4 (50.0)	8
Second	3 (33.3)	6 (66.7)	9
Third	2 (25.0)	6 (75.0)	8
Facility ownership			
Private	23 (100.0)	0 (0.0)	23
Public	433 (57.0)	326 (43.0)	759
Malaria diagnostic test done	272 (45.6)	325 (54.4)	597
Test results			
Negative	40 (97.6)	1(2.4)	41
Positive	232 (41.7)	324 (58.3)	556
Not done	184 (99.5)	1 (0.5)	185
Anti-malarial drugs			
First line ACTs	441 (58.0)	320 (42.0)	761
Other anti-malarial	15 (71.4)	6 (28.6)	21
Presence of Co-morbidities	216 (64.7)	118 (35.3)	334
HIV/AIDS	72 (60.5)	47 (39.5)	119
Tuberculosis	79 (75.2)	26 (24.8)	105
Peptic ulcers	45 (62.5)	27 (37.5)	72
Asthma	19 (82.6)	4 (17.4)	23
Hypertension	1(6.7)	14 (93.3)	15

4.1.5 Utilization of antimalarials in pregnancy

Out of the 458 women in the study, 25 (5.5%) used an antimalarial during pregnancy, 21 of them used Artemether/Lumefantrine (84%). Eight pregnant women were in their first trimester and of those 3 were treated with injectable Artesunate and 5 with an oral ACT. Only 1 pregnant woman was treated with quinine in her sec3ond trimester, and 8 were treated with an ACT in the same trimester. The other pregnant women were treated with Artemether/Lumefantrine in their third trimester.

4.1.6 The burden of adverse drug reactions

Out of 782 patients who were followed up successfully, 22.5 percent (n=176) of patients developed adverse drug reactions subsequent to anti-malarial treatment. Table 4.2 shows the distribution of suspected ADRs by the antimalarial drugs given. Some patients reported more than one ADR and a total of 245 adverse drug reactions were reported as depicted in Figure 4.2.

The most commonly reported adverse drug reactions to antimalarials were body weakness (n=58), headache (n=31), dizziness (n=27), vomiting (n=20), abdominal pain (n=17), loss of appetite (n=15), cough (n=10), diarrhea (n=9), nausea (n=9), skin and body itching (n=7), and others (n=42). Other reported adverse reactions included cold, drowsiness, skin rash, high temperature, joint pain, backache, chest pain, convulsion, insomnia, oral sores, bitter taste in the mouth, body pain, chills, diaphoresis, flu, heartburn, palpitations, stomach gas, and yellowish urine, accounting for 17.1 percent. Figure 4.3 shows the trend of adverse events reported on each day of follow up.

The SOC distribution of the reported ADRs according to MedDRA were the gastrointestinal disorders (30.6%), musculoskeletal, and connective tissue disorders (26.9%), the nervous system disorders (26.5%), skin and subcutaneous tissue disorders (5.7%), respiratory, thoracic and mediastinal disorders (4.1%), and the rest accounting for up to 6%. All the ICSRs were assessed for causality according to the Naranjo Algorithm. Twelve ICSRs were classified as doubtful, 209 reports as possibly related and 24 as probably related to the antimalarial treatment.

Table 4. 2: Antimalarial drugs and the respective ADRs reported

Drug name	Number of patients	Number of patients reporting at least one suspected ADR
ALU	761	174 (22.9%)
ASAQ	11	2 (18.2%%)
DHAPQ	3	0 (0%)
Others	7	0 (0%)
Total	**782**	**176** (22.5%)

Figure 4.2: Commonly reported ADRs

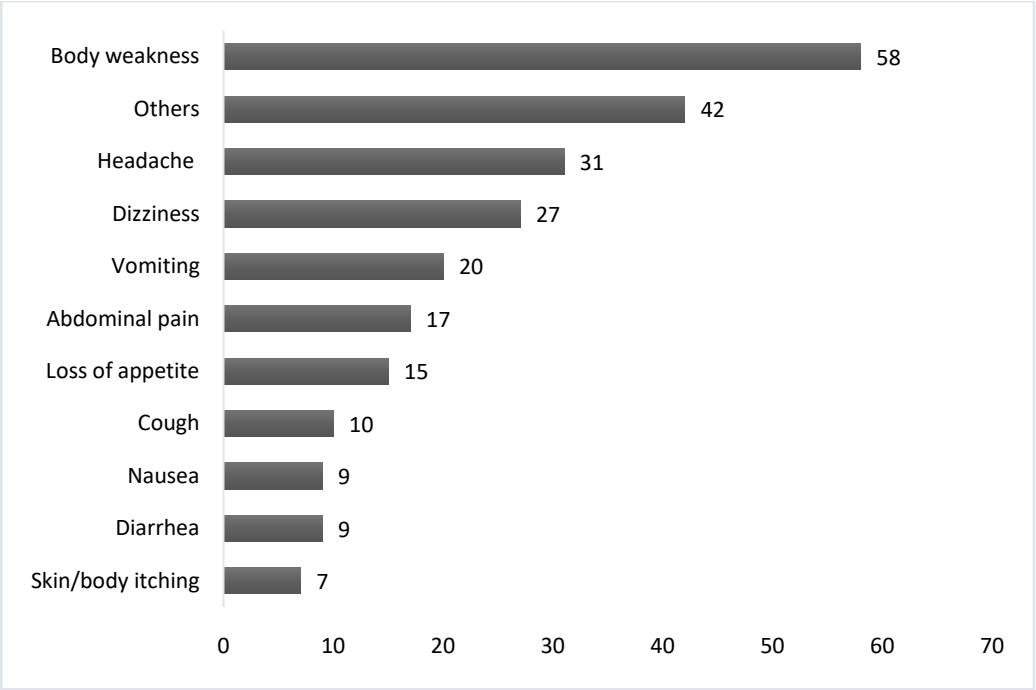
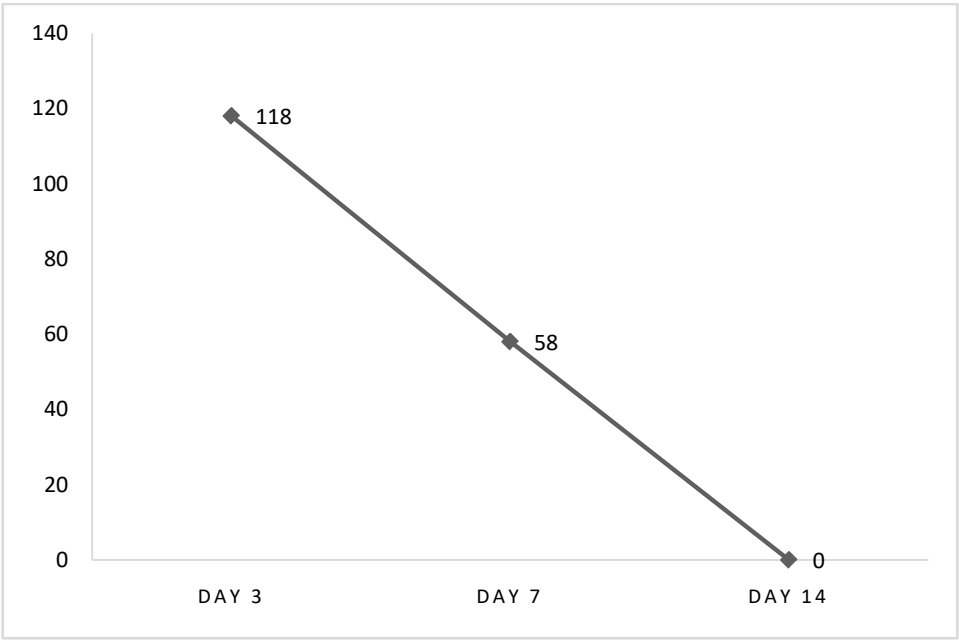


Figure 4.3: Number of reported adverse events on follow-up days



4.1.7 The risk factors for developing an ADR after taking an antimalarial treatment

The findings were subjected to multinomial logistic regressions for potential risk factors for developing ADR after taking an antimalarial drug. From the results presented in Table 4.3, gender was statistically significant with women at a higher risk of developing adverse drug reactions than men, (OR=1.8, CI: 1.1-2.9). Patients from the Kampala area were found to be at a higher risk of developing ADRs than those from Iganga/Mayuge, (OR=9.9, CI: 5.4-17.9).Patients who had comorbidities were 7 times more likely to develop adverse reactions than those without, (OR=7.4, CI: 4.4-12.3).

Table 4.3: Analysis of the determinants of developing an ADR after taking an antimalarial

Variables	Total number of patients (%)	Unadjusted OR	95% CI	P-value	Adjusted OR	95% CI	P-value
Total	782						
Age groups							
0-18	324 (41.4)	1.0	-	-	-	-	-
19 and above	458 (58.6)	1.9	1.3-2.8	0.001	1.5	0.9-2.5	0.09
Gender							
Male	324 (41.4)	1.0	-	-			
Female	458 (58.6)	1.1	0.7-1.4	0.87	1.8	1.1-2.9	0.03
Facility type							
Public	759 (93.2)	1.0	-	-			
Private	23 (2.9)	1.2	0.5-3.2	0.68	2.117	0.6-7.3	0.24
Residence							
Iganga/Mayuge	456 (58.3)	1.0	-	-			
Kampala	326 (41.7)	7.1	4.4-11.3	0.001	9.9	5.4-17.9	0.001
Diagnostic test results							
Negative	41 (5.2)	1.0	-	-	-	-	-
Positive	556 (71.1)	1.7	0.8-3.5	0.13	1.5	0.6-3.4	0.36
No test done	185 (23.7)	1.3	0.03-2.9	0.42	3.8	1.7-6.2	0.21
Antimalarial drugs							
Other antimalarials	21 (2.7)	1.0					
First line ACTs	761 (97.3)	1.8	0.5-6.1	0.37	2.4	0.4-14.3	0.32
Comorbidities							
No	448 (57.3)	1.0	-	-	-	-	-
Yes	334 (42.7)	8.6	5.7-12.9	0.001	7.4	4.4-12.3	0.001

4.1.8 Determinants of developing an ADR after taking any medicine within the past 14 days

Patients were asked if they had taken any medicine in the 14 days prior to this visit to the drug outlet. A multinomial logistic regression analysis was carried out to assess the determinants of developing an ADR after taking any medicine within the past 14 days. It was found that urban residents were 2.5 times more likely to develop adverse reactions than those from the rural area, (OR=2.5, CI: 1.38-4.54) as shown in Table 4.4.

Table 4.4: Determinants of developing an ADR after taking any medicine within the past 14 days

Variables	Number of observations (%)	Unadjusted OR	95% CI	P value	Adjusted OR	95% CI	P value
Total	782						
Age groups (yrs)							
19 and above	458 (58.6)	1.00	-	-	-	-	-
0-18	324 (41.4)	1.04	0.63-1.70	0.88	1.34	0.80-2.24	0.27
Gender							
Male	324 (41.4)	1.00	-	-			
Female	458 (58.6)	1.03	0.63-1.69	0.91	1.19	0.72-1.99	0.48
Facility type							
Public	759 (93.2)	1.00	-	-			
Private	23 (2.9)	2.92	1.05-8.11	0.40	2.19	0.77-6.19	0.14
Residence							
Iganga/Mayuge	456 (58.3)	1.00	-	-			
Kampala	326 (41.7)	2.44	1.43-4.31	0.001	2.50	1.38-4.54	0.001
Comorbidities							
No	448 (57.3)	1.00	-	-	-	-	-
Yes	334 (42.7)	1.4	0.9-2.3	0.16	1.32	0.81-2.17	0.28

4.1.9 Preventability of the ADRs

The criteria for preventability assessment according to the P-method was applied to all suspected ADRs that were possibly and probably related to the antimalarials. The proportion of the ADRs that could have been prevented was found to be 3 percent (7/233) these cases are listed in Table 4.5 below. All 7 errors were due to inappropriate doses given to patients and inadvertent practices. Among these errors, 3 of them were of patients who had been given intravenous Artesunate which is recommended for severe malaria according to Uganda treatment guidelines. On the other hand, the patients had been given less dose than is recommended in the summary product characteristics. The other four errors were children given overdose of Artemether-Lumefantrine disproportionate to their weight as prescribed in the same treatment guidelines.

Table 4.5: List of the medication errors identified

Initials	Age (yrs)	Wt. (kg)	Daily Dose of ACT given	Total Dose given (TD)	Recommended dose of ACT	Total recommended dose (TR)	Absolute DifferenceTD-TR (% dosage difference from recommended)
NR	21	53.0	120 mg intravenous Artesunate	120mg	127.2 mg intravenous Artesunate (2.4 mg/Kg)	127.2 mg	7.2 mg intravenous Artesunate (6% less)
KF	25	55.0	120 mg intravenous Artesunate	120mg	132.0 mg intravenous Artesunate (2.4 mg/Kg)	132.0 mg	12.0 mg intravenous Artesunate(9% less)
MF	24	60.0	120 mg intravenous Artesunate	120 mg	144.0 mg intravenous Artesunate (2.4 mg/Kg)	144.0 mg	24 mg intravenous Artesunate (17% less)
AM	06	20.0	3 tablets twice daily (60mg Artemether/ 360mg Lumefantrine)	360mg Artemether/ 2160 mg Lumefantrine	2 tablets twice daily (wt 15-24kg, 3-7 yrs)	240mg Artemether/ 1440mg Lumefantrine	120mg Artemether/720 mg Lumefantrine (50% more)
NRH	03	14.2	2 tablets twice daily (40mg Artemether/ 240mg Lumefantrine)	240mg Artemether/ 1440mg Lumefantrine	1 tablet twice daily (wt 5-14kg, 4 mths -3 yrs)	120mg Artemether/ 720mg Lumefantrine	120mg Artemether/720 mg Lumefantrine (100% more)
NF	06	19.0	3 tablets twice daily (60mg	360mg Artemether/	2 tablets twice daily (wt 15-24kg,	240mg Artemether/1 440mg	120mg Artemether/720 mg

Initials	Age (yrs)	Wt. (kg)	Daily Dose of ACT given	Total Dose given (TD)	Recommended dose of ACT	Total recommended dose (TR)	Absolute DifferenceTD-TR (% dosage difference from recommended)
			Artemether/ 360mg Lumefantrine)	2160 mg Lumefantrine	3-7 yrs)	Lumefantrine	Lumefantrine (50% more)
MV	09	27.0	2 tablets twice daily (40mg Artemether/ 240mg Lumefantrine)	240mg Artemether/ 1440mg Lumefantrine	3 tablets twice daily (wt 25-34kg, 7-12 yrs)	360mg Artemether/ 2160 mg Lumefantrine	120mg Artemether/720 mg Lumefantrine (50% less)

4.1.10 Discussion

The burden of suspected adverse drug reactions following exposure to anti-malarial treatment of almost one in every four patients taking anti-malarial drugs is high. A Ugandan study established the burden of ADRs in hospital setting[24], however this is the first study to document the burden of ADRs to anti-malarial drugs in the community setting with an active follow-up methodology. Artemisinin-based combination therapies for uncomplicated malaria are available at the community level and this study was set to understand the issues around the implementation of this policy.

Majority of the patients were prescribed Artemether/Lumefantrine which is administered at home for three days. Giving community members and patients the opportunity to participate in their own healthcare by reporting suspected adverse drug reactions is an important step in building trust in the country's health system. Pharmacovigilance in community settings introduced a platform to identify and mitigate ADRs. The risk factors associated with developing adverse dug reaction after taking antimalarial drugs were highlighted as gender, area of residence, and comorbidities.

The most commonly reported reactions in our study were general body weakness, headache, dizziness, vomiting, abdominal pain, and loss of appetite among others. The burden reported from other ACT safety studies was up to 5 percent for clinical trials and post-marketing studies [(25-29)]. The reported reactions to the most commonly used drug (AL) were of a similar type to those in the summary product characteristics [(25, 26, 29)]. Post-marketing studies done in other parts of Africa also revealed a similar pattern of the most commonly reported ADRs [(30, 31)].

The Ugandan ADR reports for AL substance, including instances where AL is reported as concomitant medication in Vigilyze exhibits a different pattern of more than 50 percent skin and subcutaneous disorders. Our study revealed that the most affected system organ classes were the gastro-intestinal, the musculo-skeletal and connective tissue and the nervous system. The Vigilyze reports are mainly from healthcare professionals while our study had direct contact with patients. These results emphasize the need to establish a system for direct patient reporting of suspected adverse drug reactions.

Women had an 80 percent higher risk of developing ADRs than men similar to other studies that reported a greater risk of between 50 percent and 70 percent for females [31-34]. The higher risk is possibly due to the innate biological, physiological, immunological, pharmacogenetics, pharmacokinetic, and pharmaco-dynamic differences between the two sexes [35-37]. An alternative explanation could be that women have had a lower inclusion rate in clinical trials, yet this is the only data available to compare with in post-marketing studies.

The higher risk for women could also be explained by the generally higher compliance level to healthcare resulting in a corresponding higher level of reporting adverse reactions much earlier and much more than men. Gender-related differences in the use of medicines also a likely contributor to the ADR risk profile for women given that they use oral contraceptives, iron, and other supplements during pregnancy, hormones and other products for menopausal women. Medicines are given even during the first trimester of pregnancy with less caution than is required.

In this study we found that 8 out of 25 self-reported pregnant women received ACTs in their first trimester when all medicines must be avoided. This finding means that there should be more monitoring of ADRs for women and more sensitization about these issues should be done. Many more women could be taking other drugs during their first trimester and more research in drug utilization is needed. Registries should be established to study the long-term effect of the ACTs on babies in question when they are born. A better understanding of the sex-related differences and the mechanism of how these affect drug response is needed so as to optimize drug therapy in both men and women.

Our study found that patients in urban areas were more likely to report ADRs to antimalarial treatment than those in rural areas. This is possibly because the urban population is more enlightened, have more access to information, better health infrastructure, and more experienced health workers, which makes it easier to detect, identify and report suspected ADRs than in rural areas. Other studies have also found that a difference in health seeking behaviour between urban and rural populations where urban households are more likely to consult, to be admitted to hospital, to report illness, and spend relatively more on healthcare seems to increase the burden of ADRs in urban settings[38].

According to the 2014 national census report, the bulk of Uganda's population lives in the rural areas such as Iganga/Mayuge and it is mainly composed of women[17]. The literacy rate of rural women (63%) is much lower than that of their urban counterparts (84%).The urban population reported more comorbidities than those from rural areas. A similar pattern in the rural-urban divide of private and public health facilities has been highlighted by other studies [37-41, 43]. This has policy implications for access to medicines because the urban population is about one fifth of Uganda's population yet it has 80 percent of private health facilities[42].

There is a need for a redistribution of health service delivery and re-equipment of private sector health facilities to provide better services to the rural areas. A countrywide sensitization programme for pharmacovigilance would be a useful tool to aid this re-distribution and improved interaction with the healthcare system. However, the pharmacovigilance messages must be customized to the rural setting so as to achieve the best results.

The study found that patients with comorbidities were more likely to report an adverse reaction than those without. A study from Nigeria indicated that the patients with comorbidity were 3 times more likely to have ADRs than those without[44]. The difference in the magnitude of the risk could be due to the differences in the case-control study design they used and also the fact that our study evaluated treatment of a single malaria episode with comorbidities. The Nigerian study looked retrospectively at ACT safety data that had been collected in a large cohort of patients over a long period of time.

Comorbidity increases the risk to ADRs, as multiple diseases often mean more medicines used. However, this increased use is also riddled with polypharmacy. Various studies have found that HIV increases the risk of malaria infection and clinical malaria in adults, especially in those with advanced immunosuppression [45,46]. In our study, the comorbidities reported were HIV/AIDS, tuberculosis, peptic ulcers, asthma and hypertension. Some studies have suggested that the interactions of all antiretrovirals with Artemether-Lumefantrine may require higher doses for HIV and possibly tuberculosis patients [46-51]. However, this effect was outside the scope of this study. The importance of this finding is that healthcare providers must closely monitor patients with comorbidity so as to optimize their therapy and prevent adverse reactions.

The proportion of medication errors found in our study was 3 percent of all possible ADRs. All the errors identified were due to dosage. This finding was lower than 11 percent found in Morocco[52]. The explanation for such a low level of error could be that in an outpatient or community setting, other types of errors are difficult to identify given that even the health worker suspicion index for disease is low.

The culture of documenting patient history and all that happens during the course of treatment is a challenge in Uganda, more so in an outpatient setting. There are

many missed opportunities to capture medication errors as practitioners fear to implicate themselves as some Ugandan researchers have established[53]. In 3 cases, there was underdosing for the intravenous Artesunate, a practice which could potentially contribute to anti-microbial drug resistance.

The magnitude of this practice is not clear in other parts of the country. It is important to note that the practice of giving injectable Artesunate for uncomplicated malaria is not recommended by the guidelines. Four of the cases were overdosed up to twice the recommended dose for AL tablets. The extra medication given to the four children identified in this study could have treated up to 3 children with similar age and weight. This has additional implications for cost savings for the national malaria control programme, if for every 4 doses of tablets for children, up to 7 children could be treated. Drug utilization studies ought to be conducted to assess the actual and potential cost savings of current treatment practices for children in Uganda. Policies and procedures need to be developed to detect and prevent error in Ugandan health facilities and drug outlets.

This study had limitations. The 7 percent rate of loss to follow-up was slightly more than expected, however it was not such a big loss considering that the study was a form of active surveillance of malaria patients in the community. Most of the patients preferred and were followed up on phone. Secondly, during filling in of the pre-treatment forms, patients were asked about their medication history for the past 14 days which could have introduced some recall-bias. Though the interviewers were trained to probe for information on concomitant medication, there seems to have been an under-declaration on herbal medication being used especially in rural communities. Thirdly, there were few private healthcare facilities because many of them that were included in the study had a lower patient load. In fact, we did not interview any patients attending private health facilities in the rural areas.

It is also important to note that a few of the private health facilities were hesitant to participate in the study and this could have introduced some bias but these cases were minimal. Limitations in sample size thus hampered a more stratified analysis according to facility types. The results may only be generalizable to areas with similar distribution of private facilities and operational capabilities.

Another limitation related to sample size was pregnancy. Since this was an active follow-up study, the method of identification was self-reports and this could have led to either an under-estimate or over-estimate of its effect on developing an ADR. However, this could not be ascertained due to the small numbers identified. Furthermore, the classification of Iganga/Mayuge as a rural area may be a bit misleading as several studies have been conducted in the health demographic surveillance site as was evidenced by the lower rate (4%) of patients lost to follow up compared to the Kampala region (8%). The results of this study need to be generalized with caution in this respect.

4.1.11 Conclusion

Artemisinin-based combination therapies are still highly effective in the treatment of uncomplicated malaria, however the concerns of safety and tolerability seem to be increasing with more experience in the general population.[54] The burden of one ADR for every four patients taking ACTs for uncomplicated malaria is high. The pattern of the ADRs reported is also different from what is in the current national pharmacovigilance database entered by healthcare professionals.

In this study, women were more predisposed to developing ADRs as well as patients with other underlying disease conditions. These special cases need to be studied further so that appropriate steps can be taken to protect them. Another area that needs to be considered in optimizing therapy to the majority of Ugandans is the treatment seeking behavior of urban versus rural dwellers. Also looking at the types of medication errors that have been identified, future studies should investigate emerging drug resistance and its risk-factors. More areas for research include drug utilization and cost analysis studies for pediatric drugs. The policy and practices of malaria treatment should be reviewed so as to identify areas that can be strengthened.

Finally, this study has demonstrated that active surveillance of patients in the community can be done without any major loss to follow-up and the methods used in this study are less resource demanding as compared to cohort event monitoring (CEM) and post-registration clinical trials. It will provide important lessons for active monitoring of treatment in settings with limited resources.

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Disclosure

Helen Byomire Ndagije, Victoria Nambasa, Leonard Manirakiza, Donna Kusemererwa, Dan Kajungu, Niko Speybroeck and Sten Olsson have no conflicts of interest that are directly relevant to the content of this study.

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4.2 The effect of community dialogues and sensitization on patient reporting of adverse events in rural Uganda: Uncontrolled before-after study

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Helen Byomire Ndagije,[1*] Leonard Manirakiza,[1] Dan Kajungu,[2] Edward Galiwango,[2] Donna Kusemererwa,[1] Sten Olsson,[3] Anne Spinewine,[4] Niko Speybroeck.[4]

[1] *National Pharmacovigilance Centre, National Drug Authority, Kampala, Uganda*

[2] *Makerere University Centre for Health and Population Research, Iganga, Uganda*

[3] *Sten Olsson Pharmacovigilance Consulting, Uppsala, Sweden*

[4] *Institute of Health and Society (IRSS), Université Catholique de Louvain, Brussels, Belgium*

Abstract

Background: Patients experiencing adverse drug events (ADEs) in many developing countries are in the best position to report these events to the authorities but need to be empowered to do so**.** Systematic evaluation of community engagement and patient support especially in rural areas would provide evidence for a program to monitor potential harm from medicines. The aim of this study was to assess the effects of a community dialogue and sensitization (CDS) program on the knowledge, attitude, and practices of community members for reporting ADEs.

Methods: This an uncontrolled before-after study was conducted in two eastern Uganda districts between September 2016 and August 2017.

Results: After implementation of the community dialogue and sensitization (CDS) program, there was an overall 20 percent (95% CI:16% to 25%) increase in knowledge about ADEs in the community compared to before the program began. Awareness levels increased by 50 percent (95% CI: 37% to 63%) among those with little or no education and by 41 percent (95% CI: 31% to 52%) among younger people (15-24 years). Furthermore, 5 percent (95% CI: 3% to 7%) more respondents recognized the need for reporting ADEs compared to before the program. Finally, there was a significant increase of 115 percent (95% CI:137% to

217%) in respondent recognition and reporting of ADEs compared to the beginning of the CDS program. Overall, this community found the CDS program acceptable and proposed aspects that could be improved for future use.

Conclusion: Our evaluation showed that the CDS program increased knowledge and improved attitudes by catalyzing discussions among community members and healthcare professionals on health issues and monitoring safety of medicines compared to before the program. Successful implementation of the program depends on holistic health systems strengthening and adaptation to the community's way of life.

Key words: Patient adverse drug event reporting, community dialogue and sensitization, rural health setting, before-after.

4.2.1 Introduction

Globally, adverse drug reactions account for up to 18 percent of hospital deaths [1-5]. An adverse drug event (ADE) is defined as any negative or harmful occurrence that takes place during treatment that may or may not be associated with a medicine [6]. Uganda predominantly uses spontaneous reporting of suspected ADEs by healthcare professionals to monitor the safety of medicines [7].

While Ugandan pharmacovigilance regulations from 2014 require healthcare professionals to report ADEs [6], the grossly under-resourced health sector makes effective reporting difficult [8]. A recent study reported an incidence of 25 percent of hospital-acquired suspected ADEs among inpatients in Uganda [9]. Antibiotics and antimalarials are the most commonly implicated drugs in community-acquired ADEs [10]. With increased access and use of medicines in the community, it is becoming increasingly important to collect more safety information by involving patients directly.

Community health extension workers (CHEWs) have minimized the role of healthcare professionals in the delivery of healthcare in the community [11, 12]. Healthcare professionals have insufficient knowledge of existing ADE reporting systems [13]. As ADE reporting is important to improving healthcare delivery, the National Pharmacovigilance Centre (NPC) intends to implement a program that encourages community members to directly report possible ADEs and other drug related events.

Community dialogue and sensitization (CDS), is a program designed to stimulate community support and engagement in improving health-seeking behaviour. This program builds on existing community-based structures using regular dialogues and sensitization sessions through exploring relevant health topics, identifying issues and using this information to plan improved health service delivery.

A community dialogue and sensitization (CDS) program was adopted from a similar approach in some other African countries [14]. The program added a sensitization campaign using radio messages, posters and brochures to raise drug safety awareness, encourage dialogue, and involve the community in designing pertinent solutions.

This approach involved a participatory communication process of sharing information through existing community-based structures. It was aimed at enabling communities to make informed choices and to take individual and collective action. This paper assesses the impact of a CDS program on the knowledge, attitudes, and practices (KAPs) of community members for reporting ADEs in two eastern Uganda districts.

4.2.2 Materials and methods

Study design

This uncontrolled before-after study was conducted between September 2016 and August 2017 at the Iganga/Mayuge Health Demographic Surveillance Site (IMHDSS) of Uganda. Prior to the CDS program in September 2016 and the end-line survey in July 2017, we conducted a representative, cross-sectional household baseline survey.

Setting

The CDS program was implemented in two predominantly rural districts of Iganga and Mayuge in eastern Uganda. The NPC and Makerere University Centre for Health and Population Research (MUCHAP) jointly developed the CDS toolkit. It included a facilitator guide-book with ten steps, key talking points, pictorial posters, and a monitoring and feedback tool. Tools and images were pre-tested with the target audience before finalizing the toolkit. The CDS program included several components (see Table 4.6) conducted between December 2016 and April 2017, a period of four months.

Interviews were carried out by local field researchers using a pre-tested, structured and validated questionnaire translated into the local language (Lusoga) using established guidelines [15]. Field researchers and supervisors attended a two-day training course covering data collection, field procedures, and interview techniques.

Field supervisors received an additional day of training focusing on supervision of field teams, as well as sampling procedures. Following the pilot study, a half-day training session was conducted to discuss challenges identified during pre-testing. Training materials were prepared by MUCHAP and the National Drug Authority (NDA) while MUCHAP which was responsible for coordination and supervision of field work conducted the training.

Table 4.6: Multiple program interventions that were used to improve patient reporting

Program Components	Description	Beneficiaries		Deliverers
		Individual	Others	
Community dialogue meetings	**Mobilization:** The team of CHEW & MUCHAP information officers enlisted the support of district health offices and the local council leaders. The LC provided access to the community. Public announcements about the CDS were made in churches, mosques, village meetings & women groups a day prior to the meeting. **Program activities:** The CHEW &MUCHAP information officers conducted the CDS using the toolkit containing the facilitator's 10-step process, ADEs pictorial posters and brochures in Lusoga, the local, language. Forty CDS sessions were conducted between January to April 2017. **Reach:** 658 participants (139 men, 519 women).	Primary household member in charge of health care decisions,	Community members Community leaders	CHEW MUCHAP information officer
Radio messages	**Messages:** Radio spot messages aimed at raising community awareness were aired 3 times a day (8am, 1pm & 9pm) for three days in a week (Monday, Wednesday & Friday). **Period of airing:** January to April 2017. The messages were developed by NDA & MUCHAP.	Patients and care-givers in the community	Community members, district, religious & village leaders, private &public health service providers	3 radio stations NBS FM, R FM & Safari FM covering Iganga and Mayuge districts
Focus Group discussions	FGDs in public health facilities and FGDs, which included health workers and some	Community members	Private & public health care	MUCHAP information

PART 4: PHARMACOVIGILANCE SYSTEM STRENGTHENING

Program Components	Description	Beneficiaries		Deliverers
		Individual	Others	
	community members.		providers,	officer
Brochures	Distributed 2,000 brochures in Lusoga to participants in their households and communities with information about ADEs and encouraged reporting of suspected ADEs during the HDSS routine data collection by field assistants.	Household members	Community members	MUCHAP field assistants
ADEs posters	Distributed 500 posters to private and public health facilities encouraging ADE reporting with some guidelines of how and where to report them.	Health workers	Community members Private & public health facilities	MUCHAP staff
ADEs reporting forms	Distribution of 70 booklets of 25 ADE carbonated reporting forms was accompanied by sensitization of health workers about pharmacovigilance.	Health workers in Iganga &Mayuge	Health workers beyond implementation districts	MUCHAP staff NDA staff
Advocacy	An official launch of the CDS approach to create more awareness about the well-being of the community and the importance of ADEs reporting. Posters and brochures were also distributed, 16th December 2016. Courtesy call to the district health office by NDA officials were made.	Not applicable	District health authorities Community leaders	NDA staff MUCHAP staff Jounalists

Note: CHEW=Community Health Extension Worker; MUCHAP= Makerere University Centre for Health and Population Research; ADE=Adverse Drug Event, NDA=National Drug Authority, CDS= Community Dialogue and Sensitization; LC=Local Council.

Participants

Sampling was single-stage and conducted at the household level. In each of the 65 villages in the IMHDSS surveillance area, the MUCHAP study team sampled an equal number of households using a simple random sampling approach with the help of community leaders. A household was defined as a group of people who routinely lived and ate together. One person per selected household was chosen and interviewed on the basis of their ability to answer questions on their household's health seeking behaviour.

Community members were interviewed using the community members' questionnaire (S1 File). All community-based health facilities in the program area were included in the survey. At least two healthcare professionals from each health facility were randomly selected and interviewed using a specific healthcare professionals' questionnaire (S2 File). Health facilities, both privately and publicly owned, included hospitals, Health Centre VI-II, pharmacies, drug shops and shops that sell drugs alongside other merchandise.

Variables

The primary outcomes of this study included participant KAPs towards ADEs reporting before and after the CDS program. The secondary outcome of this study was to establish the acceptability of the CDS program and the best practices for community engagement. Acceptability was defined as the extent to which the program or its attributes were sufficiently tolerable to its users, as reflected in both program uptake and perceived quality.

Data sources

The percentage difference between respondents' KAPs towards ADE reporting before and after the CDS program was measured. Knowledge was measured based on responses to the question "Do drugs "cause" negative or side effects?" For respondents who answered "yes," their attitude towards reporting ADEs was measured by asking if they considered it necessary to report such events. To understand respondent practices, we asked if they would report any ADEs, if encountered.

Bias

Random sampling was used to ensure that all community members had equal chance of participating in the study to minimize recruitment bias. Research assistants also made efforts to interview the household head or the oldest member to minimize response bias.

Study size

The entire adult population of the study area was considered as the sampling domain, where all households were eligible for selection. A total sample size of 778 respondents for each survey was determined to allow for the calculation of risk difference before and after the program. Assuming a baseline proportion of $\rho = 0.5$ and testing at the 0.05 level, a sample size of 389 respondents for each survey was needed for 80 percent power to detect a change of at least 10 percent in the primary outcome [16]. Adjusting for confounders, no-response and design effect, the sample size was doubled.

Quantitative variables

In order to measure community members' KAPs towards reporting ADEs, the same questions were asked in baseline and end-line surveys. Furthermore, the percentage difference before and after the program assessed for significance using the difference in proportions method.

Qualitative variables

We conducted interviews with community members and healthcare professionals in the study area after community dialogue meetings and focus group discussions (FGDs).During these meetings, an exploratory research strategy was used to examine attributes of the CDS program that could foster or hinder its uptake within communities. FGDs sought to explore the general trends in communities with respect to CDS, whereas the interviews explored individual experiences.

The information was collected using semi-structured interview guidelines (S3 File). Each meeting lasted between one and two hours and all interviews were recorded, transcribed, and translated. Notes were inserted in relevant sections of the transcripts to clarify the context in which statements were made, as well as to clarify statements resulting from poor sound quality.

Statistical methods

Data entry was done using EpiData 3.1 (EpiData Association) software by ten trained data entry officers. All records were double entered to ensure accuracy. Data were transferred to STATA Version 12 (Stata Corp LP) for analysis. The relative percentage difference in the responses before and after the program were analyzed using the difference in proportions method. All comparisons were done at a 5 percent level of significance with 95 percent confidence intervals for the mean difference in responses before and after the program.

The qualitative data was transcribed, and transcripts were loaded into NVivo 12 for thematic content analysis. Researchers worked together in the same room to

discuss possible interpretations, meanings and the most accurate interpretation of derived quotations. Attention was paid to words, phrases and actions of participants that best represented the meaning of what they did or said.

4.2.3 Results

Description of survey respondents

There were 1,034 household adult members in the baseline survey and 827in the end-line survey. All recruited respondents consented to participate in the study. Overall, there was a large positive difference in the KAPs of respondents towards reporting ADEs before and after the CDS program. Table 4.7 summarizes survey respondent profiles in terms of age, education, religion and occupation.

Table 4.7: Social and demographic characteristics of study participants

	Before n (%) N=1034	**After n (%) N=827**	**Total population**
Age group			
15-24	163 (15.8)	137(16.6)	21,809 (43.0)
25-34	304 (29.4)	224(27.1)	11,691(23.1)
35-44	243 (23.5)	200(24.2)	7.560 (14.9)
45-54	145 (14.0)	138(16.7)	4,966 (9.8)
55-64	105 (10.2)	54(6.5)	2,390 (4.7)
65+	74 (7.2)	74(9.0)	2,270 (4.5)
Education			
None	147 (14.2)	90(10.9)	3,279 (6.5)
Primary	532 (51.5)	422(51.0)	28,592 (56.4)
Secondary	310 (29.9)	265(32.0)	15,703 (31.0)
Tertiary	23 (2.2)	27(3.3)	2,048 (4.0)
University	22 (2.1)	23(2.8)	1,064 (2.1)
Religion			
Anglican	246 (23.8)	251(30.4)	16,431 (32.4)
Roman Catholic	93 (9.0)	82(9.9)	4,004 (7.9)
Pentecostal	103 (10.0)	103(12.5)	2,448 (4.8)
Muslim	573 (55.4)	380(46.0)	27,302 (53.9)
Other	19 (1.8)	10(1.2)	502 (1.0)

Knowledge about ADEs

After implementation of the CDS program, there was an overall 20percent (95% CI: 16% to 25%) increase in knowledge about ADEs in the community. Furthermore, there was a percentage change of 41.1 percent in the knowledge about ADEs among young people aged 15 to 24 years (95% CI:31%to52%) and 50 percent among the respondents with primary or no education (95% CI:37% - 63%) (Table 4.8).

The community demonstrated knowledge of what ADEs were as respondents shared their experiences about drugs. When a drug reaction occurred, they considered it the drug's normal mode of action, and thus did not take it seriously:

> *My child had convulsions and was treated with quinine injection but became crippled …, but I knew that it was how that medicine works* (FGD female, 34 – Buwaiswa).

Some respondents were able to differentiate between disease symptoms from the effects of the drug, based on how they felt before taking it and the long-term effects of the drug:

> *I used injection for family planning for two months and I started bleeding severely and felt like going to the radio to seek assistance. Family planning makes some people huge and others small in size. Personally, I was small but now am fat* (FGD female, 35 – Bukwaya).

However, some respondents could not differentiate between the drug and the disease:

> *I used Coartem and I felt worse than before. Too much headache and vomiting* (FGD male 22, Buwaiswa).

Table 4.8: Comparison of responses to the question of drugs causing ADEs before and after CDS program

Do drugs "cause" negative or side effects?												
	Yes				No				Don't know			
	Before (%)	After (%)	%diff.	95%CI	Before (%)	After (%)	% diff.	95 % CI	Before (%)	After (%)	% diff.	95%CI
Age group												
15-24	86 (52.8)	102 (74.5)	41.1	31.0 to 52.0	63 (38.7)	33(24.1)	-37.7	-57 to -19	14(8.6)	2(1.5)	-82.6	-122.0 to -43.0
25-34	173 (56.9)	151 (67.4)	18.5	10.0 to 27.0	110(36.2)	67(29.9)	-17.4	-32 to -3	21(6.9)	6(2.7)	-60.9	-82.0 to -39.0
35-44	145 (59.7)	137 (68.5)	14.7	6.0 to 24.0	84(34.6)	55(27.5)	-20.5	-36 to -5	14(5.8)	8(4.0)	-31.0	-50.0 to -12.0
45-54	79 (54.5)	87 (63.5)	16.5	5.0 to 28.0	51(35.2)	43(31.4)	-10.8	-30 to 8	15(10.3)	7(5.1)	-50.5	-76.0 to -25.0
55-64	54 (51.4)	37 (68.5)	33.3	18.0 to 49.0	37(35.2)	13(24.1)	-31.5	-59 to -4	14(13.3)	4(7.4)	-44.4	-80.0 to -8.0
65+	45 (60.8)	46 (62.2)	2.3	-13.0 to 18.0	26(35.1)	25(33.8)	-3.7	-30 to 22	3(4.1)	3(4.1)	0.0	-32.0 to 32.0
Education												
None	50 (34.0)	46 (51.1)	50.3	37.0 to 63.0	79(53.7)	37(41.1)	-23.5	-43 to -4	18 (12.2)	7(7.8)	-36.1	-0.6 to -0.1

Do drugs "cause" negative or side effects?												
	Yes				**No**				**Don't know**			
	Before (%)	**After (%)**	**%diff.**	**95%CI**	**Before (%)**	**After (%)**	**% diff.**	**95 % CI**	**Before (%)**	**After (%)**	**% diff.**	**95%CI**
Primary	294 (55.3)	273 (64.8)	17.2	11.0 to 23.0	191(35.9)	132(31.4)	-12.5	-23 to -2	47(8.8)	16(3.8)	-56.8	-72.0 to -42.0
Secondary	199 (64.2)	193 (72.8)	13.	6.0 to 21.0	95(30.6)	65(24.5)	-19.9	-34 to -6	16(5.2)	7(2.6)	-50.0	-68.0 to -32.0
Tertiary	19 (82.6)	25 (92.6)	121	-6.0 to 30.0	4(17.4)	2(7.4)	-57.5	-109 to -6	0(0.0)	0(0.0)	0.0	0.0
University	20 (90.9)	23(100)	10.0	-2.0 to 22.0	2(9.1)	0(0.0)	-100.0	-140 to -60	0(0.0)	0(0.0)	0.0	0.0
Religion												
Anglican	140 (56.9)	174 (69.3)	21.8	13.0 to 30.0	91(37)	69(27.5)	-25.7	-40 to -11	15(6.1)	8(3.2)	-47.5	-66.0 to -29.0
Catholic	59 (63.4)	56 (68.3)	7.7	-6.0 to 22.0	29(31.2)	23(28.0)	10.3	-35 to 15	5(5.4)	3(3.7)	-31.5	-62.0 to -1.0
Pentecostal	65 (63.1)	77 (74.8)	18.5	6.0 to 31.0	30(29.1)	25(24.3)	-16.5	-40 to 7	8(7.8)	1(1.0)	-87.2	-140.0to -34.0
Muslim	308 (53.8)	244 (64.2)	19.3	13.0 to	217(37.9)	118(31.1)	-17.9	-28 to -	48(8.4)	18(4.7)	-44.1	-58.0 to -

Do drugs "cause" negative or side effects?												
	Yes				**No**				**Don't know**			
	Before (%)	**After (%)**	**%diff.**	**95%CI**	**Before (%)**	**After (%)**	**% diff.**	**95 % CI**	**Before (%)**	**After (%)**	**% diff.**	**95%CI**
				26.0				7				30.0
Other	10 (52.6)	9 (90.0)	71.1	42.0 to 100.0	4(21.1)	1(10.0)	52.6	-124 to 19	5(26.3)	0(0.0)	-100.0	0.0
Overall	**582 (56.3)**	**560 (67.8)**	20.4	16.0 to 25.0	**371(35.9)**	**236(28.6)**	**-0.2**	**-28 to -13**	**81(7.8)**	**30(3.6)**	**-0.5**	-64.0 to -43.0

Note: ADE=Adverse Drug Event;DK=Don't Know; CI=Confidence Interval

Attitudes towards reporting ADEs

After implementation of the CDS program, there was an overall increase of 5 percent (95% CI: 3% to 7%) of respondents who considered reporting ADEs necessary. Table 4.9 presents differences in attitudes following the program based on socio demographic characteristics.

In some cases, respondents directly reported ADEs to CHEWs, upon experiencing an occurrence. They had a positive attitude towards reporting negative effects of a drug because they thought CHEWs would help and act on their report. For example, by changing their medication:

> *I tell them, when I use a drug and I see that I am not improving, I inform the health worker and he changes treatment* (FGD male, 33 – Bukwaya).

> *I went and reported to the basawo (doctors)about the medicine having burnt my skin and they changed my treatment* (FGD female, 28 – Busowobu).

On the other hand, some communities believed that CHEWs were too busy and had no time to attend to them. Community members trekked long distances from home to the health facility, spent the whole day there, and sometimes, drugs were out of stock. They felt CHEWs had not been responsive to reported ADEs. Furthermore, some respondents felt that possible side effects of a drug were not explained by the CHEWs before medicines were prescribed. Some claimed that the medicines they bought from pharmacies did not produce the same reaction as those from government hospitals. Thus, some people resorted to going directly to private drug shops and clinics instead of "wasting time" at a health facility to only receive a referral.

> *The health worker gave me the drug and he did not tell me that it might make me feel that way. He told me to swallow the tablets and that is what I did, but when I bought it from the pharmacy, it did not give me the effects that I got from what I received from the government hospital* (FGD female 36, Bukwaya).

Others had not reported these events to CHEWs as they considered the effects to be a result of the drug's "strength":

> *…I did not report to anyone because I thought it's because the drug was very strong* (FGD male 37, Buwaiswa).

Table 4.9: Comparison of study participant attitudes towards the need to report ADEs before and after CDS program[α]

Necessity to report ADEs				
Yes				
	Before (%)	**After (%)**	**% relative diff.**	**95%CI**
Age category				
15-24	144 (88.3)	133 (97.1)	10.0	4 to 16
25-34	288 (94.7)	214 (95.5)	0.8	-3 to 5
35-44	227 (93.4)	192 (96.0)	2.8	-1 to 7
45-54	133 (91.7)	134 (97.8)	6.7	2 to 12
55-64	95 (90.5)	52 (96.3)	6.4	-1 to 14
65+	67 (90.5)	73 (98.6)	9.0	2 to 16
Education				
None	127 (86.4)	80 (88.9)	2.9	-6 to 11
Primary	488 (91.7)	410 (97.4)	6.2	3 to 9
Secondary	294 (94.8)	259 (97.7)	3.1	0 to 6
Tertiary	23 (100.0)	27 (100)	0.0	-
University	22 (100)	22 (95.7)	-4.3	-13 to 4
Religion				
Anglican	225 (91.5)	248 (98.8)	8.0	4 to 12
Roman Catholic	90 (96.8)	80 (97.6)	0.8	-4 to 6
Pentecostal	97 (94.2)	98 (95.1)	1.0	-5 to 7
Muslim	525 (91.6)	362 (95.3)	4.0	1 to 7
Other	17 (89.5)	10 (100)	11.7	-2 to 26
Overall	**954 (92.3)**	**798 (96.6)**	**4.6**	**3 to 7**

[α]Details of those that answered "No" and "Don't know" are shown in S1 Table.

Respondent reporting of ADEs

The overall percentage difference in the number of respondents that reported having encountered or experienced an ADE was 115 percent (95% CI: 137 % to 217%). However, there are variations among socio-demographic groups. For example, there was a reduction among those who had attained a tertiary education level compared to other education levels after the intervention. Additionally, respondents who identified as Roman Catholic reported the highest percentage increase compared to those of other Christians (Table 4.10). On further probing, some members elaborated on their experiences:

> *I witnessed a woman who was in ART clinic. When she took drugs, the whole body was burnt out with blisters. The patient immediately reported the problem and she claimed that since she startedusing drugs, she never experienced such. I think that was the drug effect* (FGD male 40+, Busowobu).

One respondent explained how her hand had become paralyzed due to a family planning injection she was given at the clinic. Some participants admitted to taking more of a drug than was prescribed:

> *"I did not take the medicine as prescribed"* (FGD female 28, Busowobu).

Another respondent reported an eye defect that she had witnessed in her relative.

> *"[Relative] was given ARVs and Septrin tablets but got eye defect. The eye turned red and was not seeing properly"* (FGD female 35, Bukwaya).

Barriers to reporting

Respondents feared reporting ADEs and sympathized with the CHEWs who had issued the drug, they thought that the workers could possibly lose their jobs as a result.

> *"In case you report, health workers can lose their job which is not good because most of the times when you speak the truth, they ask you which doctor gave you the medication"* (FGD female 36, Bukwaya).

Others reported that CHEWs were too harsh and therefore feared reporting to them for fear of injury or harassment.

> *"Some health workers are harsh and I fear to be injured"* (FGD male 40, Busowobu).

> *"If I am given an under dose and there is no improvement, when I report health workers might harass me"* (FGD female 28, Bukwaya).

The other barrier to reporting such events was poverty. Some people who live far from the health facility might not have transport to take them to the facility:

> *"Sometimes, people don't have money to travel and take their complaints to the health facility"* (FGD female 45, Buwaiswa).

Furthermore, buying cheap drugs from illegal drug outlets in rural areas reduced confidence to report any ADEs.

Table 4.10:Comparison of respondents' having ever experienced ADEs by socio-demographic characteristics before and after CDSβ

	Yes			
Age group	**Before (%)**	**After (%)**	**% relative diff.**	**95%CI**
15-24	51(31.3)	43(43.0)	37.4	18 to 57
25-34	109(35.9)	61(42.1)	17.3	2 to 32
35-44	80(32.9)	61(47.3)	43.8	28 to 60
45-54	47(32.4)	43(46.7)	44.1	24 to 64
55-64	36(34.3)	13(35.1)	2.3	-28 to 32
65+	26(35.1)	16(36.4)	3.7	-26 to 34
Education				
Primary	180(33.8)	120(42.4)	25.4	14 to 37
Secondary	109(35.2)	73(40.1)	13.9	0 to 28
Tertiary	12(52.2)	8(40.0)	-23.4	-68 to 21
University	10(45.5)	13(65.0)	42.9	16 to 70
Religion				
Anglican	89(36.2)	66(38.6)	6.6	-9 to 22
Roman Catholic	23(24.7)	20(41.7)	68.8	41 to 96
Pentecostal	45(43.7)	32(46.4)	6.2	-16 to 29
Muslim	189(33)	115(45.6)	38.2	27 to 49
Other	3(15.8)	4(57.1)	261.4	195 to 328
Overall	349 (20.5)	237(44)	114.6	137 to 217

βDetails of those that answered "No" and "Don't know" are shown in S2 Table

Commonly reported ADEs

After the CDS program, there was a significant increase in the population who would consider reporting serious reactions (19%, 95% CI:16% to21%), reactions to newly introduced drugs (15%, 95% CI:11to18%), unexpected reactions (16%, 95% CI: 13% to 19%), and reactions due to herbal and conventional medicines taken together (20%, 95% CI: 16 to 24%) (S3 Table).When respondents ranked

potentially reportable ADEs, “serious reactions”were most commonly identified as being an ADE type compared to before the CDS program.

Acceptability of the CDS program on reporting ADEs

Community members appreciated the role of community dialogues in creating awareness of drug use and the potential effects on lives of the users.

> *“These meetings are good. It is through such meetings that community members can be aware of these effects and how to handle them”* (FGD female 28, Buwaiswa).

Community members showed willingness to participate in future community dialogues to learn more about drugs and their proper use. They requested that meetings be extended to the village level to include those who might not have transport to health facilities. They recommended more mobilization of participants through churches, mosques, and health facilities.

> *“Yes I would participate again because, I, for example, I did not know all that you have told us here. So, the health workers should be present as well. But please make it short next time”* (FGD female 39, Busowobu).

> *“I can participate again but you should consider holding these meeting in the communities as well like at the village level. Some people may not have transport to bring them at the health facility”* (FGD female 38, Bukwaya).

Some community members felt that it would be important to engage schools to deliver such messages to children, as they also need to be aware of drug-related effects:

> *“More to that, I think also the children need to know about these effects. I also suggest that you visit schools and talk to our children about these effects”* (FGD male 39, Bukwaya).

Community members also appreciated the use of community dialogues as a tool to improve or create relationships between patients and CHEWs. They believe that once the dialogues are held together with CHEWs, it would be easier for patients to report ADEs.

> *“…they help to build good relationship between patients and health workers. For example if we hold these meeting together with them, they cannot be harsh to us when we approach them.”* (FGD male 33, Bukwaya).

The communities also mentioned that these dialogues would help members appreciate the role of concerned authorities, such as the NDA:

"These meetings will help our communities to appreciate the role of organizations like NDA through educative meetings like this." (FGD male 42, Buwaiswa).

4.2.4 Recommendations

A patient-friendly environment

Community members suggested that CHEWs should change their attitude towards patients and be open and polite in their work. Thus, patients would be more willing to report any ADEs.

"Health workers should be polite and free with patients because when he becomes free with his patients, it makes it easy to report (FGD male 39, Busowobu).

Respondents also suggested that CHEWs should ask follow-up questions when patients return to the health facility to report any ADEs they had experienced after taking the drug. This can give the patient a chance to interact with CHEWs:

"We need to be asked when we come here because if the reaction was got some time back, you cannot tell it to the health worker" (FGD female 38, Busowobu).

Other respondents proposed a suggestion box at the health facility for reporting ADEs to enable patient report without revealing their identities to CHEWs:

"I think suggestion box should be brought at the facility so that the health workers does not see who has reported or not." (FGD female 27, Bukwaya).

Finally, community members suggested that CHEWs should be part of these community dialogues because the exposure would help them change their attitudes towards patients:

"The health workers should be part of these meetings as well. If they are around, they can also change their attitude." (FGD Female 36, Bukwaya)

Practical modes of information delivery

Community members suggested that information on ADEs be designed and delivered through dramatizationand skits, or played on videos. Information can include the process of taking medicine, developing ADEs, and then their reporting to respective channels. Members explained other programs that used storytelling techniques had a better turnout to the meetings.

> *"It can also be in form of drama activities. I mean if you can engage some people to play some skits about how these effects come up and how to report them, I think the whole process would be interesting"* (FGD female 32, Busowobu).

> *"There are some programs that have been coming to our communities especially for HIV and they have been playing skits and dramas to deliver the message to the members. I think you can also adopt the same technique since they are so interesting and members don't leave before it is over"* (FGD female 46, Buwaiswa).

> *"Others actually play them on videos. They come with projectors and play in the community gatherings and after the video, they interact with us trying to explain what the video was about"* (FGD female 28, Bukwaya).

More intense media engagement

In addition to community dialogues, community members also suggested the use of media in delivering information on medicine safety. They wanted more engaging radio programs as these would capture the attention of the audience more and engage listeners better through calling-ins and texting by use of short message service (SMS) on phone. The community also requested more literature, such as leaflets, in their local language.

> *"… it is good to air same information over the radios and televisions or some literature provided to community members in their local languages"* (FGD male 35, Buwaiswa).

4.2.5 Programmatic changes to community dialogues

Timing of dialogues

Community members suggested that there should be a day, and possibly a time, set aside for these dialogues to improve awareness of the sessions. The majority suggested Sunday afternoons between 4.00 or 5.00PM.

> *"We can hold them on Sunday in the afternoon around 4pm or 5pm"* (FGD male, 37 – Buwaiswa).

> *"Yes. But not every Sunday. You can choose like two Sundays in a month or every last Sunday of the month"* (FGD male 40, Bukwaya).

Duration of dialogues

Respondents suggested that dialogues should be short and precise to keep members interested and attentive. A maximum of one hour was suggested to allow the people go back to their daily chores afterwards.

> *"It would be so appropriate to shorten these meetings to allow us do other things, otherwise people will start running out before the meeting is done"* (FGD male 35, Bukwaya).

> *"They should not take too long. It should be shortened to around 1 hour or two hours maximum"* (FGD female 42, Bukwaya).

Frequency of dialogues

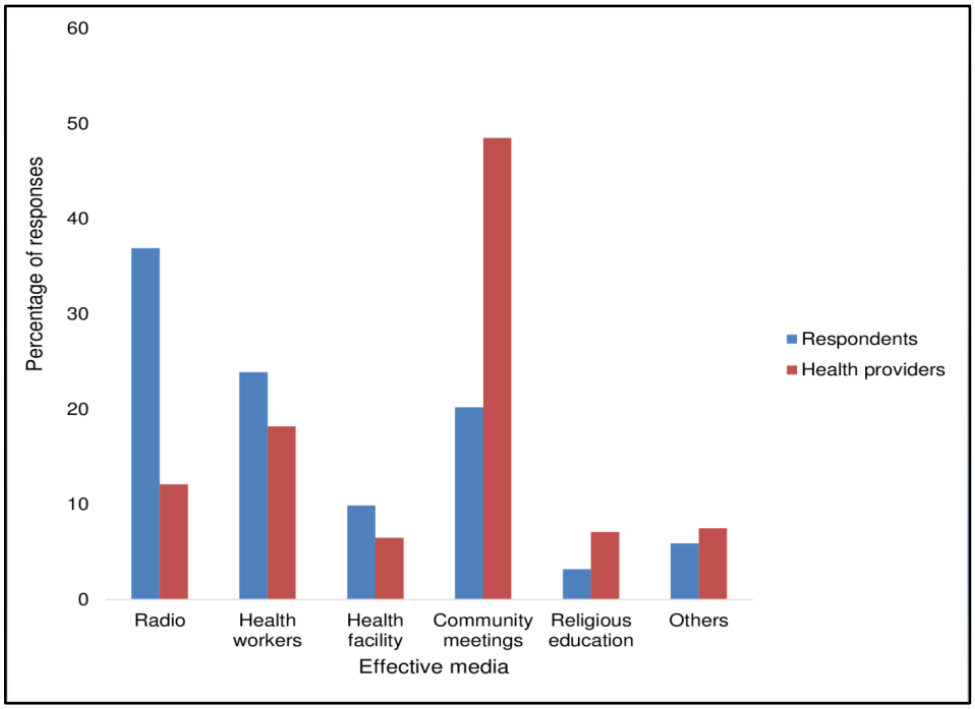
Community members appreciated the community dialogues and suggested routine sessions to stay informed.

> *"You should always come here and hold these meetings with us so that we can know more about these effects and we might even forget and return to our old ways"* (FGD male 39, Buwaiswa).

The best way to engage the community

Among respondents, the radio was reported as the best way to deliver messages for sensitizing community members to ADE reporting. In contrast, health professionals considered community meetings as the best method by which to reach the people. CHEWs and health facilities were considered to play an increasingly vital role in ADE sensitization, as perceived by both groups. Residents of the community were happy with the community dialogue meetings as a way of raising their awareness and as the best way to engage the community on ADEs (See Fig 4.4).

Figure 4.4 Best way to engage the community



4.2.6 Discussion

Community health and development work in settings with limited resources greatly benefit from program evaluations and programs developed to improve conditions in

local communities. There is a paucity of data evaluating such programs in published literature. This study, systematically investigated the merit and significance of efforts to raise community awareness of drug safety issues. Results show that the CDS program succeeded in increasing knowledge and attitudes towards reporting ADEs in rural communities like other evaluation studies of similar health programs [17-19].

Overall, the knowledge of ADEs increased in the community after the program. The program facilitators of familiar faces sparked critical thinking and open dialogue among participants. The extent to which facilitated community meetings can influence healthcare quality lies in the social capital that they raise. These meetings provided an opportunity for networking and essential practical and emotional support, leading to formulation of positive action plans and solidarity. Indeed, evaluation of a similar program in Mozambique also demonstrated an increase in community knowledge on health program interventions, despite lack of baseline data for comparison [20].

The respondent's attitudes towards reporting ADEs improved slightly after the CDS program. Community members who believed healthcare professionals were helpful were more likely to report any ADEs after the intervention. Moreover, health system factors and patient expectations of the health sector determined attitudes towards the reporting of such events. Possibly, respondent's positive attitudes towards the CDS program were borne out of the realization that an opportunity for discussing drug safety issues had been created.

The dialogues provided community members with an opportunity for improved understanding and a more active involvement in their own treatment as part of health service delivery. However, in some rural communities where patients spend long hours at government health facilities and often find drugs out of stock, health-seeking behaviors are poor and self-medicating is common [21].

Our study, found that some patients were shy to report any ADEs to the health facility when the medication had been bought from elsewhere, especially from drug shops or private clinics. Such factors contributed to a negative attitude to the CDS program. Great emphasis needs to be placed on patient education regarding drug safety issues, and a provision for direct patient reporting of such issues to the pharmacovigilance authorities, both locally and internationally to provide solutions to the community medicine safety issues. Our study was ran and assessed over a short period which could have affected the magnitude of attitude changes in comparison to similar program evaluations that have taken longer [22].

Regarding the practice of reporting ADEs, community members provided feedback on the best means by which information on drug safety issues could be communicated, as well as where they would feel most comfortable reporting. After the program, there was a relative increase in those who would consider reporting

different types of ADEs, such as serious reactions, reactions to newly introduced drugs, unexpected reactions, and those effects that occur due to herbal and conventional medications taken together. Considering the examples of ADEs given, members demonstrated their willingness to report safety issues should the CDS program be fully implemented. These findings point to an increased potential and intention of respondents to report, but may not necessarily translate into more reports following the program. Actual consumer reports made would have been a more accurate measure. In Uganda today, patients and consumers report ADEs, either indirectly through their healthcare professionals, or directly through the newly established online reporting system [23]. The positive value of direct patient reporting has also been observed in well-resourced countries [24].

This study had some limitations. Firstly, there was potential recruitment bias associated with a representative cross-sectional survey as the households and in some cases individuals from the IMHDSS sampled for the study before the program may have been different from those interviewed after the program. While it is true that community respondents could have had similar baseline information within the routine IMHDSS data collection parameters, this may have differed in the case for information on ADEs since this was the first time the topic was introduced in the area.

Secondly, the same questions were asked before and after the CDS program. Participants who were exposed to the questionnaire before and after the program could have caused response bias due to a tendency for participants under observation to give a response that they think is expected by the interviewer.

Thirdly, by design of the study, we got a snapshot of the community's views, however, the blend of quantitative and qualitative methods used enabled the study team to capture a holistic and contextual view of the CDS program on the reporting of ADEs and drug-related issues in rural communities.

Fourthly, changes in attitudes are a long-term measure, which the four-month program was too short to effectively assess. The four months of intervention coincided with the periodic data collection of IMHDSS which usually takes place biannually for three months. The intervention took a short period of four months due to logistical reasons. Ordinarily, the practice of reporting ADEs is measured by the completion of such reports. However, in this study, there was no actual reporting done. We, therefore, measured a "change in willingness to report" by community members. While members were willing to accept the program once rolled out, information on the process of rolling it out could be different during the implementation phase. Overall, these results are generalizable to similar settings with a homogeneous population.

The CDS program was widely accepted in the community. Community members benefited from the knowledge imparted about drug safety issues and appreciated

the role of pharmacovigilance authorities in promoting drug safety campaigns. Our study confirms that with well-designed effective communication and a conducive environment, the community can quickly learn new concepts. Similar results were found during the assessment of educational programs to improve attitudes of healthcare professionals, and thus, ADE reporting rates [25, 26].

During focus group discussions, respondents pointed out that improvements in patient-healthcare professional relations were pivotal in making the program acceptable to the rural community. The community members proposed more intense media engagements for mobilization, a patient-friendly environment, and a higher program coverage at the village level during program rollout. They requested that the message be dramatized. Furthermore, members proposed adjustments to the timing, duration and frequency of the community dialogue meetings, based on similar experiences from other program they had participate in [27]. An important finding from this study is that success of the CDS program cannot be separated from the performance and expectations of the healthcare system in general.

The adoption of the community dialogue toolkit made a number of assumptions. We assumed that the respondents knew the common diseases that affected the population across different age groups, as well as the treatment received. Other assumptions were that the respondents knew the different points of care in the community, were familiar with commonly experienced ADEs, and knew the reporting channels for any medicine safety issues. However, the respondents proved not to have as much knowledge as was assumed.

The CDS program had its own limitations. Community members feared victimization as a result of reporting any issues to healthcare professionals who prescribed the medications in the first place. They also feared that these healthcare professionals who frequently attend to their health needs might lose their jobs. The presence of these underlying fears, coupled with the absence of a system for directly reporting ADEs to the authorities, poses challenges for monitoring drug safety. Moreover, there is limited ability of community members to differentiate between ADEs and the progression of a disease. The implication of this, is that there should be more frequent interaction between patients and their healthcare professionals. If addressed, solutions to these issues could lead to increased knowledge of medicine safety in these rural communities.

A successful direct patient- or consumer-ADE reporting system should be accompanied by increased sensitization, delivered through multiple channels, such as radio messages, posters, and brochures to raise drug-safety awareness, encourage dialogue, and involve the community in designing pertinent solutions. It should also utilize reporting tools that are tailored to the level of literacy and understanding of rural communities, while offering effective feedback to those reporting about the ADEs.

4.2.7 Conclusion

In conclusion, the results of the current study show that the CDS program increased knowledge and attitudes towards reporting of ADEs. Despite having some prior knowledge that medicines have a potential to cause harm, the community showed signs of willingness to report the occurrence of ADEs through their healthcare professionals. This community expressed their readiness to accept the CDS program should it be rolled out and proposed adjustments for future implementation. In its current state, the CDS program was embraced as highly beneficial and could be adopted for direct patient or consumer reporting of ADEs in settings with limited resources.

A consideration for future research is the use of a control group in the evaluation of similar community programs, and the impact or long-term effects of the CDS program on the community. Further research is needed on direct patient-ADE reporting systems compared to the current indirect reporting through healthcare professionals; the cost effectiveness of various sensitization methods; and best practices for providing feedback to reporters in settings with limited resources.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Mildmay Uganda research and ethics committee (REC REF 0604-2017) and Uganda National Council for Science and Technology (HS 2247), the institution responsible for national research clearance in accordance with the World Medical Association Helsinki Declaration. Permission to conduct the study in the area was also obtained from NDA, the district administrations of Iganga and Mayuge, IMHDSS and MUCHAP. Written informed consent was obtained from the participants.

Consent to publication

Not applicable

Availability of data and material

The datasets generated and analyzed during the current study are available.

Author's contribution

Helen Byomire Ndagije (HBN) and Dan Kajungu (DK) designed the study. Donna Asiimwe Kusemererwa (DAK) made substantial contributions to conception, design of the study and acquisition of the data. Leonard Manirakiza (LM), DK, EG and HBN analysed and interpreted the data. LM was a major contributor in writing the

manuscript. Sten Olsson (SO), Anne Spinewine (AS), and Niko Speybroeck (NS) have made substantial contributions during the review of the manuscript. All authors read and approved the final manuscript.

Competing interests

HBN, LM, DK, Edward Galiwango, DAK, SO, AS, NS have no conflicts of interest that are directly relevant to the content of this study. This publication was supported by an agreement from National Drug Authority (NDA). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Drug Authority. The authors have declared that no competing interests exist. It is true that one author is employed by a commercial company, but this commercial affiliation does not alter our adherence to PLoS ONE policies on sharing data and materials.

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Supporting information

"S1 File. KAP study on adverse drug reactions – Household questionnaire". This was the questionnaire used to collect data about the households involved in the baseline and end-line surveys conducted before and after the implementation of community dialogues and sensitization.

"S2 File. Knowledge Attitudes and Practice (KAP) study on adverse drug reactions – Provider questionnaire". This questionnaire was used to collect data about the healthcare professionals in the community-based health facilities involved in the baseline and end-line surveys. At least two healthcare professionals from each health facility were randomly-selected.

"S3 File. FGD Interview Guide. Focus Group Discussion Guide". This set of questions guided the FGDs to probe for KAPs of the community and the attributes of CDS program for reporting adverse drug events that could either foster or hinder its uptake within communities.

"S1 Table. Comparison of study participants' attitude towards the need to report adverse drug events before and after the CDS program". Comparison of study participants' attitude towards the need to report adverse drug events before and after the CDS program including all responses to the question: "Is there a need to report adverse drug effects?"

"S2 Table. Comparison of reporting potential CDS. Comparison of respondents' having ever experienced ADEs by socio-demographic characteristics before and after the CDS program". A comparison of the potential to report adverse drug events in response to the question as to whether participants had ever experienced one before and after.

"S3 Table. Commonly reported ADEs". A comparison of the type of adverse events that the respondents reported before and after the CDS program.

4.3 Healthcare professionals' perspective can guide post-marketing surveillance of Artemisinin-based combination therapies in Uganda

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Helen Byomire Ndagije[1*], Ronald Kiguba[2], Leonard Manirakiza[1], Elijah Kirabira[1], Allan Sserwanga[1], Leah Nabirye[2], Jackson Mukonzo[2], Sten Olsson[3], Anne Spinewine[4], William D'Hoore[4], Niko Speybroeck[4].

[1]National Pharmacovigilance Centre, National Drug Authority, Kampala, Uganda

[2]Makerere University Department of Pharmacology and Therapeutics, Kampala, Uganda

[3] Pharmacovigilance Consulting, Uppsala, Sweden

[4]Institute of Health and Society (IRSS), Université catholique de Louvain, Brussels, Belgium

*Corresponding Author: Helen Byomire Ndagije <hndagije@nda.or.ug>

Abstract

Background

Efficient testing to identify poor quality Artemisinin-based combination therapies (ACTs) is important to optimize efforts to control and eliminate malaria. Healthcare professionals interact with both ACTs and malaria patients they treat and hence could observe, first-hand, suspect poor quality ACTs linked to poor malaria treatment outcomes and the factors associated with inappropriate use or treatment failure.

Methods:

We conducted a cross-sectional study of 685 HCP perspectives about the efficacy of ACTs between June and July 2018 at selected health facilities in Uganda. Medicine samples were obtained from the seven regions of Uganda and tested for quality using the Germany Pharma Health Fund™ minilabs.

Results

The average age of the 685 respondents was 30 (SD=7.4) years. There was an almost equal distribution between male and female respondents (51:49) respectively. Seventy percent (n=480) were diploma holders and the nurses contributed to half (49%, n=334) of the study population. Sixty one percent of the HCPs reported having ever encountered ACTs failures while treating uncomplicated malaria. Nineteen percent of HCPs thought that Dihydroartemisinin/Piperaquine gave the most satisfactory patient treatment outcomes while 80% HCPs that the Artemether/Lumefantrine gave the least satisfactory patient treatment outcomes possibly due to dosing schedule and pill burden. Healthcare professionals from the central region (OR=3.0, CI: 0.3-1.0; P=0.0001), Eastern region (OR=5.4, CI: 2.9-9.8; P=0.0001) and Northern region (OR=5.3, CI: 2.9-9.9; P=0.0001) had a higher chance of encountering ACT treatment failure in four weeks prior to the survey as compared to those from the western region. Healthcare professionals from private health facilities also had higher chances of encountering ACT treatment failures in past 4 weeks as compared to those from public health facilities (OR=2.7, CI: 1.7-3.9; P=0.0001). All 192 samples passed the quality screening tests. The random sample of 10% of all samples randomly obtained by the laboratory staff also passed the chemical content analysis and dissolution tests.

Conclusion:

The ACTs are widely available over-the-counter to the public and it is very difficult to report and monitor a decrease in efficacy or treatment failure. The perspectives of HCPs on treatment failure or lack of efficacy may potentially guide optimization efforts of sampling methodologies for the quality survey of ACTs.

Key words: Healthcare professional perspectives, Artemisinin-based combination therapy, perceived treatment failure

4.3.1 Background

The proliferation of substandard and falsified artemisinin-based combination therapies (SF ACTs) is of global concern and has disproportionately affected highly malaria-endemic Southeast Asian and sub-Sahara African (SSA) countries[1-4].Up to 66 percent of drugs studied in SSA, in a recent quality study, were found to be substandard[5]. Newton et al showed that SF ACTs account for 38 percent of artemisinin-based combination therapies (ACTs) in the private sector market in Uganda[6]. Studies have warned of a possible global spread of artemisinin-resistant parasites particularly to SSA[7].

The emergence of artemisinin-resistant strains of *P. falciparum* in SSA is of increasing concern[8] and likely results from decades of sub-therapeutic monotherapy and substandard artemisinin-derivative consumption[9]. Medicine quality is one of the many threats to appropriate and effective malaria case management and is critical in SSA countries using ACTs as first-line therapy for malaria.

National Medicines Regulatory Authorities (NMRAs) in SSA can promote regular use of Post-marketing surveillance (PMS) to curb the circulation of substandard, degraded, spurious, falsely labeled, falsified and counterfeit ACTs[10]. Post-marketing surveillance (PMS) assesses the quality of ACTs on the market and stimulates the prompt identification and withdrawal of poor-quality medicines from public use. Uganda, a country with the sixth highest number of malaria-associated deaths in Africa annually[11], is among 21 of the 55 African countries with a PMS system[12].

Various sampling techniques, including convenience, mystery and overt approaches, have been used to estimate the scale of use of poor-quality ACTs in developing countries[6]. Efficient testing to identify poor quality ACTs by use of resource-intensive high-performance liquid chromatography and mass spectrometry in developing countries[13] should focus on suspicious ACT brands. The three parallel supply chains for essential medicines in Uganda include the National Medical Stores for public health facilities, the public-not-for-profit (PNFP) supply chain led by the Joint Medical Sores and numerous procurement agents, manufacturers, distributors and retail pharmacies in the private-for-profit sector (PFP). Healthcare professionals interact with both ACTs and malaria patients they treat and hence could observe, first-hand, suspect poor quality ACTs linked to poor malaria treatment outcomes[14]. A survey to establish treatment failure of ACTs as perceived by HCPs could reveal invaluable insights into likely SF ACTs. These insights could guide PMS sampling of implicated ACT brands by Uganda's National Drug Authority. The implicated brands could be screened to evaluate their content of the active pharmaceutical ingredient and degradation products. Therefore, the objective of this study was to determine the extent of and factors associated with

HCP-perceived ACT treatment failure and identify the most implicated ACT brands on the Ugandan market.

4.3.2 Methods

Study design

We conducted a cross-sectional study of healthcare professionals' perspectives about the quality of ACTs between June and July 2018 at selected major hospitals and health centres, private community pharmacies and private not-for-profit clinics in seven regions of Uganda.

Study setting

Health services delivery is decentralized within national, districts and health sub districts. The continuum of health services in the public sector begins with a village level community health extension worker, a parish level outpatient Health Centre II, a sub-county based 8-bed in-patient Health Centre III to a 12-bed Health Centre IV facility with a theatre manned by a medical doctor. In most districts, this network of facilities is complemented by a general hospital. The 14 regional referral hospitals are at the top of this continuum. The lowest level of care in the public health system is given by the community health workers who are volunteers in villages facilitating health promotion, service delivery, community participation, and empowerment. The private health sector in Uganda is diverse, comprising both PNFP organizations (faith-based, non-governmental, or community-based) and PFP organizations (commercial, self-sustaining). The private sector players contribute to about 50% of the health service delivery[15].

The seven regions within which the National Drug Authority operates were included in this study to construct a nationally representative sample of health facilities in Uganda. One region is centrally located in Kampala and two regions distributed in each of the northern, eastern and western parts of the country. The central region is the most densely populated and is endowed with the majority of health facilities and drug outlets in the country. The West Nile and South West Regions both share borders with five neighboring countries. Each region was considered to be a cluster from which a random sample of health facilities would be drawn. The districts that were selected are Kampala (central), Iganga and Soroti (eastern), Arua and Lira (northern), Kabale and Fort Portal (western).

Study population and sample size

In Uganda, an estimated 55,966 of the 66,111 people who make up the health workforce in 2009 were of the clinical cadre who are ideally eligible to participate in

this study. To obtain the required sample size to be representative of the 55,9666 HCPs, the Krejcie and Morgan's formula was used[16]. This gave a sample of 382 HCPs to be included in the study.

In order to cater for design effect and non-responses, the sample size was increased by the original eligibility proportion of 85% to get a sample size of 707 HCPs. During data collection, there was 3.1% (n=22 HCPs) non-responses giving a total of 685 complete responses.

The majority (42%) of these HCPs were in the central region; the northern had 17 percent, western 21 percent, and eastern 19 percent. The sample of 685 healthcare professionals included in the study achieved regional representation as follows: central (n=295, 43%), northern (n=132, 19%), western (n=130, 19%) and eastern (n=128, 19%).

Doctors, dentists and clinical officers (7,837) represented 14 percent of the nationally eligible staff and were 35 of the overall sample. Pharmacists and pharmacy technicians (762) were 1.4 percent of the nationally eligible staff but 13 percent of our sample. Nurses, midwives, and nursing assistants (37,625) were 67 percent of the nationally eligible staff but 49 percent of our sample.

Data collection procedure

The field team was trained on how to use the Open Data Kit (ODK) tools, field procedures and interview techniques. During the training, the android mobile phones of each field officer was configured and uploaded with the questionnaire in the ODK Collect tool An additional file shows more detail about the questionnaire that was used. (S4File). This tool worked well with limited internet connectivity. Healthcare professionals in the selected health facilities completed the self-administered pre-formulated questionnaire. At the end of each day, each research assistant transferred the data from the paper questionnaire into the ODK tool then submitted the data to the central database server.

Data analysis

The main outcome variable was the reported ACT failure or lack of efficacy. Treatment failure has been defined as the inability to clear parasites from a patient's blood or to prevent their recrudescence after the administration of a drug[17]. This was in response to the quest for the HCPs observation or suspicion of any clinical failure to treatment with ACTs. The HCP's perception of ACT treatment outcomes was used to identify the ACT brands, registered in Uganda associated with perceived treatment outcomes to a pre-determined list of ACTs provided in the self-administered questionnaire. Perceived treatment failure was measured by the frequency with which a particular "brand" is listed. Factors associated with HCP-perceived ACT treatment failure and adherence were explored including the

demographic characteristics of the HCPs, their level of education and length of service as well as the type of health facilities where they worked.

Data were exported from the ODK tool database server into SPSS Version 20.0 for analysis. We used binary logistic regression analysis to determine the factors associated with HCP-perceived ACT treatment failure. Associations between independent variables (respondents' gender, region, level of education, sector of practice, age, professional experience) and the outcome variable (HCP-perceived ACT treatment failure) were assessed. Measures of association between categorical independent variables and the outcome variable were established using Chi-square tests. The measure of association for each categorical variable was the odds ratio (OR) with its 95 percent confidence intervals. The odds ratio was used to compare the chance of the outcome among the variables. Confounding and interaction between the various factors (region, gender, age, level of education, professional experience, sector of practice) were assessed using multivariate logistic regression.

Quality tests for ACTs using minilabs

According to the WHO for selection of collection sites, guidelines[18], samples were collected, coded and recorded using the in a ratio sampling ratio of 1:3:1 representative of the 3 levels of distribution in the supply chain respectively. Level one involved ports of entry, warehouses of the largest importers for both the public and private sector. The second level included wholesale pharmacies, retail pharmacies, drug shops, public and private hospitals, faith-based organizations, clinics and treatment centers and level three included informal outlets like kiosks, street vendors and grocery shops. Due to the complex nature of the environment at level 3 sites, covert sampling was used to obtain required samples.

Risk-based PMS sampling was performed after training and a risk estimation exercise for the regions of Uganda according to the United States Pharmacopoeial Convention guidance tool[19]. The choice of medicines was based on suspicion of or documented inferior quality with actual or potential serious implications for public health, such as treatment failures, high product turnover, exposure of patients to the medicine, seriousness of potential harm, products with a high potential for diversity on the market, where various generic alternatives are available as well as products at risk of being substandard and falsified due to potential high returns or demand in the market. Different brands of products containing ACTs were sampled from the seven National Drug Authority regional of Eastern, central, South Eastern, Northern, South Western, Western, Western and West Nile. The ACTs sampled included Amodiaquine hydrochloride/Artesunate tablets (AAT), Artemether/Lumefantrine tablets (ALT), Artemether/Lumefantrine dispersible tablets (ALD) and Dihydro-artemisinin/Piperaquine phosphate tablets (DPT). The sampling of ACTs was independent of the respondents and followed the Global Pharma Health Fund (GPHF) testing protocols[20]. The screening tests included

visual inspection, disintegration test and qualitative analysis using the Thin Layer Chromatography (TLC) technique as prescribed in the GPHF-Minilab™. The dosage units, primary packaging, secondary packaging and product information insert were also inspected for any defects which were then recorded. A full monograph testing that assessed parameters of appearance, identification, chemical content and dissolution was performed in the National Drug Quality Control laboratory (NDQCL) on all failed, samples categorized as doubtful and 10% of all passing samples collected from each region.

4.3.3 Results

Demographic and professional characteristics of healthcare professionals

A total of 685 HCPs from the seven regions participated in the study with an average age of 30 (SD = 7.4) years. There were slightly more male (n=349, 51%) than female (n=336, 49%) respondents. The majority of HCPs had at least Diploma-level education (n=480, 70%) with median experience of 3 (interquartile range, IQR of 2 to 6) years. Most of the HCPs were nurses (n=334, 49%) and most participants were working in hospitals (n=351, 51%). The majority of respondents worked in private facilities (n=409, 60%). The median number of patients seen per day at the health facilities was 6 (IQR, 3 to 10) patients as summarized in Table 4.11 below.

Table 4.11: Demographic and professional characteristics of healthcare professionals

Total number of participants =685	
Regions	
Central Eastern Northern Western	295 (43%) 128 (19%) 132 (19%) 130 (19%)
Age	
Mean years (SD); median, IQR	30 (7.4); 28; 26-32
Gender	
Male Female	349(51%) 336(49%)
Highest education level	
Certificate Diploma Bachelors' degree or higher	205(30%) 245(36%) 235(34%)

Professional cadre	
Pharmacist/Pharm tech	92(13%)
Nurse	334(49%)
Medical officer	110(16%)
Clinical officer	114 (17%)
Others	35(5%)
Professional experience (years)	
0-1 years	152 (22%)
2-3 years	217 (32%)
4-5 years	143 (21%)
>=6 years	173 (25%)
Health Facility Status	
Hospital or HC IV	354(52%)
HC III/ HC II	45(7%)
Pharmacy / Pharm tech	123(18%)
Drug shop	114 (17%)
Private clinic	163(24%)
Sector of practice	
Public	276(40%)
Private	409(60%)

Factors associated with having ever encountered ACT treatment failure

Overall, a majority of the respondents reported having ever encountered ACT treatment failure in treating uncomplicated malaria (n=421, 61%). Healthcare professionals from the central region had a higher chance of encountering ACT treatment failure in four weeks prior to the survey as compared to those from the western region (OR=3.0, CI: 0.3-1.0; P=0.0001). This was also true for the HCP from Eastern region (OR=5.4, CI: 2.9-9.8; P=0.0001) and Northern region (OR=5.3, CI: 2.9-9.9; P=0.0001). As shown in Table 4.12.

The longer the professional experience, the more likely a healthcare professional was to report an encounter of ACT treatment failure in the previous two weeks. As compared to the health care professionals with experience of 1 year or less, those with experience of 4-5 years (OR=2.4, CI: 2.2-10.2; P=0.0003) and 6 years and above (OR=3.2, CI: 1.6-11.4; P=0.0001) had higher chances of encountering ACT treatment failure in previous two weeks.

Healthcare professionals from private health facilities had higher chances of encountering ACT treatment failures in past 4 weeks as compared to those from public health facilities (OR=2.7, CI: 1.7-3.9; P=0.0001)

Healthcare professionals attending to more than 10 malaria patients a day had high chances of encountering ACT treatment failure than those attending to less than 10 patients (OR=2.5, CI: 1.6-6.6; P=0.0001).

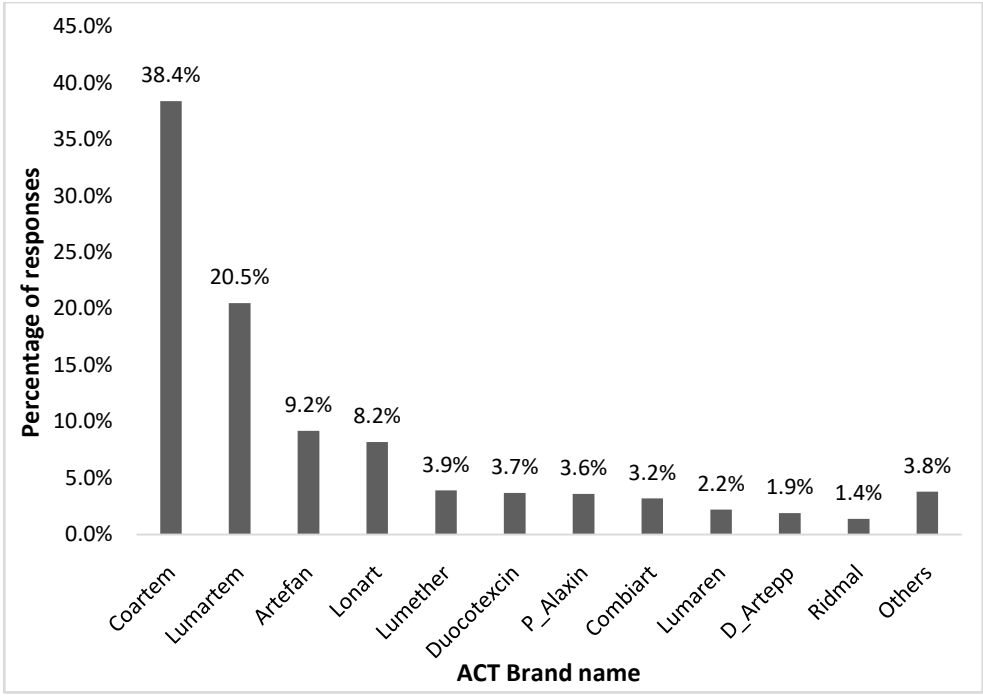
Table 4.12: Extent of and factors associated with having ever encountered ACT treatment failure among 685 healthcare professionals using Multivariate logistic regression

Category	Ever encountered ACT treatment failure				
	Yes, n(%)	No, n(%)			
Overall	421(61)	264(39)	OR	CI	P-Value
Region					
Western	50 (38)	80 (62)	1.0	-	-
Central	184 (62%)	111(38%)	3.0	1.7-5.2	0.0001
Eastern	99 (77%)	29 (23%)	5.4	2.9-9.8	0.0001
Northern	88 (67%)	44 (33%)	5.3	2.9-9.9	0.0001
Gender					
Male	214(61%)	135(39%)	1.0	-	-
Female	207(62%)	129(38%)	0.8	0.6-1.2	0.311
Age category					
<25	55 (49%)	47 (51%)	1.0	-	-
25-34	267 (61%)	172 (31%)	0.9	0.5-1.4	0.538
35 and above	99 (74%)	35 (26%)	1.1	0.5-2.5	0.734
Education level					
Certificate	129 (63%)	76 (37%)	1.0	-	-
Diploma	165 (67%)	80 (33%)	0.9	0.5-1.6	0.775
Bachelors or higher	127 (54%)	108 (46%)	1.0	0.5-1.9	0.973
Professional experience					
0-1 years	60 (39%)	92 (61%)	1.0	-	-
2-3 years	129 (59%)	88 (41)	1.2	1.6-5.6	0.511
4-5 years	104 (73%)	39 (27%)	2.4	2.2-10.2	0.003
>=6 years	128 (74%)	45 (26%)	3.2	1.6-11.4	0.001
Sector of practice					
Public	157(57%)	119(43%)	1.0	-	-
Private	264(65%)	145(35%)	2.7	1.7-3.9	0.0001
Professional cadre					
Medical officer	58 (53%)	52 (47%)	1.0	-	-
Pharmacist/Pharm	50 (54%)	42 (46%)	0.6	0.5-2.9	0.121
tech	218 (65%)	116 (35%)	0.7	1.3-7.2	0.337
Nurse	81 (71%)	33 (29%)	1.3	1.1-7.8	0.514
Clinical officer	14 (40%)	21 (60%)	0.2	0.5-4.5	0.110
Other					
Malaria patients per day					
<10 patients	223 (52%)	215 (48%)	1.0	-	-
>=10 patients	188 (79%)	49 (21%)	2.5	1.6-6.6	0.0001

Commonly used ACTs

The study further investigated commonly used ACTs, suspected failures and ACTs that give satisfactory results in health facilities. The six most commonly used ACT brands in the health facilities labelled and provided as Coartem, Lumartem, Duocotecxin, Lonart, P-Alaxin, Artefan. Coartem was the leading ACT drug suspected by health workers for treatment failure as illustrated in figure 4.5. The top five ACT treatment failures associated drugs contributed to 80.2% of all suspicion and were all Artemether/Lumefantrine combinations).

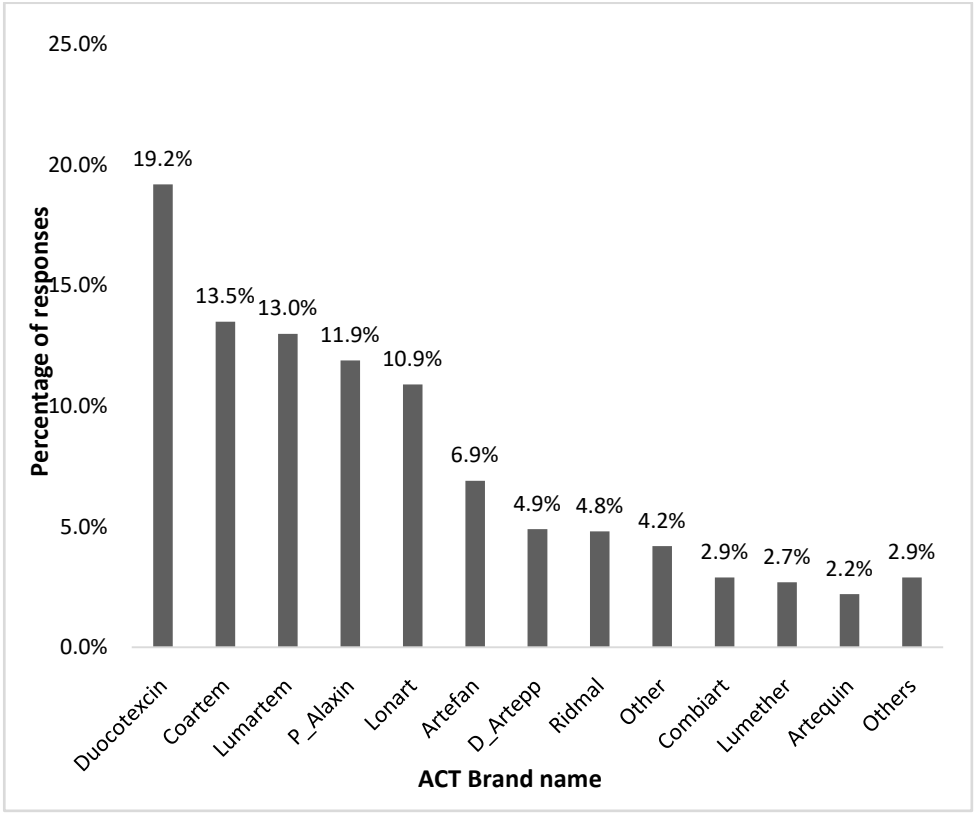
Figure 4.5 Profile of suspected ACT failure rates in health facilities



Drugs that were perceived to give satisfactory results in health facilities

Duo-cotecxin was ranked first with a score of 19.2% among the ACTs that gave satisfactory patient outcomes by health workers as demonstrated in figure4.6.

Figure 4.6. ACT Drugs with perceived satisfactory results



Characteristics associated with perceived ACT treatment failure

Some of the respondents agreed that ACT colors (n=183, 27%) could result in poor patient compliance, hence, treatment failure. Whereas some health workers explained that the color of the medicine does not affect the effectiveness of the drug, they explained that some patients associated color yellow with bitterness and, hence, nausea.

"*Most people are too much into political parties so some refuse to take yellow colored ACTs like Coartem*" Nurse, Northern region.

"*Patients tend to think yellow tablets are bitter probably due to past experience with bitter tablets that are yellow like Chloroquine*" Nurse, Central region.

"People are used to white tablets. They think yellow tablets are bitter. This causes poor compliance

The yellow color together with the nauseating smell makes it hard to swallow such that patients end up vomiting" Clinical officer, Eastern region.

Regarding the size of the ACT tablets; some health workers (n=285, 42%) agreed that it can lead to lack of compliance and hence treatment failure. They observed that Artemether/Lumefantrine and Duo-cotecxin tablets are relatively bigger and patients associated the size of Duocotecxin with ARVs. They explained this as follows:

"Double strength Coartem tablets and Duocotecxin are bigger than most other ACTs. Despite the other advantages, they may be taken wrongly or halfway," Nurse, Eastern region.

"If the size is big, it might be hard to ingest also swallowing many tablets at once induces nausea in some patients and hence vomiting out the medicines," Nurse, Western region.

"Patients don't like big tablets which resemble ARVs and that they may be perceived as HIV positive," Clinical officer, Northern region.

Most respondents agreed that the ACT drug taste (n=470, 68%) could result in poor patient compliance, and eventually treatment failure. Health workers reported that most patients complain about the unpleasant taste of Coartem and makes them nauseous.

"Bad taste affects the will to take the medication and sometimes result into nausea and vomiting," Clinical officer, Western region.

"Children often resist swallowing them and also sometimes may lead to vomiting which discourages mothers from giving their children ACTs," Nurse, Central region.

Most of the respondents also agreed that ACT dosing frequency (n=411, 60%) and number of ACT tablets (n=562, 82%) could result in poor patient compliance, consequently treatment failure. Health workers explained that patients prefer drugs that are taken once a day such as Duo-cotecxin, as opposed to more than once daily. For example, patients do not usually finish doses of Coartem, Lumartem, Lonart, because they are twice daily dosing. They also pointed out that too many tablets of Coartem and Lumartem required per dose, bother patients and make it hard for them to complete doses. In their explanations they said:

> *"Coartem, which has 4 tablets taken at once, for example, adult dose 4 tablets at once are many hence poor patient compliance",* Nurse, Eastern region.

> *"Coartem, you take 4 tabs morning and evening. It discourages patients. Once daily is preferred to 2 tablets twice daily. And if they have to Co-administer with other drugs such as Paracetamol, bill burden is high",* Pharmacist, Northern region.

> *"Coartem, Lonart, Lumartem oral tablets are too many. Patients don't finish them",* Nurse, Central region.

Inadequate knowledge about ACT drugs was another factor that was associated with poor patient compliance by majority health workers (n=580, 85%). They explained that some health workers do not fully equip the patients with the information regarding drug use. They also explained that in Uganda, the literature about use of ACTs is limited.

> *"ACTs have been in Uganda for sometime but literature on it is not enough. People still have to depend on the prescribers to determine use in pregnant mothers,"* Nurse, Northern Uganda.

> *"Failure to warn a patient about an ACT's potential side effects can lead to patients intentionally missing doses,"* Clinical Officer, Central region.

> *"Some of the health workers don't give patients full information on how to take the medicines,"* Nurse, Western region.

Perceptions about ACT resistance

About one third of health workers (32%, 220/685) felt that ACT resistance was a growing concern nationally. However, an equal number (31%, 210/685) felt

otherwise. Thirty-seven percent of them (255/685) did not know whether drug resistance was of national importance.

More than a quarter of the health workers (28%, 192/685) felt that ACT resistance was a growing concern in their institutions whereas about one fifth (22%, 148/685) felt otherwise. Half of them (50%, 345/685) did not know whether the ACT resistance was of concern in their institutions. Those who thought so associated the issue with patient self-medication and poor compliance as a great threat to ACT efficacy.

Respondents raised concern that malaria is still among the leading causes of hospital visits. The tendency for patients to self-medicate with over-the-counter ACTs and not complete the anti-malarial doses was considered to cause resistance especially if the anti-malarials were taken when malaria was not confirmed. They said:

> *"ACTs are now our first line and when they fail we don't have cheaper better alternatives so we need to be concerned. Also, the rate at which patients self-medicate is high",* Nurse, Northern region.
>
> *"A lot of patients do self-medication when they feel they have malaria symptoms even before confirming. Others abuse treatment given, they do not accomplish their doses, so after they start feeling a relief they stop",* Clinical Officer, Eastern region.
>
> *"ACTs are our first line for uncomplicated malaria and with cases of reports of resistance in South East Asia we need to worry that it may come to our nation",* Medical Officer, Central region.
>
> *"ACTs are widely used over the counter, this increases the chances of misuse by the patients and this can increase the risk of resistance",* Nurse, Western region.
>
> *"Because of easy uncontrolled access of these medicines to the general public and poor patient compliance whereby a patient takes one or two doses and stops when they get symptomatic relief".* Clinical Officer, Northern region.

The GPHF-Minilab™ test results

All samples passed the authenticity evaluation using the GPHF^{TM} mini-lab. The sample distribution included 55% (106/192) samples of Artemether/Lumefantrine,

18% (35/192) of Artesunate/Amodiaquine and 27% (51/192) of Dihydroartemesinin/Piperaquine.

On visual inspection, 48 defects were detected, one third (n=16; 11 ALT, 1 AAT and 4 DPT) were dosage unit related. The commonest dosage unit related defects observed were orange peel and poor de-bossment. The orange peel defect is a coating related defected that could be linked to the viscosity of the coating solution during manufacture. The four DPT defects were related to the tablet coating integrity and included orange peel, mottled tablets and dents on the tablet surface.

One quarter (n=12) of the 48 reported defects were from covertly sampled Artesunate/Amodiaquine tablets in the West Nile region. These covert samples mainly from the informal sector had secondary packages with fading or dirty marks on the outside or inside of the carton and additionally, some had scratched blister packs. The samples appeared to have been exposed to poor sanitary conditions as some of them contained earth and dead insects in the secondary pack. Three of the AAT secondary packages were labelled as “Government of Uganda, Not for Sale”.

Twenty three percent (n=11; 5 ALT, 4 AAT and 2 ALD) of all observed defects were related to secondary packaging presenting mainly as varying degrees of black marks inside the cartons. The black marks were more common in cases where the carton contained more than 3 strips of dosage units.

There were seven (4 ALT, 3 AAT) primary package related defects that presented as scratches, creases or dirty marks on the primary packaging. Of concern also were two Lonart samples where the de-bossment of the expiry dates and batch number on the primary package were illegible and appeared to have been substituted with imprinting using ink. There were also two ALT cases with missing product information leaflets in all the collected samples.

All ACT samples that had been screened at the regions were transported to the National Drug Quality Control Laboratory for confirmatory testing. Since all samples obtained from the different regions had passed the screening stage, 10% of these samples were randomly selected and subjected to analysis following internal procedures. The tests conducted included appearance, identification, dissolution and assay for content of the active pharmaceutical ingredient. All the selected samples passed the full monograph second level testing as indicated in Table 4.13.

Table 4.13: Results for full monograph testing of the ACT drug samples from the NDA regions

Region	Samples sent for level II	Tested	Passed
Eastern	26	3	3
Central	24	2	2
South Eastern	33	3	3
Northern	26	3	3
South Western	23	2	2
Western	31	3	3
West Nile	29	3	3
Total	**192**	**19**	**19**

4.3.4 Discussion

In this study, we found that six out of every ten healthcare professionals perceived having encountered treatment failure while treating uncomplicated malaria. The highest level of perceived treatment failure was reported among the Artemether-Lumefantrine (AL) containing ACT brands of Coartem, Lumartem, Artefan and Lonart. On further probing, one of the factors likely to be associated with the HCP perceived treatment failure was the region of work. This perceived treatment failure was validated with a countrywide regional sampling and testing of oral ACT medicines. Some product defects were detected on visual inspection. The West Nile Region stood out with one quarter of the visual defects because sampling was done covertly from the informal sector in this region on the border with the Democratic Republic of Congo and Southern Sudan. However, from the laboratory analysis, the quality of antimalarial medicines in all the regions of Uganda was found to be good. Regulatory quality assurance measures such as post-market surveillance contribute considerably to prevention, detection and response to the circulation of substandard medicines on the market but are resource intensive[21]. Insights from healthcare professionals who interact much with the patients and with the medicines result in more targeted and cost-effective PMS efforts especially for limited resource settings.

Healthcare professionals are one of the important partners in tackling the problem of substandard and falsified medical products on the market[1]. Their perspectives count especially in detecting and preventing the circulation of these products.

National medicines regulatory authorities can take cues from them during PMS. In our study, insights from HCPs guided the covert sampling that led to the discovery of visually defective products in the informal sector that could have easily crossed the border into neighbouring countries. From our findings, at least three things need to be investigated further even though they did not affect the chemical content analysis of the concerned products at our internationally recognized NDQCL[22]. Earlier studies have reported presence of non-quality assured anti-malarial medicines in many sub-Saharan countries including Uganda[23,24]. Firstly, possible pilferage of government drugs with the cooperation of other stakeholders like the local government authorities, customs officials, the police and other law enforcement agencies in the affected region. The drug regulatory authority also needs to conduct more covert operations more regularly in similarly affected regions. This very resource-intensive exercise is not easily sustained by many low and middle-income countries but can be better implemented by cross-border regional collaboration. Modification of the WHO methodology can also be made to conserve medicine samples and also include them among those that can contribute to the next stage sampling if they can be visually inspected without damaging their primary packaging. Secondly, coating defects for ALT and DPT could indicate a possible break down during the manufacturing process or possible falsification. The respective manufacturers need to be notified about this. Lastly, the cases of missing product information leaflets (PIL) of all samples of a drug that were collected needs to be addressed as soon as possible and the regulatory requirement for PILs should be enforced strictly as it could also be an indicator of product falsification.

From the perceptions of healthcare professionals in this study, the once-a -day dosing schedule and low pill burden of Dihydroartemisinin/Piperaquine (DHP) was considered to be more favourable to patients and to have more satisfactory treatment outcomes than the AL- containing ACT brands. This finding was similar to another study that recommended the use of DHP in the Ugandan malaria treatment policy due to its less intense dosing schedule and requirements[25]. The top four most frequently used AL brands of Coartem', Lumartem, Artefan and Lonartsuspected to be failing to result in the desired patient outcome in this study contributed to 80 percent of the suspicion. Misdiagnosis of non-malaria febrie illness as malaria and self-treatment with anti-malarials, especially in areas with limited access to health services[26, 27] has greatly contributed to the overuse of the AL containing ACT brands and possibly to the notion among HCPs that this group of medicines do not give the desired outcomes. A bioequivalence analysis of these four ACT brands with the highest perceived treatment failure rates is highly recommended to verify this view. In addition, the efficacy of 5-day and 7-day ACT regimens against the standard 3-day regimen in treatment of uncomplicated malaria would also need to be evaluated to support the malaria policy. As a follow on for policy makers, mapping and predicting ACT resistance trends would then provide information necessary to take early action to preserve the performance of these drugs for as long as possible, also taking into account the resources needed

in a good prediction model. The relationship between ACT resistance and ACT use in the various regions also needs to be established in future studies. The outcome of such studies would be of much interest to the drug regulators since bioequivalnce analysis is not a pre-condition for registration of medicines, yet it determines the performance of the many generics that are used on the Ugandan market. The test, treat and track malaria policy in Uganda[28] if reinforced will be beneficial in terms of reducing the cost of treatment and quality of healthcare provided.

We found that the longer one's professional experience, the more likely it was to acknowledge the encounter of perceived treatment failure. One study has shown that although an individual health worker's years of experience influence their level of expertise, gains in the probability of an individual worker being an expert can also be achieved through having more years of service and more educated staff overall[29,30]. The hospital practice context and the general work environment greatly enhances the clinical practice expertise, including reporting and handling treatment failure in the context of our study. Thus, in the search for better health worker performance, other factors such as job satisfaction, workload and other health system factors may be important considerations[31]. These factors will need a deeper understanding for the NPC to establish and maintain an effective system for managing treatment failure or lack of efficacy. The accreditation of the NPC as a provider of continuing professional education points will also increase the level of pharmacovigilance awareness and engagement among the different medical professions through their professional associations.

Poor adherence to medicines and drug resistance were identified, in this study, as the main factors that could lead to possible perceived treatment failure. In general, HCPs agreed that dosing schedules, pill burden and drug aesthetics affect patient adherence[32,33]. Since the majority of respondents spent the most time with patients, they described the patients' views in detail. However, future studies could get more accurate patients' views directly from the patients. A study in Ghana reported that 57.3% of patients were adherent to prescribed ACTs[24]. About one quarter of the HCPs associated yellow colour with the political party in power and also with bitterness, making the AL brands unpopular in some regions. The ACTs tend to be bigger than the older anti-malarial medicines. Despite the once daily dosing schedule that Dihydroartemesinin/Piperaquine was favoured for, the big size of these tablets likened it to anti-retroviral medicines, which are associated with the stigma of HIV in the community. Majority of the HCPs identified the bad taste of the Artemether/Lumefantrine brands to affect the will of the patients to take medicines. When the prejudice of patients and healthcare professionals are sufficiently handled with proper education at the point of care, adherence to prescription medicines will most likely improve. The views of patients and consumers have been used in high-resourced countries to report ineffective drugs through a labour-intensive manual process[34]. However, this manual process of reporting drug quality problems could be adapted for low and middle-income

countries like Uganda due to a higher prevalence of substandard and falsified products on the market.

The majority of health workers, interviewed for this study, neither thought nor knew that ACT resistance was a growing concern nationally. The WHO states that ACT resistance is growing worldwide. Non-synonymous propeller-region PfKelch 13 mutants associated with delayed clearance have been reported in Africa[17]. What may be of greater concern still, is the presence of multicopy Pfplasmepsin 2-3 that could lead to piperaquine resistance[35].In Uganda, *Plasmodium* genotypes with decreased sensitivity to Artemether-Lumefantrine increased from 2008 to 2012[36]. Elsewhere, there are increasing reports of the emergence of less sensitive strains of *Plasmodium* to Artemisinin, Lumefantrine and Piperaquine[37, 38]. The issue raised here is the sources of health literacy for the majority of HCPs are limited. However, the smartphone coverage for them could be explored with the intention of introducing a smartphone application with personalized medicine information. For the national malaria program and NPC, routine monitoring for emergence of artemisinin resistance to ensure that the recommended ACTs are effective for as long as possible and that timely changes to national treatment policies can be implemented. Many health workers think that the threat to ACT efficacy is mainly from self-medication and poor compliance to antimalarial treatment. Self-medication is common in Uganda[39]. However, lack of awareness of the regulations regarding the appropriate use of medicines, illiteracy and poverty have been cited as major drivers to self-medication. Therefore major communication and education efforts have to be customized to the general public as well as HCPs.

The major limitation of this study was the use of healthcare professionals' perspectives as a surrogate measure to assess lack of efficacy or treatment failure. Healthcare professionals do not usually report this. For all cases that mentioned having ever encountered ACT treatment failure, a confirmatory visit was made to the health facility to rule out brand confusion. A prospective observational design would have given better evidence about the treatment failure. However, since this outcome is very rare, such a study was esteemed to be too resource intensive in terms of time and funds. Like other cross-sectional surveys, biases in the survey instrument, information bias, interviewer, recall and selection bias could have affected the internal validity of the study. Since ACT failure was a new concept in adverse event reporting, we used four weeks instead of two weeks so as to enable capture of more encounters with the outcome variable. Selection bias was of greater concern since we had to sample the HCPs and the ACTs. We sampled health facilities in the regions and applied the national ratios to the available HCPs in the health facilities as much as possible. The sampling of ACTs was independent of the respondents and followed the GPHF testing protocols and the WHO guidelines for collecting samples for quality surveys of medicines. The national estimates for HCPs were more than ten years old and could have also affected the representativeness of our samples. Lastly, the results may be generalized with caution to other similar low-and-middle income countries to the

Ugandan health system context. Given the low number of valid samples in some categories of ACTs due to convenience risk-based sampling, generalization of the observations may not hold statistical validity and a targeted PMS strategy should be adopted to give a more in depth and generalizable assessment.

The findings here can serve as a basis for the search into more cost-effective means to identify leads for ACT optimization and PMS sampling methodologies in sub-Saharan Africa. Sub-saharan countries are net importers of pharmaceutical products and have recently individually or regionally began to build or boost their PMS and pharmacovigilance systems. HCPs have given their views; however, future studies should concentrate on acquiring patients' views on the performance of medicines directly. Some ACT brands were identified by HCPs. It would be very useful to conduct bioequivalence studies to verify treatment failure and to follow up on identified cues to product falsification or pilferage of medicines with the relevant authorities. Continued resistance monitoring to identify early artemisinin resistance and re-inforcement of the "diagnosis before treatment" policies would be of great value to national malaria treatment programs. For the HCPs, it would be a worthwhile venture to explore the best means of availing them personalized health and drug information to aid their decision making on a real-time basis.

4.3.5 Conclusion

Currently, malaria endemic African countries use ACTs for treating uncomplicated malaria. The ACTs are widely available over-the-counter to the public and it is very difficult to report and monitor a decrease in efficacy or treatment failure. Clinical efficacy studies for the combination ACT medicines or any sort of post-marketing quality control tests are very resource-intensive and complex. Findings from this study will inform policy of efficient means of screening for substandard and falsified products on the market in Uganda and other low -income countries. The perception of most of the healthcare professionals interviewed in this study was that the risk of ACT treatment failure has been associated with both their overuse that is commonly associated with high rates of re-infection and substandard drug formulations. In settings with limited resources, a risk-based approach is necessary to select mainly high-risk brands for testing. Since HCPs, during patient care, always interact with medicines, their opinions made on the basis of observing the ways in which patients respond to medicines can guide their selection of high-risk brands in order to carry out sustainable quality testing. However, other quality assurance measures should be maintained while the search for more cost-effective identification of leads for PMS investigation continues.

In addition, other behavioral factors, which could lead to perceived treatment failure and antimalarial resistance identified in this study need to be addressed. Of importance is poor patient adherence, which could be improved if patients are

properly educated in medicine use at the point of care. Proper education for patients needs to address their concerns on colour, size, and number of tablets prescribed based on patient-based survey results. Healthcare professionals should also be empowered with information to make more informed decisions at the point of care. Future studies helpful in dealing with ACT resistance and ACT treatment failure will benefit from simulation over a long period to come up with cost-effective strategies aimed at conserving efficacy of ACTs.

Declarations

Ethics approval and consent to participate

The School of Biomedical Sciences Higher Degrees research and ethics committee (SBS REC 357) issued ethical approval to this study in accordance with the World Medical Association Helsinki Declaration. Permission to conduct the study in the area was also obtained from NDA. Each respondent provided consent to participate in the study by signing the informed consent form.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Author's contribution

Helen Byomire Ndagije (HBN) and Jackson Mukonzo (JM) designed the study. Ronald Kiguba (RK) participated in the design, analysis and interpretation of the data and writing of the manuscript. Elijah Kirabira (EK), Leah Nabirye (LN) and Allan Serwanga(AS1)played a big role in data collection. Leonard Manirakiza (LM), JM and HBN participated in the analysis and interpretation of the data. LM was a major contributor in writing the manuscript. Sten Olsson (SO), Anne Spinewine (AS2) and Niko Speybroeck NS made substantial contributions during the review of the manuscript. All authors read and approved the final manuscript.

Competing interests

Helen ByomireNdagije, Ronald Kiguba, Leonard Manirakiza, Elijah Kirabira, Allan Serwanga, Leah Nabirye, Sten Olsson, Anne Spinewine, Jackson Mukonzo, Niko Speybroeck have no conflicts of interest that are directly relevant to the content of

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Supporting information

S4 File. Study questionnaire to assess Clinician-perceived failure rates of commonly used ACTs. This was the questionnaire used to collect data about the HCP perceived failure rates of commonly used ACTs. Healthcare professionals in the selected health facilities completed this self-administered formulated questionnaire.

PART 5: GENERAL DISCUSSION AND PERSPECTIVES

5.1 Discussion

One of the most important determinants of success in any field or in life is an acknowledgement of failure and a willingness to learn from it, progress and excel. To face the black-box truth like in the aviation industry is what will help any system to develop. Monitoring safety of medicines in systems with limited resources is not any different. The growth and strength of a pharmacovigilance system or any health system will depend on its readiness to address the root causes of events and circumstances. At the launch of the NMS enterprise resource planning system in February 2019[(1)], the minister for health, Honourable Dr. Jane Ruth Aceng admitted a major challenge to the sector and said, “with this new system, we shall be able to track down individuals stealing medicines and deal with them accordingly”. She demonstrated a willingness at the highest level possible within the health sector to identify, learn from past mistakes, progress and possibly excel. It is criticalfor the medicines to be available and traceable before their safety can even be mentioned. This research project gives provides evidence of the medicine safety issues that exist and presents some modifications of existing methods or health interventions to improve the pharmacovigilance systems for medicines used in the treatment of malaria and other diseases in Uganda. The experiences and lessons learnt can be applied to other low and middle-income countries.

Medicines are one of the six major building blocks of a health system. Only a thorough understanding of the dynamic interplay among health system components and actors can lead us to sustainable solutions to the issues therein. Above all, it is important to know how medicines policies and medical interventions affect and are affected by the system’s ever-changing nature and complexity. Global spending on medicines is expected to reach US$1,500 billion by 2021 [(2)], accounting for up to 67% of total health expenditures in LMICs [(3)] which is mostly paid out-of-pocket by consumers. Given that about half of the medicines in primary care settings are inappropriately prescribed and dispensed [(4, 5)], ensuring quality and appropriate use is of utmost importance for health systems. Prescribing in the private-for-profit sector is worse than in the public sector, associated with an overall poor compliance to standard treatment guidelines and hardly using the essential medicines’ list. According to WHO, the essential medicines’ list contains medicines intended to satisfy the priority needs of a given population [(6)]. This concept of the list entails availability of medicines within a functioning health system at all times in adequate amounts, in the appropriate dosage forms, with assured quality, and at a price the individual and the community can afford.The private health sector often has informal prescribers, and the prescribing practices by doctors, nurses and paramedical staff are also worse in the private sector. Poorer prescribing in the private sector has been noted in individual studies [(7,8)]. For the LMICs, this situation has to be addressed as the private and informal sector practitioners are a

significant source of health services for their populace yet engaging the private sector in provision of health services may not necessarily deliver better healthcare [9].

By 2040, low- and lower-middle-income nations are expected to see a dramatic increase from mainly infectious to more of non-communicable diseases in various demographic and epidemiological predictions [10]. Yet, these group of nations have the least capacity to deal with the shift of disease profile. Africa constitutes 12% of the global population but bears a disproportionate disease burden of about 30%, with 69% of deaths on the continent being attributable to infectious diseases, particularly HIV/AIDS, tuberculosis, and malaria [11]. Africa continues to confront huge public health hurdles arising from poverty related diseases. The rate of maternal and new-born mortality in the region remains the highest in the world. The annual increase in non-communicable diseases further strains already weak health systems. Over the past decade, efforts have been made to accelerate the clinical development of safe, effective, affordable and accessible interventions to address some of the challenges of poverty related diseases. Products are gradually being introduced onto the market as a result of development partnerships. Government expenditure on health is generally low. Patients pay out-of-pocket for most health services. Due to inadequate local pharmaceutical analytical capacity, Africa remains a target for substandard, counterfeit and inappropriate medicine formulations. The use of a wide variety of essential medicines and health technologies in Africa creates a need for robust pharmacovigilance systems to promote patient safety across the continent.

Adverse drug events contribute to a significant proportion of patient morbidity and mortality. The nature and scope of harm resulting from unsafe medication differs across healthcare systems and within various resource settings. A systematic review revealed that four groups of drugs accounted for more than 50% of preventable drug-related hospital admissions in developed countries [12]. While one in 10 patients from a developed country is estimated to be harmed while receiving hospital care [13], the probability of patients facing preventable harm in a developing country is expected to be much higher. The harm may result from a range of errors or from adverse drug events. The evidence is limited, but the adverse event rate estimates in LMICs are about eight percent with 83% being preventable, while about 30% being associated with death of the patient [14,15]. Apart from additional hospitalisation, such harm catapults the cost of providing and seeking healthcare in form of litigation costs, infections acquired in hospitals, lost income, disability and medical expenses. These ADEs form the minimal evidence profile upon which clinicians and patients refer to optimize patient safety once a medicine has been granted market authorization and is available for widespread use [16]. However, not all important ADEs are usually identified, particularly rare, hazardous and novel ADRs [17] and hence the need for pharmacovigilance. Besides the impact of ADEs on morbidity and mortality and the direct cost of managing the ADEs also have other associated costs in terms of the loss of confidence in the health system,

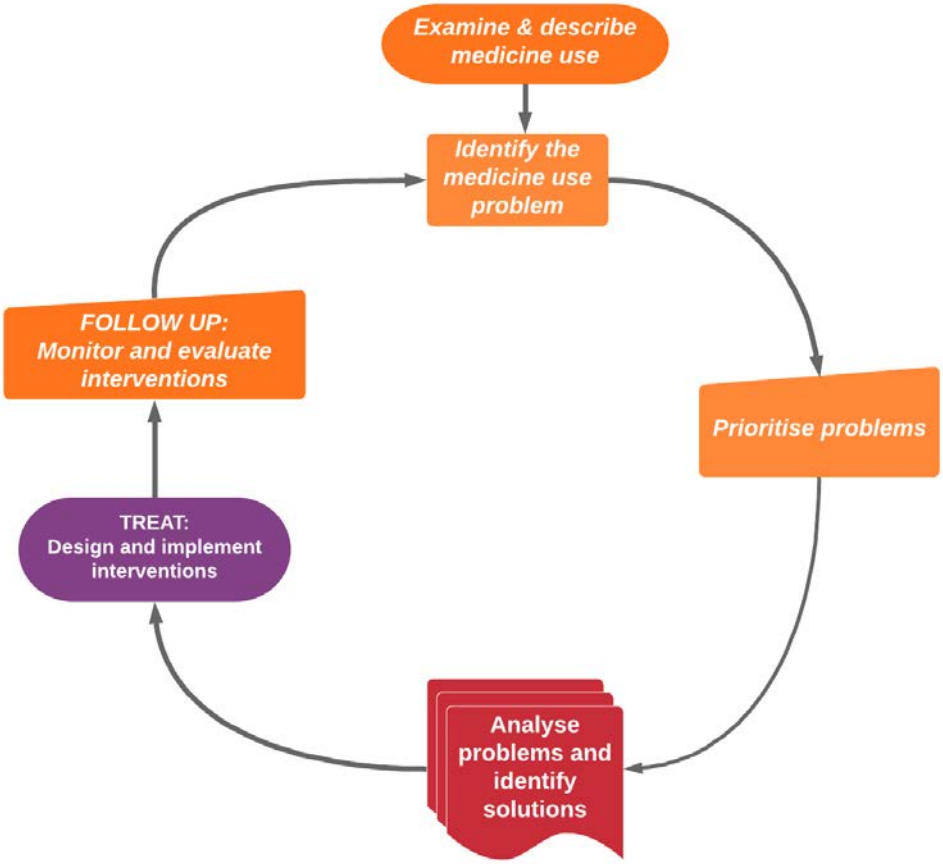
economic loss to the pharmaceutical industry, non-adherence to treatment, and development of drug resistance. The solutions to the challenges of post-marketing evaluation of drug safety are complex and also require highly collaborative interactions among the national medicines regulatory authorities, and industry regarding product label changes and the development of epidemiological and statistical methodology for detecting and interpreting adverse event signals [18]. Methods and resources for rapid collection of adverse event data and further study when necessary should be considered and specified before marketing. Countries with limited resources, therefore, should develop strategies and evidence-based interventions to protect their citizens from possible medication-related harm at every point in the process of health care delivery.

National medicine regulatory agencies authorise medicines to be manufactured, distributed, sold and used in their countries based on their expected net benefit to patients. Regulation of the pharmaceutical sector, including import and export controls and post marketing surveillance, is critical to ensure that the public is protected from harmful medicines. The highest priority of National Drug Authority is to enhance the safety, efficacy and quality of medicines on the Ugandan market and increase public confidence in the quality of medicines by strengthening the pre and post-market regulation for all medicines and health care products imported, manufactured, distributed, and used in the country [19]. The goal of pharmacovigilance, one of the regulatory functions is to promote patient safety. However, many countries now recognise that the views of patients were missing in matters of medicine safety and are setting up systems to reduce the burden of unsafe medication. The WHO declared the first World Patient Safety Day on 17th September 2019 that was celebrated globally [20]. The nature and scope of harm resulting from unsafe medication differs across healthcare systems and within various resource settings. Countries with limited resources, therefore, should develop strategies and evidence-based interventions to protect their citizens from possible medication-related harm at every point in the process of health care delivery. These efforts are the essence of pharmacovigilance and can only be sustained with involvement of all stakeholders including patients and healthcare professionals.

The objective of the research project was to inform development of an evidence-based policy that promotes patient safety. According to the WHO concept of a drug use problem [11], this project designed two interventions to solve some of the challenges faced by pharmacovigilance systems in limited resource settings. Evidence-based policies and intervention begin with examination and description of the medicine use problem as illustrated in the figure 5.1 below. During this search process, the problem is identified and characterised. In this project, problems about the safety and use of medicines were identified. Systematically, the magnitude of the burden of adverse drug reactions and other drug related issues in outpatient settings and the community was established to be higher than the expected or clinical trial settings. The increase in reports could be explained by the closer

interaction between the healthcare professional and the patient which created a conducive environment for reporting the adverse events and any other issues. The methodology of collecting, analysing and disseminating information about the safety and use of medicines needs re-evaluation for improvements especially in the ease of use. Apart from issues regarding the use of medicines, the presence of substandard and falsified medicines on the market needed to be addressed as it had an effect on the quality of medicines. Due to scarce resources, the system issues were prioritised in the context of the current pharmacovigilance system and subsequently, solutions have been proposed as part of the project.

Figure 5.1 Change of a drug use problem: an overview



Malaria endemic countries, such as Uganda, would benefit from an evaluation of the safety data of Artemisinin-based combination therapies that have been in use for more than ten years now [21, 22]. However, given the heavy reliance on the spontaneous method of reporting of adverse drug reactions, mainly from healthcare professionals, such an evaluation is likely to be misleading [23, 24]. It might give an incomplete picture of the performance of this group of medical products on the market because of possible under-reporting. The first study in the fourth part of this thesis on the burden of ADEs in Artemisinin-based malaria therapy found a higher incidence of ADRs than clinical trial, post-market and other previous community studies. This is expected since the adverse event reported could have been prompted by the phone calls and home visits that were implemented as part of follow up on day 3, 7 and 14. This finding is closer to the real-life situation in which the level of control of extraneous factors is less ideal than in a clinical trial setting. In this active follow up study of outpatients, we established that suspected adverse drug reactions occurred to the level of almost one in four patients taking ACTs and that looking out for safety information especially directly from patients and consumers of medicines is complicated but beneficial.

The lesson learnt for countries with limited resources that even with a manual system, consumers and patients could be a very good source of information about the quality of medicines. Looking for safety and quality information from patients and consumers of medicines is complicated but beneficial[25]. The US Food and Drug Administration evaluated the “Drug Ineffective” code in MedDRA database and extracted useful information from consumers, especially about the quality of products. However, the process of getting this information consumed a lot of time and resources. The complaint handling system for the National Drug Authority provides an opportunity for feedback from patients and consumers about the performance of medical products on the market. So far, this is the main source of quality complaints about medicines for the authority where up to 50 complaints are handled annually. In the last financial year, the NDA made about 20 recalls of products from the market due to quality and safety concerns from such a simple system.If the design and efficiency of such a system is improved, more reports of defective products will be captured since the prevalence of substandard and falsified products products is estimated to be higher in the LMICs than in the developed world.

Our findings indicate that it is just poor-quality medicines that the consumers or patients can report. Patients are capable of reporting more adverse drug events and in more detail than healthcare professionals and should therefore be empowered. The pattern of reported ADEs varied between the two categories, with half of healthcare professionals reporting skin effects like body itching and the patients instead reporting internal organ issues in the gut, musculoskeletal, connective tissue and the nervous system. Regulators must innovate more ways of reaching out to consumers and figure out ways to diversify data collection methods directly from consumers. Use of social media for promoting reporting and collecting

data concerning safety or quality issues as well as adverse drug events is recommended. However, also the development of skills to search such graphic data for signals will also be necessary.

Pharmacovigilance services will be more beneficial to consumers when they are closer to them. Women had a higher chance or developing and reporting an ADE in our study.Additionally, they have long been underrepresented in clinical trials, historically due to concerns to involve women in reproductive ages due to risks for pregnant women and the foetus.Since womenare the usual primary care givers in homes, a sensitization programme targeted toward them and the household would be great. Monitoring of adverse events during pregnancy is one thing that we found ignored sometimes. For eight out of the 25 pregnant women to have received any form of ACT in their first trimester is a matter that should be taken seriously. The reproductive health program should work very closely with the disease control programs to sensitise women on testing for pregnancy and to avoid taking medicines in their first trimester. This message should get to the public. Funds for health promotion can be raised by charging a minimum amount of tax on some fast-moving goods like fuel that can contribute to sustaining such public health campaigns. In that case, then, the men should be sensitized to report adverse events so that the pharmacovigilance policy makers can get a more balanced evidence base for their decisions. The silence of men in issues of health seeking behaviour and reporting could be culturally entrenched to be seen as weakness. More recent research into 50 years' work of the global database of ICSRs indicates that men tend to report the more serious and fatal reactions[26]. Two of the studies in the research project confirmed that segmentation of the audience according to gender, age-group, rural-urban groupings, education levels and education was very important. The message to the LMICs regulatory authorities in this regard is that they should employ qualified communication specialists to advise on these messages other than leave them to the technical scientific staff managing the safety data to communicate to the general public.

The strength of a pharmacovigilance program relies on the health system in which it operates. The active follow up study of the burden of anti-malarialswas based on a limited sample size due to resource constraints, however, important lessons can be drawn from it to develop or enhance the monitoring of drug safety in other public health programs. For instance, public health programs have invested more in increasing adequate access to and initial uptake reproductive health commodities but not safe follow up care, particularly when adverse effects occur. The NPC has not received any adverse event report on sexual and reproductive health products in ten years or more. Yet a recent Japanese study found a close correlation between combined oral contraceptives andthrombo-embolismin their spontaneous reporting system database and recommended close monitoring for a close onset of the thrombo-embolism within three weeks[27]. For such close monitoring of a serious adverse event, similar active-surveillance for a short timewould be relevant. In siettingss with scarce resources, the NPC and the Expanded program on

immunisation should work closely together from the start to identify and manage adverse events following immunisation in the shortest time possible as form of confidence building in the program and health services generally. The active surveillance of and quick response to vaccine safety issues would be beneficial to such a collaboration. This active methodology can also be applicable where the determination of the risk of a medicine requires additional focused post-market surveillance studies, or in the case of follow up of specific product quality issues and suspected medication errors or in drug to drug interactions of interest in a big public hospital setting.

Another important lesson was from medication errors identified from the artesunate given in out-patient departments beyond the recommendations of the standard treatment guidelines for uncomplicated malaria. We found that the three percent of patients who developed ADRs were exposed to dosing errors. Medication errors are under-reported, partly due to the fear of litigation [28,29] and other reasons such as lack of a platform for reporting them. Healthcare professionals ought to be assured that identification and prevention of medication errors is part of the health facility quality improvement and not a fault-finding exercise. Drug utilization and cost analysis studies are required for paediatric drug treatment to reduce on the level of wastage of medicines to almost half as indicated in this study.

In settings with limited resources, community health and development programs based on evaluations in published literature are a rare occurrence. In the second chapter of part four of this thesis, we show the effect before and after development and implementation of a community dialogue and sensitisation program on patient reporting of adverse drug events. The increased knowledge and awareness about medicine safety issues and improved attitudes about healthcare professionals and the health service delivery created a conducive environment for reporting adverse drug events. The CDS intervention was a hybrid modification of the community dialogue previously used to stimulate community support and engagement in the context of integrated community case management of childhood diarrhoea, pneumonia and malaria by Malaria Consortium in Zambia, Mozambique and Uganda [30]. The CDS model added a sensitization campaign using radio messages, posters and brochures to raise drug-safety awareness encourage dialogue and involve the community in designing solutions to pertinent issues. This intervention involved a participatory communication process of sharing information through existing community-based structures and enabled communities make informed choices and to take individual and collective action. The messages developed for this study focused on informing communities that any drug was capable of causing ADEs and monitoring them was essential in improving drug safety.The research assistants were social workers that regularly collected information from this community for the Iganga Mayuge Health demographic surveillance site. During the focus group discussions and community meetings, they interviewed participants until saturation.

The opportunity to discuss patient and community concerns about medication during meetings in a neutral setting led to renewed interest in health service delivery. The village leaders mobilised the communities in the best way they knew. Community health extension workers (CHEWs) delivered messages on medicine use as well as other health intervention messages more efficiently. The CHEWs and village leaders supported the initiative as they experienced more relevance because they were consulted about the health of their people. The people welcomed dialogue meetings, especially on days when they had to wait long at health facilities or on weekends when they were relatively free from their gardens. These meetings provided a place for learning through peers and colleagues with similar issues or knowledge gaps on safe medication. The community members also shared challenges with regard to medication and medicine use and possible solutions to complications. Generally, this kind of dialogue improved community health seeking behaviour. Patients gained confidence to return to healthcare professionals and ask questions or even report any adverse drug event. One of the factors eroding this confidence in the public health system was fear of being discovered as having gone to drug-shops and private clinics, in spite of medicine stock-outs being common. The community dialogue and sensitization program laid the foundation for direct patient reporting of ADEs from rural communities in Africa. The community engagement is also a very important tool for getting feedback on various social services. Our work confirmed that when the community is engaged on important health issues and supported with good communication and a conducive environment, there is quick learning about new concepts that can be leveraged to grow the program in a rural setting.

Throughout the research project, differences were noted in the perspectives between patients and healthcare professionals. Much as the patients and community members were most comfortable with the radio communications, the healthcare professionals expressed the best communication channel to reach the community was through the dialogue meetings. The disconnect between patients and their healthcare providers usually happens in resource-limited settings where the patients spent almost the full day at the health facility, after having travelled to get reasonable or free medical care. Some of these communities are poor but are willing to sacrifice their day's work seeking healthcare even though at the end of the day they do not receive all the drugs they are supposed to get. The option of going to buy medicines in a private facility is the last resort for many. Consequently, the numbers pile up at the public health facility and the healthcare professional usually has to attend to many patients each day. In addition, there are few health workers who want to remain in the rural settings.Health care practitioners focus more on the cost of the products, details about administration of the medicines and the numbers of patients on the register for the day, instead of immediate patient concerns, and the discomfort of adverse events. Therefore, for a good consumer reporting system, these aspects should be addressed in addition to the patients' fear of being victimised by the HCP.

Rural communities face the paradox of a higher disease burden and lower access to medicines than their urban counterparts, according to our study. The people living in urban areas, who are about one fifth of Uganda's population have better health services [31] where there is more access to information, better health infrastructure and possibly more experienced healthcare professionals when compared to rural areas. These are some of the factors that were identified in our work that will contribute to the ease of detection, identification and reporting of suspected adverse drug reactions to ACTs and possibly other medicines. In order for the populace to appreciate pharmacovigilance, therefore, it is important for the regulatory authorities to comprehensively understand the patients' medicine safety needs and before attempting to design and implement a system that promotes patient safety.

Uganda is a multi-denominational society and religion cannot be ignored in planning for the introduction or uptake or health programs. The consideration of engaging the religious leaders in community activities facilitated access to members. The Roman Catholic community do not believe in contraception, and their adverse event reports would exclude adverse events on contraceptives. Muslims usually have more than one wife and this affected our sampling since we expected to get one representative from each household. During the launch of the October 2019countrywide immunisation campaign against measles-rubella and polio diseases targeting all children under 15 years of age, the minister of health in Mayuge district with a hight muslim population was quoted saying, "I am aware of certain religious sects and tribes that don't want to vaccinate children. I appeal to you to bring your children for vaccination. We love your children that's why we are providing these vaccines free of charge"[1]. Religion was included as one of the variables in our study and should thus be included be in future sensitization for health and pharmacovigilance programs.

This study was implemented in two predominantly rural districts in eastern Uganda where part of the study on the burden of anti-malarials was done. Generally, there is need across the country for sensitising the masses about medicine safety and to have a consumer-led reporting of adverse events. The scale up of the CDS from the rural setting may not be wholly acceptable or feasible in the urban setting because of the different lifestyles. What is scalable is reaching out to the community through audio and visual messages. It would require more resources to also scale up the focus group discussions and the community meetings part of the intervention.

In the third chapter three of the part four of thesis, the perceptions of healthcare professionals about lack of efficacy of medicines for the treatment of uncomplicated malaria were analysed. The AL containing ACTs were thought to give less satisfactory patient outcomes than the DHP containing ACTs because of a more convenient dosing schedule and a lower pill burden. Artemether/Lumefantrine is the most commonly used ACT as it is the first-line treatment for uncomplicated

malaria.Misdiagnosis of non-malaria febrie illness as malaria and self-treatment with anti-malarials, especially in areas with limited access to health serviceshas greatly contributed to the overuse and possibly to the notion among HCPs that this group of medicines do not give the desired outcomes. Fortunately, the test, treat and track malaria policy launched in 2016, if re-inforced will be beneficial in terms of reducing the cost of treatment and quality of healthcare provided. The region of work for the HCPs was significantly associated with the suspected treatment failures and going by appearances, the West Nile region had one quarter of the visual defects in the study. Most of the samples from this region were obtained covertly from the informal sector with leads from a risk-assessment that was informed by among other things, the HCP perspectives. However, the national quality control laboratory proved that the ACT medicines collected from all the regions were of good quality. There are clear challenges in the detection and reporting of SF medical products, including the fact that they can be very difficult to identify. An unexpected lack of efficacy is sometimes the only signal that there may be an issue in either the quality of the medicine or the existence of resistance in the patient. What our study shows is that only when a medicine has been subjected to a comprehensive screening process or further comprehensive laboratory analysis is it revealed that the medicine was in fact substandard or falsified. The views of the HCPs are still important to the patients, they cannot be ignored in the process of improving healthcare delivery as they can provide useful insights to risk-based PMSsampling. During policy formulation especially for prevention of ACT resistance, the HCPs have to be sensitized more about the new interventions and their importance in daily practice.

From our findings, the pilferage of possible pilferage of government drugs into neighbouring countries like South Sudan and the Democratic Republic of Congo raises concern. Cross-border regional collaboration will be needed to stamp out access not only to stolen drugs but to other non-quality assured medicines that have been documented previously. This is a very resource-intensive exercise is not easily sustained by individual low and middle-income countries. The drug regulatory authority also needs to conduct more covert operations in the Central, Eastern and Northern regions of the country as indicated by our study. The manufacturers of products with coating defects have to be notified and asked to explain such incidences which may be indicative of a break down during the manufacturing process or possible falsification. Our study also revealed some laxity in the enforcement of regulatory requirement for product information leafletsthat should be addressed as it could also be an indicator of product falsification or deny users of the necessary information about the products. Such simple visual inspections are important and LMICs can enforce these at the very minimum and can engage the general public as partners to report substandard and falsified medicines on the market.

Perceived treatment failure was measured by the frequency with which a particular “brand” was listed from a pre-determined list of ACTs registered in Uganda. The

challenge experienced during the identification of the ACT brands was the multitude of branded generics on the market. There is no harmonised labelling for the different products; banded and unbranded generics. In Uganda, most of the products are imported and the generic market share is likely to be over 80%. During registration, a sample of the labelling and packaging of the product with certain minimum details is required and also data on the interchangeability for generic products but these requirements are not prescriptive. However, working with a pre-determined list made work simpler but also exposed the study to excluding certain brands which were not known to the research team. The recommendation is that for the LMICs, during harmonisation of guidelines in the regional economic blocks, details like labelling should be considered.

This study also emphasized the need to empower the patients to be able to report ADEs.The views of patients and consumers have been used in high-resourced countries to report ineffective drugs through a labour-intensive manual process that could be adapted for low and middle-income countries like Uganda due to a higher prevalence of substandard and falsified products on the market. An interesting finding from our study was that HCPs had higher chances of noticing a higher perceived ACT treatment failure rate than those from the public health facilities. This could be because the study was not collecting information on details as the first study. Possibly, the fear of litigation contributes to the closing up and guarding of information by the private sector and should be noted in future collaboration with the private sector. On the other hand, this reveals the importance of the private sector in the healthcare and for pharmacovigilance. Global pharmaceutical companies have facilitated in the costly identification offalsification of the innovator products. However, some of the manufacturing defects that we observed could be due to some of the private profit-hungry manufacturers presenting products of a lower standard than what was registered in the country. This is an area that countries with LMICs and weakly regulated markets should look out for.

The integration of both the qualitative and quantitative methods in this research projects allowed for a more complete and synergistic utilization of the data generated to contribute to best practise. The data collection, analysis and interpretation involved a lot of collaboration across different fields like social science, medicine, pharmacy, epidemiology, economics and pharmacovigilance. It enabled the research team to understand multiple perspectives on the same issue of reporting adverse events. The information from the project is very rich and will influence policy in a way that using either the quantitative or the qualitative method individually. One advantage it added was validation of findings using quantitative and qualitative data sources. It involved collecting both types of data at about the same time; assessing it using parallel constructs for both types of data; separately analyzing both types of data; and comparing results through a side-by-side comparison during discussion, transforming the qualitative data set into quantitative scores, or in the second and third studies, jointly displaying both forms of data. The data collection tools for the consumer reporting system or medication error

reporting system will benefit from some of the exploration with data that has been collected during these studies that has not been published. Despite the expense of the CDS, it was an excellent way of engaging the community and obtain almost total buying of the project. The multiple phases of engagement ended up with suggestions of implementation of the intervention. However, the mixed methods increased the complexity of the planning and implementation of the research. Utmost care had to be taken in planning the sample size, integrating the data in discussion and presentation, getting the right experts and also convergence on the analysis within the resource constraints. In the end, it was worthwhile.

A new methodology for pharmacovigilance was developed that was a form of active follow up that is not as resource intensive as the traditional cohort event monitoring with minimal loss to follow up. The community dialogues and sensitization intervention was adapted in a rural health demographic site setting to stimulate adverse drug reactions directly from patients in the community and generate new interest in healthcare services. The effect of CDS intervention has been evaluated in a before-and-after study whose findings will inform the pharmacovigilance policy on patient involvement in a rural environment. An analysis of healthcare professionals' perspectives revealed useful insights in the optimization of malaria therapy in resource limited settings where reporting lack of efficacy is almost non-existent. The results of these studies will contribute greatly to the global movement of making healthcare safer especially in LMICs. There is now better understanding of the need for health systems strengthening along the rural- urban divide and secondly along the private and public-health sector. The factors that drive pharmacovigilance and health systems in these loci are different and subsequent to this understanding, new solutions or modifications in existing services can happen.

In a nutshell, the strength of a pharmacovigilance system depends on the strength of the health system in which it operates. Universal health coverage needs resilient health systems that are efficiently managed, with adequately trained and motivated human resource, and able to provide good quality, safe and efficacious medicines. Globally, gaps in access to and use of medicines lead to wastage. More dollars are spent on medicines, yet the prescribing habits do not generally comply with the standard treatment guidelines. The profit motive among those providing medicines in the private sector in weakly regulated markets emphasizes the need for regulation of the activities and the product quality so as to deliver better health care services. Governments with low healthcare budgets usually have high disease burdens and less regulated markets. Under these circumstances, pharmacovigilance enables post-approval monitoring of adverse events and medicine-related issues. These adverse effects must be reported. The capacity to assess these reports is progressively increasing, but there is still room for improvement in terms of HCPs and the regulators involvement. Uganda, with an ambitious target of achieving the sustainable development goals, has made strides in improving public health overall. Some examples of implemented evidence-based

policies have been given. This thesis has gathered evidence on policy enhancements and establishment that will go a long way in strengthening the pharmacovigilance system for Uganda and other LMICs. Improvement in data collection for pharmacovigilance, especially for short term out-patient treatments like the ACTs, will benefit from the adaptation of our active follow up of adverse events study. The CDS intervention based on the community culture and practices has demonstrated ways in which pharmacovigilance can be incorporated into daily life activities and in the long-term making pharmacovigilance a household name.

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5.2 Perspectives

“For every dark cloud, there is a silver lining” is the message of hope for countries that do not yet have a fully functional pharmacovigilance system. Limitation of resources should lead them think of more strategic and cost-effective ways to providing safer medicines and healthcare for the population. However, how the health system is organized and how the components of the systems interact determines how successful a medicines safety monitoring program will be. A good pharmacovigilance system needs to ensure that emergent problems are promptly recognized and efficiently dealt with, and that information and solutions are effectively communicated to all parties concerned.

Over the years,strong drug safety monitoring systems have been laid in many high-income countries, although sometimes it was in response to disasters. The Thalidomide tragedy of phocomelia following use as an anti-emetic in pregnancy that started in Europe resulted in the formation of a global pharmacovigilance program. A pharmacovigilance system has been defined as a system used by an organization to fulfil its legal tasks and responsibilities in relation to pharmacovigilance and designed to monitor the safety of authorized medicinal products and detect any change to their risk-benefit balance [(1)].The study of the benefits and risks of drugs plays a major role in pharmacotherapeutic decision-making, whether it is individual, regional, national or international.

The scope for pharmacovigilance has widened in the last ten years and has evolved pharmacovigilance into a new scientific discipline in its own right. However, the burden of adverse drug reactions is underestimated globally due to under-reporting. Research among hospitalized patients in high-income countries revealed that half of the medicine-related harm is preventable. The United States recently demonstrated that it is possible to save billions of dollars if such harm is avoided. There is now a global paradigm shift from engaging mainly healthcare professionals in reporting adverse drug events to including the patient’s voice in providing safer patient care. Another challenge is that gaps in knowledge still exist regarding the safety and quality of medical products even after they have been authorized. International harmonization initiatives have thus focused on continuous sharing of experiences and knowledge among regulatory agencies and possibly other stakeholders.

Governments of LMICs as well as development partners have concentrated on making medicines available. However, more efforts must be put into making them safe, efficacious and of good quality. World Health Organization has developed a global benchmarking tool to not only assess the pharmacovigilance system but also other regulatory functions and make recommendations for improvement. It is clear that it is not only financial resources that matter in building and sustaining a strong system for monitoring safety and quality of medicines but also how they are

utilized to achieve the desired outcomes. The goal of pharmacovigilance should be patient safety.

In Uganda and most African countries, health service delivery tends to have a more curative than a preventive outlook. Looking to the future, this mindset must change so that people will be healthier and to take less drugs and subsequently there will be fewer resources for pharmacovigilance. The future of pharmacovigilance depends on strong collaborative networks in the medicine supply chain, the health sector and other service sectors generally. It will be a dream come true when the local pharmaceutical manufacturing industry importers and distributors conduct pharmacovigilance for their generic products on the market. This target of the NPC for the next 5 years is achievable and other countries in the region should plan in such small steps in order to rid our regional markets of poor quality and unsafe products. For instance the regulators must involve the local industry to understand the newly introduced EAC requirement for a qualified pharmacovigilance focal person and work closely with the companies to monitor their risk minimization plans for selected priority products. In that way, the pharmacovigilance system of countries will have a more preventive outlook that is currently the case.

The pharmaceutical market in LMICs is wide ranging from first aid, over-the-counter medicines, herbal medicines, veterinary pharmaceuticals, vaccines and to highly specialized hospital administered products. The manufacturers, dealers and stakeholders are numerous and wide and there is no single reliable source of information on trade, production, consumption and use. This is one of the challenges of regulating the activities in such a market. One of the ways to deal with informational imbalance between the manufacturers, prescribers, sellers and consumers of medicines is to regulate practices and products in the pharmaceutical market. This imbalance creates a weak regulatory environment where the legal framework is non-existent and law enforcement is not easy. It is clear that in the LMICs, that it is better to place more emphasis on post-marketing activities and control of regulation of drug information than the pre-marketing activities in order to provide better quality assurance of the pharmaceutical products, For instance, the legal requirements in many African countries [(2)] do not require market authorization holders to submit risk management plans as part of the introduction of new medicines on the market. Secondly, the capacity to assess the safety information in the risk management plans on an ongoing basis by the regulator is still limited. However, as part of the African Medicines Regulatory Harmonization initiative, capacity is being built in regional economic blocks through the regulatory regional centres of excellence. Hopefully, in a short time, that capacity will be more readily available across the continent.

Government also corrects this drug informational asymmetry by providing information and training about the medicines and their use to consumers and prescribers. The provision of the information needed for the evaluation of the benefits and risks of drugs is in the first place a scientific challenge for all involved

in the medicine supply chain in limited resource settings. In Uganda, the majority of medical courses teach pharmacovigilance and also in-service training is now regularly. All the health practitioners' governing bodies have embraced pharmacovigilance and are supported by the NPC to run pharmacovigilance courses as a form of continuing professional education.Everyone must be educated about medicine safety including children in school. Like the saying goes, "catch them young". School going children have to be exposed to the concept of medicine safety like they are exposed to immunization messages in the primary school curriculum. This will in the long term contribute to addressing the knowledge gap within the community. Currently, in Uganda and recently in developed nations, it is possible that a regulator recalling a defective medicine off the market is accused of having allowed it on the market in the first place. A good media rapport works well to educate and sensitise the public but could also spin the situation out of hand. In settings with scarce resources, wise investment choices have to be made on the best course of action and documentation of these events is necessarily to enable medicine regulation to learn from history. Going forward, the lesson for especially African medicine regulatory authorities is to document.

The intervention of community dialogues and sensitization that was developed as part of this research project is resource demanding, however, it can be integrated within the community health programs. As the ministry of health seeks to make the CHEWs more effective, this is a model to use. It worked for intergrated-management of childhood illnesses at community and household level, it can also work for medicine safety and other forms of health education. As a government, it can also work beyond the health sector. The value for money for CDS can be increased if each rural community was well coordinated and had a program line up of discussion drawn from all areas of life like agriculture, health, sanitation, finances, parenting and so on. Even in its current state, CDS can help to quickly create confidence in an immunization mass campaign programme.

Healthcare professionals are also one of the main building blocks of a functioning health system in which pharmacovigilance operates. The knowledge from healthcare professionals is usually not effectively utilized in daily practice. The health workers from all sectors including public, private, pharmaceutical manufacturers and academia should be more fully engaged in pharmacovigilance activities. Our study revealed that relying on only healthcare professionals to guide the assessment of drug efficacy and drug quality does not work. The long lines of patients that the health workers have to attend to, the limited time for each patient, biases of the health workers and the capacity to identify issues such as lack of efficacy affect the detection of the harm. Multi-tasking and re-tooling the lower level staff giving ART has ended up with an increased number of cases not adhering to treatment guidelines. For the healthcare professionals that administer medicines to patients, smarter and faster ways of disseminating this information will become a necessity more than ever before to improve the quality of care. For instance, some healthcare professionals were not aware about emergence of ACT resistance and

yet they are major stakeholders in the responsible use of the ACT medicines to preserve these new medicine molecules that do not have easily have an alternative. Public health programs need to integrate PV to monitor new vaccines and medicines introduced through these programs such that more ADE reports are collected. Signal analysis should focus on high-burden preventable adverse drug problems so that the cost of providing healthcare can be reduced in due course.Continued resistance monitoring to identify early artemisinin resistance or early indicators for antimicrobial resistance and re-inforcement of the “diagnosis before treatment” policies would be of great value to national disease programs. For the HCPs, it would be worthwhile venture to explore how best to them personalized health and drug information to aid their decision making on a real-time basis, after all the world trend is now personalized digitalized medicine.

It is clear from practice and literature that in many LMICs, you get a better health services in urban areas. African tradition has been preserved mainly by word of mouth from generation to generation. It is now high time that documentation of structures, processes and outcomes becomes a regularpart of our efforts to protect the people and provide access to safer medicines. Governments should establish policies to retain human resources in the rural areas as a part of confidence building in the health service delivery.

Self- medication is a very common practice that is a key driver of anti-microbial resistance. It makes healthcare more costly given that a certain amount of drug information is necessary to optimize drug therapy which is the preserve of a healthcare professional. For some diseases, the same event has to be treated more than once. In a fragmented complex health system, where consumers and patients neither recall nor declare all their medicines it becomes difficult to accurately assess and prevent adverse drug effects. The patients also easily identify with the community health workers that the government promotes in rural settings that have limited education and help them deal with simple fevers and childhood illnesses.

According to the WHO global surveillance and monitoring system for substandard and falsified medical products,the most frequently reported SF medicines are antibiotics and antimalarials comprising approximately 40% of the database.As the criminals become more skilled, the well-resourced countries have access to sophisticated analytical techniques that are not accessible to poorly resourced countries. The need for African countries and other low-resourced settingsis for simplified screening methods which are rugged, portable and do not need sophisticated laboratories or costly reagents to determine candidate samples for further full analysis. With the scarce resources, the WHO methodology on sampling for quality surveys of medicines seems to be extravagant and can be modified to conserve medicine samples used only for visual inspection without damaging their primary packaging to contribute to the next stage of sampling for confirmatory testing in the laboratory.SF medical products can promote antimicrobial resistance

and the spread of drug-resistant infections. Unless action is taken, SF medical products in one country can make diseases difficult to treat in another. To paint a clearer public health picture, surveillance and monitoring of SF medical products must link to existing systems and networks, including those that track antimicrobial resistance. Taken together, this data will be able to better assess the extent of the problem and impact to public health.

The general public should be assured of a safe environment for drug therapy. Communication challenges about the safety of medicines and vaccines exist especially in the African context. The ethnic, religious, cultural issues and rumors influence popular perception, shaping public opinion and official responses to events. International multiple stakeholder efforts like the Erice declaration [(3)] and the international celebration of World Patient Safety Day emphasize the critical role of communication in drug safety. More creative ways of engaging stakeholders especially in preventing, detecting and responding to substandard and falsified products on the market and in other regulatory processes including drug development are likely to feature prominently in pharmacovigilance system strengthening efforts. Following global efforts to include direct reports from patients, more African countries will embrace this effort. As the NPCs receive more reports they will have to find better and more sustainable means of providing feedback to all reporters. Active forms of surveillance are also on the rise and modification of existing methods and newer interventions like those of the community dialogue and sensitization will be used to stimulate interest in reporting ADEs, quality issues and these will improve the healthcare service delivery.

The aspiration of this research project has been to present contributions that strengthen cross-disciplinary conversations across the relatively new discipline of pharmacovigilance. Not only for the purpose of innovation but for also telling the story of pharmacovigilance and regulation in resource-limited settings. Innovation often occurs on the boundaries and not the centre, as the centre is blinded by methodological and theoretical straitjackets that define a discipline. This cross-disciplinary engagementwas meant to move this regulation research outside the ‘comfort zones’ of established areas of investigation. A vision of greater cross-disciplinarity is likely to provide for innovative answers to the traditional questions about the subject of pharmacovigilance and to trigger its own questions. In that way, making the pharmacovigilance practitioners more relevant to the concerns of the people that we serve.

Many questions have been raised along the course of studies and gaps to be filled have been identified. The access to the private sector in the study to establish the burden of adverse drug events was limited, primarily because of the HCP attitude that this was a fault-finding mission. It is therefore important to study the driving factors for health worker involvement in drug safety monitoring activities so as to design interventions that can lead to attitude change. The study provided an opportunity to understand the nature of medication errors in an outpatient setting.

Drug utilization and cost-analysis studies will be required for paediatric ACT treatment to reduce the level of wastage in some health facilities. Since many medication-error studies have been conducted in hospitals, more studies on medicines used in both in- and out-patient settings should be done and a national policy for detection and prevention of such errors established in collaboration with the quality assurance department of the ministry of health. Pregnancy registers which until recently only been in research settings have to be implemented in capable surveillance sites in the face of signals of serious adverse events to a new drug like Dolutegravir. The detection of adverse events like hyperglycaemia which have not been listed arise out of active surveillance studies that are likely to be conducted more often in LMICs in the near future.

A consideration for future research from our findings is the use of a control group in the evaluation of similar community programs, and the impact or long-term effects of the CDS program on the community. Further comparisons will have to be made between direct patient-ADE reporting systems and the current indirect reporting through healthcare professionals; the cost effectiveness of various sensitization methods; and best practices for providing feedback to reporters in settings with limited resources.

It would be very useful to conduct bioequivalence studies to verify treatment failure and to follow up on identified cues to product falsification or pilferage of medicines with the relevant authorities. The outcome of such studies would be of much interest to the drug regulators since bioequivalence analysis is not a pre-condition for registration of medicines, yet it determines the performance of the many generics that are used on the Ugandan market.As a follow on for policy makers, mapping and predicting ACT resistance trends would provide information necessary to take early action to preserve the performance of these drugs for as long as possible, also taking into account the resources needed in a good prediction model. The relationship between ACT resistance and ACT use in the various regions also needs to be established in future studies.

There are important ethical, logistical, legal, financial and commercial constraints that need to be addressed to deliver stronger pharmacovigilance systems. The stronger pharmacovigilance systems can only work in stronger healthcare system which are a target of the international sustainable development goals. The African contribution to the global database of adverse drug effects and medication related harm is bound to increase as more countries and regional economic blocks strengthen their pharmacovigilance systems. For countries with limited resources, more robust systems will mainly be as a result of better knowledge management of medicine safety information among the various stakeholders.

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Appendices

S1 Table: Comparison of study participants' attitude towards the need to report adverse drug events before and after the CDS intervention

	Yes				No				Don't know			
	Before (%)	**After (%)**	**% diff.**	**95% CI**	**Before (%)**	**After (%)**	**% diff.**	**95% CI**	**Before (%)**	**After (%)**	**%diff.**	**95% CI**
Age category												
15-24	144 (88.3)	133 (97.1)	10.0	4 to 16	12 (7.4)	4 (2.9)	-60.8	-88 to -33	7 (4.3)	0 (0)	-100.0	0
25-34	288 (94.7)	214 (95.5)	0.8	-3 to 5	8 (2.6)	8 (3.6)	38.5	21 to 55	8 (2.6)	2 (0.9)	-65.4	-88 to -42
35-44	227 (93.4)	192 (96.0)	2.8	-1 to 7	10 (4.1)	7 (3.5)	-14.6	-33 to 4	6 (2.5)	1 (0.5)	-80.0	-111 to -49
45-54	133 (91.7)	134 (97.8)	6.7	2 to 12	7 (4.8)	1 (0.7)	-85.4	-128 to -43	5 (3.4)	2 (1.5)	-55.9	-83 to -29
55-64	95 (90.5)	52 (96.3)	6.4	-1 to 14	4 (3.8)	1 (1.9)	-50.0	-90 to -10	6 (5.7)	1 (1.9)	-66.7	-113 to -20
65+	67 (90.5)	73 (98.6)	9.0	2 to 16	5 (6.8)	0 (0.0)	-100.0	-	2 (2.7)	1 (1.4)	-48.2	-
Education						0 (0.0)						
None	127 (86.4)	80 (88.9)	2.9	-6 to 11	12 (8.2)	7 (7.8)	-4.9	-30 to 20	8 (5.4)	3 (3.3)	-38.9	-67 to -10
Primary	488 (91.7)	410 (97.4)	6.2	3 to 9	22 (4.1)	7 (1.7)	-58.5	-74 to -43	22(4.1)	4 (1.0)	-75.6	-95 to -56
Secondary	294 (94.8)	259 (97.7)	3.1	0 to 6	12 (3.9)	6 (2.3)	-41.0	-59 to 0	4 (1.3)	0 (0.0)	-100.0	0
Tertiary	23 (100.0)	27 (100)	0.0	-	0 (0.0)	0 (0.0)	0.0	-	0 (0.0)	0 (0.0)	0	-

	Yes				No				Don't know			
	Before (%)	**After (%)**	**% diff.**	**95% CI**	**Before (%)**	**After (%)**	**% diff.**	**95% CI**	**Before (%)**	**After (%)**	**%diff.**	**95% CI**
University	22 (100)	22 (95.7)	-4.3	-13 to 4	0 (0.0)	0 (0.0)	0.0	-	0 (0.0)	0 (0.0)	0	-
Religion												
Anglican	225 (91.5)	248 (98.8)	8.0	4 to 12	12 (4.9)	2 (0.8)	-83.7	-114 to -53	9 (3.7)	1 (0.4)	-89.2	-126 to -52
Roman Catholic	90 (96.8)	80 (97.6)	0.8	-4 to 6	1 (1.1)	2 (2.4)	118.2	-	2 (2.2)	0 (0.0)	-100.0	-
Pentecostal	97 (94.2)	98 (95.1)	1.0	-5 to 7	3 (2.9)	3 (2.9)	0.0	-27 to 27	3 (2.9)	2 (1.9)	-34.5	-62 to -7
Muslim	525 (91.6)	362 (95.3)	4.0	1 to 7	30 (5.2)	14 (3.7)	-28.9	-42 to -15	18 (3.1)	4 (1.1)	-64.5	-82 to -47
Other	17 (89.5)	10 (100)	11.7	-2 to 26	0 (0.0)	0 (0.0)	0.0	-	2 (10.5)	0 (0.0)	0	-
Overall	**954 (92.3)**	**798 (96.6)**	**4.6**	**3 to 7**	**0 (0.0)**	**0 (0.0)**	**-43.2**	**-53 to -33**	**33(3.3)**	0 (0.0)	**-75.8**	**-89 to-62**

S2 Table: Comparison of respondents' having ever experienced ADEs by socio-demographic characteristics before and after CDS

	Yes				No				Don't know			
	Before (%)	After (%)	% age diff.	95% CI	Before (%)	After (%)	% age diff.	95% CI	Before (%)	After (%)	% age diff.	95% CI
Age group												
15-24	51 (31.3)	43 (43.0)	37.4	18 to 57	108 (66.3)	57 (57)	-14.0	-29 to 1	4 (2.5)	0 (0.0)	-100.0	-
25-34	109 (35.9)	61 (42.1)	17.3	2 to 32	183 (60.2)	84 (57.9)	-3.8	-16 to 9	12 (3.9)	0 (0.0)	-100.0	-
35-44	80 (32.9)	61 (47.3)	43.8	28 to 60	159 (65.4)	67 (51.9)	-20.6	-34 to -7	4 (1.6)	1 (0.8)	-50.0	-76 to -24
45-54	47 (32.4)	43 (46.7)	44.1	24 to 64	96 (66.2)	47 (51.1)	-22.8	-40 to -6	2 (1.4)	2 (2.2)	57.1	31 to 83
55-64	36 (34.3)	13 (35.1)	2.3	-28 to 32	68 (64.8)	24 (64.9)	0.2	-22 to 22	1 (1.0)	0 (0.0)	-100.0	-
65+	26 (35.1)	16 (36.4)	3.7	-26 to 34	46 (62.2)	28 (63.6)	2.3	-20 to 25	2 (2.7)	0 (0.0)	-100.0	-
Education												
Primary	180 (33.8)	120 (42.4)	25.4	14 to 37	340 (63.9)	161 (56.9)	-10.9	-20 to -2	12 (2.3)	2 (0.7)	-69.6	-91 to -48
Secondary	109 (35.2)	73 (40.1)	13.9	0 to 28	194 (62.6)	109 (59.9)	-4.3	-16 to 7	7 (2.3)	0 (0.0)	-100.0	-
Tertiary	12 (52.2)	8 (40.0)	-23.4	-68 to 21	10 (43.5)	12 (60.0)	-86.2	-118 to -55	1 (4.3)	0 (0.0)	-100.0	-
University	10 (45.5)	13 (65.0)	42.9	16 to 70	12 (54.5)	7 (35.0)	-35.8	-73 to 1	0 (0.0)	0 (0.0)	0.0	-
Religion												
Anglican	89 (36.2)	66(38.6)	6.6	-9 to 22	152 (61.8)	104 (60.8)	-1.6	-14 to 11	5 (2.0)	1 (0.6)	-70.0	-98 to -42
Roman Catholic	23 (24.7)	20(41.7)	68.8	41 to 96	69 (74.2)	28 (58.3)	-21.4	-41 to -1	1 (1.1)	0 (0.0)	-100.0	-

	Yes				No				Don't know			
	Before (%)	**After (%)**	**% age diff.**	**95% CI**	**Before (%)**	**After (%)**	**% age diff.**	**95% CI**	**Before (%)**	**After (%)**	**% age diff.**	**95% CI**
Pentecostal	45 (43.7)	32(46.4)	6.2	-16 to 29	55 (53.4)	37 (53.6)	0.4	-20 to 21	3 (2.9)	0 (0.0)	-100.0	-
Muslim	189 (33)	115(45.6)	38.2	27 to 49	369 (64.4)	135 (53.6)	-16.8	-26 to -7	15 (2.6)	2 (0.8)	-69.2	-92 to -47
Other	3 (15.8)	4(57.1)	261.4	195 to 328	15 (78.9)	3 (42.9)	-45.6	-98 to 7	1 (5.3)	0 (0.0)	-100.0	-
Overall	**349 (20.5)**	**237(44)**	**114.6**	**137 to 217**	**660 (63.8)**	**307 (29.7)**	**-53.5**	**-84 to -3**	**25 (2.4)**	0 (0.0)	**-87.9**	**-50 to 21**

S3 Table: **Commonly reported ADEs*by the respondents before and after the CDS intervention***

	Yes/Agree n (%)				**No/Disagree n (%)**				**Don't know n (%)**			
	Baseline	**End-line**	**%change**	**95% CI**	**Baseline**	**End-line**	**%change**	**95% CI**	**Baseline**	**End-line**	**%change**	**95% CI**
Uncertain or suspected ADEs	807 (78.0)	721 (87.3)	11.92	9-15	133 (12.9)	84 (10.2)	-20.93	-28--14	94 (9.1)	21 (2.5)	-72.53	-80--65
Certain negative ADEs	697 (67.4)	634 (76.7)	13.80	10-18	235 (22.7)	168 (20.3)	-10.57	-17--4	102 (9.9)	24 (2.9)	-70.71	-78--63
Serious reactions	797 (77.1)	756 (91.5)	18.68	16-21	143 (13.8)	57 (6.9)	-50.00	-57--43	94 (9.1)	13 (1.6)	-82.42	-90--75
Mild reactions	728 (70.4)	573 (69.4)	-1.42	-6-3	243 (23.5)	246 (29. 8)	26.81	20-33	63 (6.1)	7 (0.9)	-85.25	-93--78
Reactions to drugs which have been on market for a long period	718 (69.4)	649 (78.6)	13.26	10-17	223 (21.6)	146 (17.7)	-18.06	-24--12	93 (9.0)	31 (3.7)	-58.89	-65--52
Reactions to newly introduced drugs	770 (74.5)	706 (85.5)	14.77	11-18	147 (14.2)	73(8.8)	-38.03	-46--31	117 (11.3)	47 (5.7)	-49.56	-57--42

	Yes/Agree n (%)				No/Disagree n (%)				Don't know n (%)			
	Baseline	**End-line**	**%change**	**95% CI**	**Baseline**	**End-line**	**%change**	**95% CI**	**Baseline**	**End-line**	**%change**	**95% CI**
Common or well-known reactions	639 (61.8)	483 (58.5)	-5.34	-10--1	285 (27.6)	315 (38.1)	38.04	32-44	110 (10.6)	28 (3.4)	-67.92	-75--61
Unexpected reactions	737 (71.3)	683 (82.7)	15.99	13-19	186 (18.0)	107 (12.9)	-28.33	-35--21	111 (10.7)	36 (4.4)	-58.88	-66--52
Possible interaction with other drugs	660 (63.8)	582 (70.5)	10.50	6-15	231 (22.3)	179 (21.7)	-2.69	-9-4	143 (13.8)	65 (7.9)	-42.75	-50--35
Reaction due to herbal medicine	573 (55.4)	520 (62.9)	13.54	9-18	370 (35.8)	279 (33. 8)	-5.59	-11-0.00	91 (8.8)	27 (3.3)	-62.50	-70--55
Reactions due to herbal & conventional medicine taken together	643 (62.2)	616 (74.6)	19.94	16-24	301 (29.1)	179 (21.7)	-25.43	-31--19	90 (8.7)	31 (3.7)	-57.47	-64--51

ADEs = adverse drug events

S1 File : Household questionnaire (6 pages)

MAKERERE UNIVERSITY Center for Health & Population Research (MUCHAP) Iganga/Mayuge HDSS
KAP STUDY ON ADVERSE DRUG REACTIONS
RESPONDENT SHOULD BE ADULT (18 YRS +) USUAL RESIDENT OF THE HOUSEHOLD

IDENTIFICATION

FA CODE ☐☐☐ INTERVIEW DATE ☐☐☐☐☐☐☐☐

DISTRICT ……..

VILLAGE NAME AND CODE ……☐☐☐☐☐☐

LOCATION ID ☐☐☐☐☐☐☐☐☐☐☐☐

RESPONDENT NAME …… RESPID: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

HOUSEHOLD HEAD NAME ……

HOUSEHOLD HEAD ID ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐

Status of Visits by Interviewers:	
*Result Codes 01 Completed 02 Respondent not at home at the time of visit 03 Respondent absent for extended period of time 04 Postponed	05 Refused 06 Others_____ (Specify)

Editor **Code** ☐☐ **Date** ☐☐☐☐☐☐☐☐
Supervisor **Code** ☐☐ **Date** ☐☐☐☐☐☐☐☐
Data Entry **Code** ☐☐ **Date** ☐☐☐☐☐☐☐☐

QUESTIONS AND FILTERS	CODING CATEGORIES	SKIP
1. Wazalibwa mwaka ki, mwezi ki era lunaku ki? *In what year, month and Day were you born?* IF MONTH NOT KNOWN RECORD 99 & ALSO, IF YEAR IS NOT KNOWN RECORD 99	Years ☐☐☐☐ Months ☐☐ Day ☐☐	
2. Wali nemyaka emeka ku mazalibwa go agasemba yo? *How old were you on your last birthday?* COMPARE & RECONCILE Q1 AND Q2 IF NOT CONSISTENT	Age ☐☐	
3. Wasomaku? *Have you ever attended school?*	Yes 1 No 2	→5
4. Kibiina ki ekyawaigulu kyewamaliliza? *What is the highest grade you completed?*	1 – Primary 2 – Secondary Class ☐☐ 3 – Tertiary 4 – University	
5. Obaire oviira mu maka gaano bulidho? *Are you a usual resident of this household?*	Yes 1 No 2**(End)**	
6. Oli mufumbo? *Are you currently married?*	Yes 1 No 2	
7. Oliwa eidhini ki? What is your religion?	Christian(Anglican)……..1 Christian (Roman catholic)……2 Christian (Pentecostal)……3 Muslim……4 Other (specify)……5	
8. Omukulu wa maka gaano akweta atya? What is your relationship with the Head of Household?	Head of Household……01 Spouse……02 Son/Daughter……03 Step child……04 Adopted/Foster child……05 Son in law/Daughter……06 Parent……07 Step-Parent……08 Parent-in-law……09 Brother/sister……10 Brother-in-law/Sister-in-law……11 No relation……12 Other (specify)……13	

9. Okola mulimo ki omukulu? (Omulimo ogusinga okutwala ebiseera byo buli lunaku) What is your **main** occupation (ie. Activity that regularly takes most of your day time) **PLEASE CIRCLE ONLY ONE RESPONSE**	None……..1 Public sector employee (Professional)….. 2 Public sector employee (Manual)…….3 Private sector employee (Professional)… 4 Private sector employee (Manual) ……..5 Self-employed (business)……..6 Self-employed (Agric/fishery) ……..7 Domestic work in Household…… 8 Teacher…….. 9 Student……..10 Job-less……..11 Incapacitated……..12 Other(specify)……..13	
SECTION 2: OBULWAIRE OBUMANHIKWA MU MAKA **COMMON ILLNESSES IN THE HOUSEHOLD**		

10. Buti, nandyenze okukubuzaku ku'ndwaire eghe oba abantu bo mumaka gaano dhebaalwalaku mu myezi esatu egibise n'obwiidandhabi bwemwafunaku okudidandhaba. Nkusaba onkobereku amainha ag'omuntu, emyaka, obulwaire n'obwiidandhabi obwa mughebwa.

Now, I would like to ask you about the illnesses that you or members of your household have experienced in the last 3 months and the treatment you received to manage them. I request you to tell me the name of the person, age, illness and drugs/treatment taken.

Name	AGE	ILLNESS	TREATMENT TAKEN	
i).				
ii).				
iii).				
iv).				
v)..				
vi).				

11a. Ighe oba abantu b'omumaka gaano mufunawa obwiidandhabi bwemukozesa? Where do you or members of your household usually get the treatment you use from? **(CIRCLE ALL APPLICABLE)**	Drug shop ……1 VHT……..2 Private clinic ……..…….3 Government HC……4 Hospital……5 Relative/Neighbour ……6 Other patients……..7 Herbalist ……..8 Friends……..9 Other shops/Market ……10 Bus……..11 Other, Specify……..12	
11b. Abasawo bakuwaku amawulire gaano wamanga agagema kubulezi nga ogiire okufunha obwiidandhabi? **Do health care providers give you the following information about the medicines when you seek treatment**	Drug name.... 1. Yes 2. No 3. DKN What it treats 1. Yes 2. No 3. DKN How to take it 1. Yes 2. No 3. DKN	
SECTION 3: AMAWULIRE AGAGEMA KU BULEZI, OBUZIBU N'OKULOOPA **KNOWLEDGE ABOUT DRUGS, SIDE EFFECTS AND REPORTING**		

12. Obaire okiidhi nti mukwongereza kukwiidandhaba obulwaire oba endwaire, obulezi bwonabwona busobola okuleeta obuzibu ku muntu abukozeyisa? Are you aware that in addition to treating illness/diseases, any medicine has potential to cause negative effect to person taking it?	Yes ……1 No ……2 Don't know ……3	
13.Mu myezi esatu egibise, wawulilaku obubaka bwonabwona obugemagana nobulabe oba obuzibu obulezi bwebusobola okututuusaku nengeri y'okuloopa obuzibu obwo? In last 3 months, have you heard any information about the possible negative effects of the medicines/drugs that we take and how to report these effects?	Yes …… No ……	
14.Wawulirawa obubaka obugemagana kubulabe obuva ku bulezi mu myezi 3 egibise? Where did you hear information about the drug /medicine effects in last 3 months? **(MULTIPLE RESPONSE ALLOWED)**	Radio……1 Health worker told me……2 Discussion at Health facility……3 Discussion in the community……4 Poster/publications……5 Other(Specify)……6	
15.Okukubagania ebidhubo nokusomesa abantu munkiiko kubulabe obututusiibwaku okuva ku obulezi n'okuloopa obulabe obwo, olowooza nganenkola enayongera mubantu okuloopa obulabe obuva mubulezi? Do you think conducting community meetings to discuss and sensitize people about possible drug effects and reporting is an effective way to increase reporting of drugs reactions?	Yes …… No ……	
16.Okukubagania ebidhubo nokusomesa abalwaire mu malwaliro kubulabe obututusiibwaku okuva ku obulezi n'okuloopa obulabe obwo, olowooza nganenkola enayongera mubantu okuloopa obulabe obuva mubulezi? Do you think conducting health facility meetings with patients to discuss and sensitize them about possible drug effects and reporting is an effective way to increase reporting of adverse drug reactions?	Yes …… No ……	
17.Mu ndowoozayo, **ngeriki esingirailala obulungi mukwongera** okuloopa obulabe obututusibwaku nga buva kubulezi? **(DON'T READ OUT OPTIONS)** In your opinion, what is the **most effective** way to increase reporting of effects the drugs/medicines that we take in this community?	Radio……1 Health education by health worker …2 Discussion at Health facility……3 Discussion in community meetings…4 Education by religious leaders ……5 Other, specify……6	
18.Wa ensonga lwaki olowooza nga nesinga? Give reasons why you think it's the best way?	…… …… ……	
19.Ngeliki edhindi dholowoza nga nedhandi kozeseibwa mu kumanisa abantu kubulabe obuva kubulezi nho kuloopa? Which other ways would you suggest to be used in informing community members about ADRs and reporting?	Way 1 :…… Way 2:…… Way 3:……	
20. Eghe oba omuntu w'omumaka gaano wafunaku obuzibu bwonabwona obuva ku bulezi? Have you or a member of your household ever experienced any negative effect of the medicines	Yes ……1 No ……2 **(Skip to q22)** Don't know… ……3 **(Skip to q22)**	

21. Wakolaku ki oba omuntu w'omumaka gaano yakola ki nga afunye obuzibu obwo? What did you or member of your household do in the event that you/other member experienced that negative effect?	Report it back to provider……..1 Treat it myself……..…..2 Ignored it……..3 I stopped the drug.....4 Don't know……..5	
22. Osobola okunkoberaku nti obulumi bwowulira nga omazze okufunha obwiidandhabi buva oba bwali buva ku bulezi bwewakozesa? Would you tell if the unwellness or suffering you feel after treatment is/was as a result of the medicine you took?	Yes ……..1 No……..2 Dont know.....3	
23a. Wandilopye? Would you report such?	Yes……..1 No…… 2(**SKIP TO Q24**) Don't know……..3	
23 b. Waloopa? Did you report the Adverse Drug Reactions:	Yes……..1**Skip to q25a)** No…… 2 Don't know…… 3	
24. Oba mbe, lwaki ti waloopa buzibu buno obw'obulezi? If No, why wouldn't you report the negative effects of the medicines?	Cannot tell if due to drug or not…..1 Health workers have no time…….2 I fear being victimised.....3 It will disappear shortly.....4 It is not necessary……..5 Other, specify……..6	Skip to Q26
25a. Okuva ebiseera byewazuura obuzibu, wamala eibanga ki okuloopa obuzibu bunno? From time of detection of the Adverse reaction, how long did you take to report that adverse Event?	……days or ……weeks or …… Months ……N/A (CHOOSE Appropriately)	
25b. Oba waloopa, kyikyi ekyakolebwawo? If you reported what happened?	Counselled about the effect of drug.....1 Retreated.....2 Drug was changed.....3 Told to continue taking the drug.....4 Treatments was dicontinued .....5 I was ignored.....6 Clinician was busy treating others…..7 Other, specify……..8	Q27
26. Singa wali wa kuloopa, wandi loopye gha? If you were to report where would you report it to?	To the nearest health facility……..1 Report to where drug was got from.....2 VHT……..3 District Health Office (DHO).....4 Local authorities (S/County health worker & LCs.....5 National Drug Authority (NDA).....6 Other, specify……..7	
27a. Okusinziira kwiighe, ngeri ki dhobona nga nesinga era nga nungi ku kuloopa embera embi mu maka gaano? According to you, what method, would you prefer as the **best** and **convenient** system for reporting an adverse event in this household?	……	
27b. Okusinziira kwiighe, ngeri ki kudhino wamanga doboona nga nedisinga era nga nungi ku kuloopa embera embi mu maka gaano? According to you, which of the following methods, would you prefer as the **best** and **convenient** system for reporting an adverse event in this household? (**SELECT ONLY ONE**)	Phone call to the clinic……..1 Phone call to NDA.....2 Phone call to DHO.....3 SMS……..4 Returning to the drug seller……..5 Report to VHT……..5 Local authority(S/County health worker & LCs).....6 Other, specify……..7	

28. Olowooza okuloopa obuzibu obuva mu kukozesa obulezi kyetagisa? Do you think reporting adverse drug reaction is necessary?	Yes.....1 No.....2 Dont know.....3	

Section 4

Mu kitundu kino, nkusaba nti owulilize ku bintu bino byenja okukusomera, era nsaba okunkobera nti yii, mbe oba tiidhi

In this section, I request that you listen to the statement I am going to read to you, and please tell me you "Agree"/"YES" or "Disagree"/"No" OR "Don't-know"(Tick in the appropriate box provided)

	Bino bili n'okuloopebwa? *These should be reported?*	*Yes/Agree*	*No/Disagree*	*Don't Know*
1.	Obuzibu obulowozebwa okuva ku bulezi obutamanikwa Suspected negative effects for which suspected drugs is uncertain			
2.	Obukakafu okuva ku bulezi oba obuzibu Certain/sure reactions or negative effects			
3.	Obuzibu obw'amanhi einho nga okuvaku enviiri, nebindhi okuva mubwiidandhabi bwa kokolo Serious reactions e.g. sight loss due to quinine, hair loss from cancer drugs etc			
4.	Obuzibu nga butono nga okusesema, okwiidhukana Mild reactions e.g. side effects such as vomiting & diarrhea			
5.	Obuzibu nga obufunye okuva mu bulezi obubaire butundibwa mu butale okuswiika emyaka eikumi Reactions to drugs which have been on sale (in the market) for more than 10 years			
6.	Obuzibu okuva ku bulezi obuyaka obufulumizibwa mu butale Reactions to newly introduced drugs in the market			
7.	Obuzibu obumanhikwa obulungi Common or well known reactions			
8.	Obuzibu obutasubirwa oba obutali bwa bulidho Unexpected/Unusual reactions			
9.	Okusobola okugemaganhia n'obulezi obundhi Possible interaction with other drugs			
10.	Obuzibu obuva mu kukozesa eidhagala lyekinaasi Reactions that may result from taking herbal medicine			
11.	Obuzibu obuva mu kukozesa eidhagala lyekinaasi ghalala n'obulezi obwekizungu okugeza nga mukiseera kya mabundha, akakowoolo, omusudha n'ebindhi. Reactions from taking herbal and modern medicine together eg. During pregnancy, for cough, fever etc			

Ndowooza ki dhowa kukuloopa obuzibu bw'ofuna nga omazze okukozesa obulezi era dhandisanile dhiloopebwe dhitya?

What are your comments about reporting adverse drug reactions and how they should be reported.

……

……

……

S2 File: Provider questionnaire (10 pages)

MAKERERE UNIVERSITY CENTER FOR HEALTH & POPULATION RESEARCH
(MUCHAP) - Iganga/Mayuge HDSS
National Pharmacovigilance Centre (NPC), National Drug Authority (NDA)

KAP STUDY ON ADVERSE DRUG REACTIONS - PROVIDER QUESTIONNAIRE

Questionnaire-No.....
FA-Name: ……..FA CODE:……..
Respondent's identification information

Date	Respondent Surname: …..... .....
	Other Names: ……
Name of the facility	Age
FIN:	Gender: 1 =Male 2= Female
Village	Parish
District	**Cadre/Qualification**
	1. Doctor/Medical officer
	2. Clinical officer
	3. Nurse/Midwife
	4. Nursing Assistant
	5. Pharmacist
	6. Lab technician/ Assistant
	7. Counsellor
	8. Other (Specify)
	Maximum education level attained
	1. Masters
	2. Bachelors
	3. Diploma
	4. Certificate
	5. Secondary
	6. Primary
	7. None

Eidwaliro lino liri mu eidhala ki? What is the facility classification	Hospital.....1 Health Centre IV.....2 Health Centre III.....3 Health Centre II.....4 Private Clinic.....5 Drug Shop.....6 Pharmacy.....6 Shop.....7 Other (Specify).....8
Eidwaliro lino litwalibwa anhi? What is the ownership of this facility	Government owned……1 NGO/Faith-based……..2 Private.....3

Section A

1.	Olowooza abantu b'omukitundu munno bateera kufunha gha obulezi? Where do you think community members commonly get their medicines from? **(MULTIPLE ANSWERS ALLOWED)**	Drug shop .....1 VHT .....2 Private clinic .....3 Government clinic.....4 Relative .....5 Other patients .....6 Herbalist .....7 Friends .....8 Internet.....9 Market .....10 Bus .....11 Shops .....12 Other, Specify.....13
2.	Obaire okidi nti obulezi bwonabwona busobola okuba n'obuzibu/obulabe ku mulwaire? Are you aware that any medicine may have negative effects on the patient?	Yes .....1 No.....2 Don't know 3

3.	Mu myezi esatu egibise, wawulilaku obubaka bwonabwona obugemagana nobulabe oba obuzibu obulezi bwebusobola okututuusaku nengeri y'okuloopa obuzibu obwo? In last 3 months, have you heard any information about the possible negative effects of the medicines/drugs that we take and how to report these effects?	Yes .....1 No.....2
4.	Wawulirawa obubaka obugemagana kubulabe obuva ku bulezi mu myezi 3 egibise? Where did you hear information about the drug /medicine effects in last 3 months? **(MULTIPLE RESPONSE ALLOWED)**	Radio……..1 Health worker told me……..2 Discussion at Health facility……..3 Discussion in the community……..4 Poster/publications……..5 Other(Specify)……..6
5.	Okukubagania ebidhubo nokusomesa abantu munkiiko kubulabe obututusiibwaku okuva ku obulezi n'okuloopa obulabe obwo, olowooza nganenkola enayongera mubantu okuloopa obulabe obuva mubulezi? Do you think conducting community meetings to discuss and sensitize people about possible drug effects and reporting is an effective way to increase reporting of drugs reactions?	Yes .....1 No.....2
6.	Okukubagania ebidhubo nokusomesa abalwaire mu malwaliro kubulabe obututusiibwaku okuva ku obulezi n'okuloopa obulabe obwo, olowooza nganenkola enayongera mubantu okuloopa	Yes .....1 No.....2

	obulabe obuva mubulezi? Do you think conducting health facility meetings with patients to discuss and sensitize them about possible drug effects and reporting is an effective way to increase reporting of adverse drug reactions?	
7.	Mu ndowoozayo, **ngeriki esingirailala obulungi mukwongera** okuloopa obulabe obututusibwaku nga buva kubulezi? **(DON'T READ OUT OPTIONS)** In your opinion, what is the **most effective** way to increase reporting the effects of drugs/medicines that we take in this community?	Radio……..…….1 Health education by health worker ……..2 Discussion at Health facility……..……..3 Discussion in community meetings……..….4 Education by religious leaders ……5 Other, specify.....
8.	Wa ensonga lwaki olowooza nga nesinga? Give reasons why you think it's the best way?	……. …….. ……
9.	Ngeliki edhindi dholowoza nga nedhandi kozeseibwa mu kumanisa abantu kubulabe obuva kubulezi nho kuloopa? Which other ways would you suggest to be used in informing community members about ADRs and reporting?	Way 1.:..... Way 2:..... Way 3:.....
10.	Magezi ki g'owa omulwaire okukola singa aba afunye obuzibu? What would you advise a patient to do in case they experienced a negative effect? (MULTIPLE ANSWERS ALLOWED)	Report it to a health worker.....1 Treat it themselves.....2 Ignore it/do nothing.....3 Stop the medicine.....4 Report to NDA/DHO.....5 Don't know .....6 Other (specify).....7
11.	Oba ti kuloopa, lwaki? If not reporting, why?	Cannot tell if ADR or not 1

		I have no time ..... 2 The fear of being sued or victimised ..... 3 It will disappear shortly ..... 4 It is not necessary ..... 5 Don't know ..... 6 Other, specify 7
12.	Singa obaire wa kuloopa obuzibu obwo obuva ku bulezi, wandibaire oloopa gha? If you are to report the negative drug effect or ADR, where would they/you report it to?	District Health Office (DHO) ..... 1 District Drug Inspector (DDI) ..... 2 Send to nearest health facility ..... 3 Send to NDA regional office ..... 4 Call the clinic where drug was purchased ..... 5 VHT ..... 6 Local authorities (Sub County health workers & LCs) ..... 7 Other, specify 8
13a.	Okusinziira kwiighe, ngeri ki dhobona nga nesinga obulungi okuloopa obuzibu obuva ku bulezi; **nga buva ku mulwaire okujja eri omwiidandhabi?** According to you, which method would you prefer as the best system for reporting an adverse event from patient to healthcare provider?	.....
13b.	Okusinziira kwiighe, ngeri ki kudhino wamanga doboona nga nedisinga obulungi okuloopa obuzibu obuva ku bulezi; **nga kuva ku mulwaire okujja eri omwiidandhabi?** According to you, which of the following methods would you prefer as the best system for	Phone call to provider ..... 1 SMS ..... 2 Report to the drug seller ..... 3 Report to PV coordinator at hospital ..... 4 Report by email ..... 5 Report using mobile app ..... 6 VHT 7

	reporting an adverse effect from patient to healthcare provider? **(READ OPTIONS ALOUD)**	Local authorities .....8 Other, specify 9
14a	Okusinziira kwiighe, ngeri ki dhobona nga nesinga obulungi okuloopa obuzibu obuva ku bulezi **nga kuva eri omwiidandhabi oweby'obulamu okutubutuusa waigulu?** From healthcare provider onwards	…….
14b.	Okusinziira kwiighe, ngeri ki kudhino wamanga doboona nga nedisinga obulungi okuloopa obuzibu obuva ku bulezi nga **kuva eri omwiidandhabi oweby'obulamu okutubutuusa waigulu? From healthcare provider onwards (READ OPTIONS ALOUD)**	Phone call to NDA.....1 SMS to NDA .....2 Report to the drug seller.....3 Report to PV coordinator at hospital .....4 Report by email.....5 Report using mobile app.....6 Local authorities .....7 Other, specify 8
15a. 15b	Nga omwiidandhabi, waloopaku obuzibu omulwaire wo bweyafuna ng'omaze okumuwa obwiidandhabi? As a provider, have you ever reported an adverse event after treatment? Waloopa gha? Where did you report?	Yes .....1 No……2 (**SKIP to Q17**) ……
16	Waloopaku mubwangu ki? How soon did you report that Event?	1 ……days 2 ……weeks 3……months 4……N/A (Choose Appropriate)
17.	Olowooza okuloopa obuzibu	Yes 1

	obuva ku bulezi nga kyetagisa? Do you think reporting adverse drug reaction is necessary?	No.....2
18.	Omwiidandhabi weby'obulamu asobola okuloopa obuzibu obuva ku bulezi mukitundu kino? Can healthcare provider report ADR in this community?	Yes .....1 No.....2
19.	Omulwaire asobola okuloopa obuzibu obuva ku bulezi mukitundu kino? Can a patient report ADR in this community?	Yes .....1 No.....2
20.	Ofunaku amawulire ku bulezi n'obuzibu obuva mu bulezi bulidho? Do you obtain information on medicines and their effects regularly?	Yes .....1 No.....2**(Skip to Q22)**
21.	Okuva gha? From what source?	Online- internet .....1 National Drug Authority and other government agencies.....2 Non Governmental Organisations (NGOs).....3 Friends and relatives.....4 Leaflets in medicine package .....5 Radio announcements.....6 Newspapers .....5 Advertisements.....6 Markets.....7 Clinicians and drug sellers 8

	Posters at health facilities.....9 Other, specify 10

Section B

Buti ndhikusaba okwiiramu nti yii, mbe oba tiidhiku bibuuzo bino;

*Now I would like to request you to respond either **Yes, No or Don't know** to the following questions.*
Bintu ki kubiino by'olowooza nti bili n'okuloopebwa?
*Which of these do you think should be reported? (**Tick** in the box provided)*

Bintu ki kubiino by'olowooza nti bili n'okuloopebwa? *Which of these do you think should be reported?*	*Yes=1*	*No=2*	*Don't Know=99*
22. Obuzibu obulowozebwa okuva ku bulezi obutamanikwa Suspected effect (for which suspected drugs is uncertain)			
23. Obuzibu okuva ku bulezi obumanikwa/obukakasibwa Effects or reactions that are Certain/sure			
24. Obuzibu obw'amanhi einho nga buyinza okuviraaku okufa, okwegharikiriza obulamu, bwetagisa okugha omulwaire ekitanda oba buleteera okuba mu eidwaliro okumala eibanga eiwavu, ekiviraaku okweyongera obutesobola, kyaleteera okuzaala omwana ali n'obukosefu, oba kyetagisa okuyambibwa okutangira obukosefu obutali bwankalakalira Serious reactions e.g. (***Results in death, life-threatening, requires inpatient hospitalization or causes prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or requires intervention to prevent permanent impairment or damage***)			
25. Obuzibu nga butono okuva ku bulezi okugeza nga omutwe okulumilira, okusesema n'okwiidhukana Mild reactions e.g. side effects such as headache, vomiting & diarrhoea			
26. Obuzibu nga obufunye okuva mu bulezi obubaire butundibwa mu butale okuswiika emyaka eikumi Reactions to drugs which have been on sale (in the market) for more than 10 years			
27. Obuzibu okuva ku bulezi obuyaka obufulumizibwa mu butale Reactions to newly introduced drugs in the market			

28.	Obuzibu obumanhikwa obulungi Common or well known reactions			
29.	Obuzibu obutasubirwa oba obutali bwa bulidho Unexpected/Unusual reactions			
30.	Okusobola okugemaganhia n'obulezi obundhi Possible interaction with other drugs			

Section C

	Buti ndhikusaba okwiiramu nti yii, mbe oba tiidhi ku nsonga dhenja okusomera edhiyinza okukulemesa okuloopa obuzibu obulowoozebwa okuva mu kukozesa obulezi *Now I request you to respond YES, No or DK to each of the factors im going to read to you that may discourage you from reporting a suspected Adverse Drug Reaction or negative effects.*	*Yes=1*	*No=2*	*Don't Know=99*
31.	Nali tiidhi nti obuzibu obuva mu kukozesa obulezi buli n'okuloopebwa I didn't know ADRs should be reported			
32.	Tyekakasa kyika kya buzibu obw'okuloopebwa I am not sure of the type of reactions to be reported			
33.	Obutamanhisibwa bikka eby'okuloopa Lack of knowledge of the forms for reporting			
34.	Empapula nzibu dakwiidhuza Complex to fill the forms			
35.	Obutekakasa kubuzibu obuva ku bulezi obumilibwa Uncertainty about reaction being due to drugs ingested			
36.	Okutya okuvunhanizibwa mu mbuga dha mateeka Fear of a consequent law suit			
37.	Obutasasulwa nga oloopye Non-remuneration for reporting			
38.	Obutaba nabiseera bya kuloopa buzibu obuva mu kukozesa obulezi Lack of time to report ADR			
39.	Ensonga endhala etaloopebwa teyinza kukosa eiterekero ly'amawulire ag'obuzibu obuva mu kukozesa obulezi A single unreported case may not affect ADR database			
40.	Obukalubiriivu okusalawo oba obuzibu okuva mu kukozesa obulezi			

bubairewo oba mbe Difficult to decide whether ADR has occurred or not			

Gabanaku niife kundhowooza dho edhiyinza okutumbula mu kuloopa obuzibu obuva mu kukozesa obulezi
Share with us some suggestions on the possible ways to improve the ADR reporting.

.....

.....

.....

.....

.....

S3 File: Focus Group Discussion Interview Guide (1 page)

FOCUS GROUP DISCUSSION INTERVIEW GUIDE

INTRODUCTION SCRIPT: *To be read by researcher/group facilitator*

You have been invited to take part in this research study which aims to assess community knowledge, practices and attitudes towards reporting of adverse drug events (ADEs). We also want to assess how best these ADEs can be identified, reported and acted upon.

For this discussion group, I will invite you to share as much as you feel comfortable sharing with the other patients and community members. This conversation will be recorded for only the researchers to hear. Any recording of you taken today will not be used without your express consent. You may choose not to speak, or may leave the discussion at any time, for any reason, without explanation. Your information will be treated with ultimate anonymity and confidentiality. Thanks.

QUESTIONS FOR DISCUSSION

1. Please tell us some experiences of you or any household member who has ever experienced any of this negative effect?
2. How could you tell if un-wellness you or other household member is feeling or suffering from is as a result of the medicine you/he/she took?
3. What would you do if you or a member of your household experiences that negative effect?
4. In this community where does one go to report any ADEs experienced? What are the available means of reporting these ADEs? Have you ever reported an adverse event?
5. Why do you think reporting adverse drug events is necessary?
6. In this community, what may be the reasons/factors for some people not reporting ADEs?
7. In your view, how can the reporting of these ADEs be improved so that we see increased reporting of ADEs in this community?
8. Tell me what you thought about participating in the Community Dialogues or meetings like this one
9. So what is your perceived appropriateness of having community dialogues?
10. What are your views on the potential effect these meetings can have on ADE reporting?
11. So how would you like to see these community dialogues occur in the future?
12. Would you participate in these again? Please tell me why or why not.

S4 File: A study to assess Clinician-perceived failure rates of commonly used ACTs (5 pages)

A study to assess Clinician-perceived failure rates of commonly used ACTs

Interviewer's Name: _____ Code: ☐

Region: _____ Code: ☐

Health Facility Name: _____ Code: ☐

Date of Interview: ____/_____/_____

Clinician-perceived ACT Treatment Failure: *The failure of a malaria-patient to improve despite having received an Artemisinin Combination Therapy (ACT) regardless of artemisinin resistance.*

SECTION A: DEMOGRAPHICS

1. Gender: [1] Male [2] Female
2. Age (*in completed years*): ……
3. Education Level:
   - [1] Certificate
   - [2] Diploma
   - [3] Bachelor
   - [4] Masters
   - [5] Other (*specify*)._____
4. Professional experience (Years): ☐
5. If less than 1 year in **Q4**, state number of completed months ……
6. Professional Cadre:
   - [1] Physician
   - [2] Medical Officer
   - [3] Pharmacist
   - [4] Nurse
   - [5] Clinical Officer
   - [6] Pharmacy Technician
   - [7] Other (*specify*)._____
7. Health Facility Type:
   - [1] Public
   - [2] Private Not-for-Profit
   - [3] Private for-Profit
8. Health Facility Status:
   - [1] Hospital
   - [2] Health Centre III
   - [3] Health Centre II
   - [4] Private Clinic
   - [5] Pharmacy
   - [6] Drug Shop
   - [7] Other, (*specify*)._____

SECTION B: PERCEIVED ACT FAILURE

Please, complete the questionnaire by indicating the appropriate responses.

1. What is the approximate number of malaria-patients you see per day? ……

2. In the use of ACTs in treating uncomplicated malaria, have you ever encountered any treatment failure(s) in your malaria-patients?
   [1] Yes [2] No

3. Have you suspected any ACT treatment failure in the past 4 weeks?
   [1] Yes [2] No

4. If ***YES*** to **Q3**, how many cases of ACT treatment failure? .....

5. Have you received patient-complaints of ACT treatment failure in the past 4 weeks? [1] Yes [2] No

6. If ***YES*** to **Q5**, how many patient-complaints of ACT treatment failure? ……

7. Briefly describe the most recent case of ACT treatment failure you have encountered providing information on patient age, brand of ACT involved, clinical outcome & action taken; e.t.c.

_____
_____
_____

8. Have you reported any ACT treatment failure(s) in the past 6-months? (***Please tick one***)
   [1] Yes [2] No (***Skip to 13***)

9. If ***YES*** to **Q8**, to whom have you reported the most recent ACT treatment failure(s)? (***Please tick all applicable***)

   [1] District Health officer
   [2] Health Management Information System
   [3] Immediate Supervisor
   [4] National Pharmacovigilance Center
   [5] Others, (*specify*). _____

10. If ***YES*** to **Q8**, how did you report the most recent ACT treatment failure(s)? (***Please tick all applicable***)
    [1] Verbally
    [2] Written report
    [3] Other, (*specify*)…….

11. What motivates you to report ACT treatment failure(s)?

_____
_____
_____

12. Do you get feedback on the ACT treatment failure(s) you report?
    [1] Yes [2] No

13. Do you feel that circumstances in your setting make it difficult to report treatment failure to ACTs? [1] Yes [2] No

14. Explain your response to **Q13**

_____
_____
_____

15. What can be done to improve the reporting of treatment failure to ACTs in your setting?

_____
_____
_____

16. What are the commonly used ACTs at your health facility? (***Please tick all appropriate***)

Brand			Coartem	
D-Artepp (GPSC)			Lumartem	
Artequin			Malfan	
Combiart			Artem	
Ridmal			Arexel	
Glumac			Lonart	
Duocotecxin			Lumether	
P-Alaxin			Lumaren	
Artefan			Other, (*specify*)……..	

17. Which ACT brand(s) have you observed to result in treatment failure? (***Please tick all appropriate***)

Brand			Coartem	
D-Artepp (GPSC)			Lumartem	
Artequin			Malfan	
Combiart			Artem	
Ridmal			Arexel	
Glumac			Lonart	
Duocotecxin			Lumether	
P-Alaxin			Lumaren	
Artefan			Other, (*specify*) ……..	

18. Do you think ACT resistance is a growing concern nationally?
[1] Yes [2] No [9] Don't Know

19. If yes to **Q18,** briefly describe why?

_____
_____
_____

20. Do you think ACT resistance is a growing concern in your institution?
[1] Yes [2] No [9] Don't Know

21. If yes to **Q20**, briefly describe why?

_____
_____
_____

SECTION C: DRUG FACTORS RELATED TO ACT FAILURE

22. Do you think the **color** of an ACT could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

23. Briefly describe why giving examples?

_____
_____
_____

24. Do you think the **taste** of an ACT could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

25. Briefly describe why giving examples?

_____
_____
_____

26. Do you think the **size** of an ACT tablets could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

27. Briefly describe why giving examples?

_____
_____
_____

28. Do you think the number of tablets swallowed could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

29. Briefly describe why giving examples?

_____
_____
_____

30. Do you think that inadequate information about an ACT could lead to patient misuse of the drug hence treatment failure? [1] Yes [2] No

31. Briefly describe why giving examples?

_____
_____
_____

32. Do you think the dosing frequency of an ACT could lead to poor patient compliance hence treatment failure? [1] Yes [2] No

33. Briefly describe why giving examples?

_____
_____
_____

34. What other factors in the practice of <u>patients</u> are responsible for the poor response of patients to ACT? (***Please briefly outline***)

_____
_____
_____
_____

35. What other factors in the practice of <u>clinicians</u> are responsible for the poor response of patients to ACT? (***Please briefly outline***)

_____
_____
_____
_____

We appreciate your time taken to respond to this questionnaire. Thank you

This a collaborative study between
National Drug Authority and Makerere University Department of Pharmacology and therapeutics.

RESUME

Period	Institution	Academic Award
2014-2019	Université Catholique de Louvain, Belgium	PhD candidate
2009-2014	Herriot-Watt University, UK	Masters in Business Administration
2001-2003	Makerere University	M.Sc. Clinical Epidemiology &Biostatistics
1995-1999	Makerere University	Bachelor of Pharmacy
1993-1995	Mt. St. Mary's Namagunga	A' Level
1989-1992	Mt. St. Mary's Namagunga	O' Level

PROFESSIONAL MEMBERSHIPS

President, International Society of Pharmacovigilance, Africa Chapter

Member of the National Taskforce on Anti-Microbial Resistance, 2015 to date

Member of the Advisory Committee of the Pan African Clinical Trials' Registry Advisory Group

Vice Chair of the African Vaccine Regulator's Forum (AVAREF) September 2011-Nov 2014

Member of the Medicines' Transparency Alliance (MeTA) Council, Uganda 2012 to date

Member of the HIV Drug Resistance Network, Uganda

Member of the East African Community (EAC) Pharmacovigilance and Post Market Surveillance expert working Group

Member of Uganda Society for Health Scientists

PROFESSIONAL EXPERIENCE

1st July 2017 - to date, Director Product Safety, National Drug Authority, Kampala.

Duty - To oversee the identification, evaluation and management of safety risks for all of NDA approved, marketed and investigational drugs and healthcare products in Uganda. This includes oversight of the national pharmacovigilance activities,

regulation of drug-related clinical trials, regulation of drug promotion, dissemination of information and conduct of research in National Drug Authority.

September 2016 – October 2019, Part time Lecturer

Teaching at the Department of Pharmacy, Makerere University College of Health Sciences in the Masters class course unit on drug policy and regulations; Topics on clinical trials, drug imformation and pharmacovigilance.

April 2006 –June 2017, Head Drug Information Department, NDA, Kampala.

Duty – To coordinate all pharmacovigilance programs and adverse drug reaction reporting, supervise the conduct of drug related clinical trials in Uganda, ensure efficient regulation of drug promotional materials, disseminate drug information to the public and other stakeholders.

Jan 2005 – March 2006, Medical Research Council / Uganda Virus Research Institute (MRC / UVRI) Research Unit on AIDS in Uganda.

Duty - Development of Anti-retroviral Therapy (DART) Trial Manager.

August 2003 – Jan 2005, Medical Research Council Programme on AIDS in Uganda.

Clinical Trial Coordinator, PRO 2000 microbicide gel study

Duty - To coordinate and monitor data, samples, supplies and analysis from an international randomized, double blind placebo controlled phase II microbicide clinical trial between Nsambya and Entebbe.

November 2000 –March 2003, Orient Pharmacy, Kampala

Role -Pharmacist

Duties - Monitoring flow of inventory in the pharmacy, evaluating needs Assessment for purchases based on past consumption of drugs and training pharmacy staff on use of new products.

COLLABORATIONS

WHO Lead Assessor for Vigilance and Assessor for clinical trial activities using Global Benchmarking tool for Regulatory systems, since 2018

Advisor, Joint review of Fosravuconazole trial in Sudan, 26-27 August 2016

Advisor to the WHO panel on “Ethical considerations for use of unregistered interventions for Ebola viral disease” since August 2014

Co-Principal Investigator, EDCTP Grant collaboration between Uganda National Council for Science and Technology, Uganda National Health Research Organisation, Mulago Hospital and Mbale Hospital

List of Publications

1. Manirakiza L, Nambasa V, Nanyonga S, Serwanga A, Denis N, Ndagije H. Drug Use Evaluation (DUE) of Ceftriaxone in Mubende Regional Referral Hospital , Uganda : A Cross-Sectional Survey. J Pharm Pharmacol Res [Internet]. 2019;3(3):105–15. Available from: http://www.fortunejournals.com/articles/drug-use-evaluation-due-of-ceftriaxone-in-mubende-regional-referral-hospital-uganda-a-crosssectional-survey.pdf

2. Ndagije H, Byomire, Manirakiza L, Kajungu D, Galiwango E, Kusemererwa D, et al. The effect of community dialogues and sensitization on patient reporting of adverse events in rural Uganda : Uncontrolled before- after study. PLoS One [Internet]. 2019;1–19. Available from: https://doi.org/10.1371/journal.pone.0203721

3. Kiguba R, Ndagije HB, Nambasa V, Bird SM. Adverse Drug Reaction Onsets in Uganda ' sVigiBase ® : Delayed International Visibility , Data Quality and Illustrative Signal Detection Analyses. Pharmaceut Med [Internet]. 2018;32(6):413–27. Available from: https://doi.org/10.1007/s40290-018-0253-7

4. Ndagije HB, Nambasa V, Manirakiza L, Kusemererwa D, Kajungu D, Olsson S, et al. The Burden of Adverse Drug Reactions Due to Artemisinin-Based Antimalarial Treatment in Selected Ugandan Health Facilities: An Active Follow-Up Study. Drug Saf [Internet]. 2018 Aug 7;41(8):753–65. Available from: http://link.springer.com/10.1007/s40264-018-0659-x

5. National Pharmacovigilance Centre Uganda. Annual Pharmacovigilance Report 2016. Kampala; 2016.

6. Ndagije H, Nambasa V, Namagala E, Nassali H, Kajungu D, Sematiko G, et al. Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda. Drug Saf. 2015;38(4).

7. Kiguba R, Waako P, Ndagije HB, Karamagi C. Medication Error Disclosure and Attitudes to Reporting by Healthcare Professionals in a Sub-Saharan African Setting: A Survey in Uganda Europe PMC Funders Group. Drugs Real World Outcomes Sept. 2015;1(23):273–87.

8. Kiguba R, Karamagi C, Waako P, Ndagije HB, Bird SM. Rare, serious, and comprehensively described suspected adverse drug reactions reported by surveyed healthcare professionals in Uganda. PLoS One. 2015;10(4).

9. Kiguba R, Karamagi C, Waako P, Ndagije HB, Bird SM. Recognition and reporting of suspected adverse drug reactions by surveyed healthcare professionals in Uganda: key determinants. BMJ Open. 2014;4(11).

10. World Health Organisation G. Ethical considerations for use of unregistered interventions for Ebola viral disease Report of an advisory panel to WHO [Internet]. Geneva Switzerland; 2014. Available from: http://apps.who.int/iris/bitstream/10665/130997/1/WHO_HIS_KER_GHE_14.1_eng.pdf?ua=1

11. Kamali A, Byomire H, Muwonge C, Bakobaki J, Rutterford C, Okong P, et al. A randomised placebo-controlled safety and acceptability trial of PRO 2000 vaginal microbicide gel in sexually active women in Uganda. Sex Transm Infect [Internet]. 2010 Jun [cited 2013 Aug 9];86(3):222–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20444744.