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PHARMACOVIGILANCE CAPACITY IN EAST AFRICA WITH FOCUS ON NEGLECTED TROPICAL DISEASES

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PHARMACOVIGILANCE IN EAST AFRICA WITH FOCUS ON NEGLECTED TROPICAL DISEASES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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Dedicated to the memory of Sten Olsson (1950 – 2022).

ABSTRACT

Pharmacovigilance aims to enhance patient safety in relation to the use of medicines by reducing the incidence and severity of adverse events which includes supporting public health programs by providing information on the safety profile of medicines used by the programs. In Africa, the increased access to medicinal products is not well-matched with the pharmacovigilance capacity to monitor drug safety. The aim of this thesis was to assess the national pharmacovigilance centres and neglected tropical diseases public health programs' pharmacovigilance capacity and performance, to identify gaps for targeted interventions to strengthen the national pharmacovigilance systems. Additionally, the safety of mass praziquantel (PZQ) co-administered with albendazole for the control of schistosomiasis and soil transmitted helminths was also investigated. Lastly the influence of pharmacogenetics (PG) variations on pharmacokinetics (PK) and safety was investigated as well.

Firstly, in **paper I** the national pharmacovigilance centres hosted at the national medicine regulatory authorities in Ethiopia, Kenya, Rwanda, and Tanzania were assessed to identify gaps for targeted interventions. Based on our findings, the national pharmacovigilance systems in all four countries were supported with legal framework. Except for Rwanda, all the other countries had systems to receive, process, and communicate suspected adverse event reports in place. However, reporting of suspected medicine-related harm from stakeholders including public health programs was inadequate in all countries. Overall, ≤ 1% of the total number of health facilities per country submitted Individual Case Safety Reports (ICSRs).

In **paper II**, the pharmacovigilance systems of the neglected tropical diseases public health program in Ethiopia, Kenya, Rwanda, and Tanzania were assessed to identify missing pharmacovigilance components for targeted interventions. All four neglected tropical diseases programs although limited had some elements of pharmacovigilance within their programs; this included having pharmacovigilance components in their strategic masterplans and some mechanisms to disseminate pharmacovigilance information. However, none of the four programs had a specific budget for pharmacovigilance and no ICSRs were submitted to the programs or national pharmacovigilance centres in 2017/2018. Furthermore, the programs had not investigated the safety of the medicines used during mass drug administration (MDA) to prevent, control and eliminate selected neglected tropical diseases, this is especially important because the medicines are given to all at-risk populations.

Therefore, in **paper III,** the safety of mass PZQ and albendazole administration for the control of schistosomiasis and soil transmitted helminths respectively, was investigated in 8037 school children aged 5–15 years in Rwanda. Adverse events were actively monitored on 1-, 2-, and 7-days post MDA. 20.6% of the children experienced at least one type of transient mild to moderate, and in few cases severe, adverse events. The most reported adverse events were headache (21%), dizziness or fainting (15.2 %), nausea (12.8%) and stomach pain (12.2%). The incidence of adverse events varied significantly between sex and age groups. Females, older children (10-15 years versus 5-9 years), those who had reported symptoms before treatment (pre-MDA), and/or received two or more PZQ tablets had an increased risk of

experiencing adverse events. Pharmacovigilance during MDA is recommended for timely detection and management of adverse events.

Lastly, in **paper IV** the objective was to investigate the effect of PG variations on PZQ plasma drug concentration and treatment associated adverse events. A total of 462 school children who received single dose PZQ co-administered with albendazole were enrolled in this study. Whole blood samples were collected for genotyping of *CYP3A4*1B*, *CYP3A5* (*3, *6, *7), *CYP2C19* (*2, *3, *17), *CYP2C9* (*2, *3) and *CYP2J2*7*. Two hours post-dose plasma samples were collected, and PZQ, *trans*- and *cis*-4-OH-PZQ concentrations were quantified using LCMS/MS. *CYP2C9* and *CYP2C19* genotypes were significantly associated with PZQ plasma concentrations and its metabolic ratios. Children who carried *CYP2C9* (*2, *3) and *CYP2C19* (*2, *3) had significantly higher PZQ concentration and lower trans and cis metabolic ratios compared to those with wildtype. Children who were *CYP2C19* (*1/*17 or *17/*17) had the lowest PZQ concentration and highest trans and cis metabolic ratios. *CYP3A4* genotype was associated with increased cis PZQ metabolic ratio. There was no significant association between the genotypes and adverse events, but those who experienced adverse events had a significantly lower mean *cis*-4-OH-PZQ metabolic ratio compared to those who did not.

In conclusion, the pharmacovigilance systems in Ethiopia, Kenya, Rwanda, and Tanzania are supported by laws, regulations, and guidelines. However, other missing key pharmacovigilance indicators makes it challenging for the pharmacovigilance centres and the NTD programs to identify medicine safety issues. The active safety surveillance of mass PZQ and albendazole administration showed that more than one in five children experienced at least one adverse event post MDA, most of which were mild to moderate, but few were severe. Factors associated with experiencing adverse events included age, sex, pre-treatment condition (pre-MDA), type of meal taken before drug intake and increased number of PZQ tablets. PZQ pharmacokinetics is mainly influenced by *CYP2C19* genotype, and to lesser extent by *CYP2C9* and *CYP3A4* genotypes. Although the tested genotypes had no significant effect on and safety outcomes, variation in PZQ PK specifically, *cis*-4-OH-PZQ/PZQ metabolic ratio is associated with experiencing adverse event. Overall findings from this thesis underscores the need to strengthen the pharmacovigilance systems of the national pharmacovigilance centres and NTD programs, and to monitor the safety of the medicines used in MDA.

LIST OF SCIENTIFIC PAPERS

I. **Barry A**, Olsson S, Minzi O, Bienvenu E, Makonnen E, Kamuhabwa A, Oluka M, Guantai A, Bergman U, van Puijebroek E, Gurumurthy P, Aklillu E. Comparative Assessment of the National Pharmacovigilance Systems in East Africa: Ethiopia, Kenya, Rwanda and Tanzania. **Drug Saf.** 2020 Jan 09. https://doi.org/10.1007/s40264-019-00898-z

II. **Barry A,** Olsson S, Khaemba C, Kabatende J, Dires T, Fimbo A, Minzi O, Bienvenu E, Makonnen E, Kamuhabwa A, *et al*. Comparative Assessment of the Pharmacovigilance Systems within the Neglected Tropical Diseases Programs in East Africa—Ethiopia, Kenya, Rwanda, and Tanzania. **Int. J. Environ. Res. Public Health.** 2021, 18, 1941. https://doi.org/10.3390/ijerph18041941

III. Kabatende J, **Barry A,** Mugisha, M, Ntirenganya L, Bergman U, Bienvenu E, Aklillu E. Safety of Praziquantel and Albendazole Coadministration for the Control and Elimination of Schistosomiasis and Soil-Transmitted Helminths Among Children in Rwanda: An Active Surveillance Study. **Drug Saf.** 2022, 45, 909–922. https://doi.org/10.1007/s40264-022-01201-3

IV. **Barry A**, Kabatende J, Telele NF, Mnkugwe RH, Mugisha M, Ntirenganya L, Bienvenu E, Aklillu E. Effect of pharmacogenetic variations on praziquantel pharmacokinetics and safety outcomes among school children in Rwanda. (***Submitted to Scientifc Reports***)

SCIENTIFIC PAPERS NOT INCLUDED IN THE THESIS

I. Khaemba C, **Barry A,** Omondi WP, Bota K, Matendechero S, Wandera C, Siyoi F, Kirui E, Oluka M, Nambwa P, Gurumurthy P, Njenga SM, Guantai A, Aklillu E. Safety and Tolerability of Mass Diethylcarbamazine and Albendazole Administration for the Elimination of Lymphatic Filariasis in Kenya: An Active Surveillance Study. **Pharmaceuticals**. 2021; 14(3):264. https://doi.org/10.3390/ph14030264

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V. Kabatende J, **Barry A**, Ntirenganya L, Mugisha M, Bergman U, Bienvenu E, Aklillu E. Efficacy of single dose albendazole for the treatment of soil-transmitted helminthic infections among school children after a Decade of Preventive Chemotherapy in Rwanda. ***(Submitted to Pharmaceuticals)***

CONTENTS

LIST OF ABBREVIATIONS

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AEFI	Adverse Events Following Immunization
AMA	African Medicines Agency
AMRH	African Medicines Regulatory Harmonization
BAZ	Body Mass Index (BMI) for Age Z score
CDDs	Community Drug Distributors
CEM	Cohort Event Monitoring
CHEWs	Community Health Extension Workers
CYP450	Cytochrome P450
DALYs	Disability-Adjusted Life Years
DTC	Drug and Therapeutics Committees
EAC	East African Community
EFDA	Ethiopian Food and Drugs Authority
GBT	Global Benchmarking Tool
HAZ	Height for Age Z score
HIV	Human Immunodeficiency Virus
ICSRs	Individual Case Safety Reports
IPAT	Indicator-Based Pharmacovigilance Assessment Tool
LC-MS/MS	Liquid Chromatography - tandem Mass Spectrometry
LF	Lymphatic Filariasis
MAHs	Marketing Authorization Holders
MDA	Mass Drug Administration
MR	Metabolic Ratio
MRH	Medicines Regulatory Harmonization
NMRA	National Medicines Regulatory Authority
NTD	Neglected Tropical Disease
PBRERs	Periodic Benefit–Risk Evaluation Reports
PC	Preventive Chemotherapy

PCR	Polymerase Chain Reaction
PD	Pharmacodynamic
PG	Pharmacogenetics
PHP	Public Health Program
PIDM	Programme for International Drug Monitoring
PK	Pharmacokinetics
PMS	Post Marketing Surveillance
PPB	Pharmacy and Poisons Board, Kenya
PSURs	Periodic Safety Update Reports
PZQ	Praziquantel
QPPV	Qualified Person responsible for Pharmacovigilance
Rwanda FDA	Rwanda Food and Drugs Authority
SAC	School-Aged Children
SAEs	Serious Adverse Events
SDGs	Sustainable Development Goals
SPS	Strengthening Pharmaceutical Systems
SSA	Sub Saharan Africa
STHs	Soil Transmitted Helminths
TMDA	Tanzania Medicines and Medical Devices Authority
ToT	Training of Trainers
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

1 INTRODUCTION

1.1 PHARMACOVIGILANCE IN A GLOBAL CONTEXT

The thalidomide disaster prompted the evolution of pharmacovigilance and structured drug regulation. In 1960's, globally, more than 10,000 babies from 46 countries were born with congenital malformations (phocomelia) due to adverse effects related to maternal use of thalidomide [1]. It was reported that approximately 40% of thalidomide victims died within the first year of birth [2]. This disaster highlighted the need for closer drug safety monitoring to detect adverse reactions and led to the systematic collection of suspected medicine related adverse events at national and global levels [3]. In 1968, the World Health Organization (WHO) established the WHO Programme for International Drug Monitoring (PIDM) to collect safety data on medicines from different countries (WHO member states), for the timely detection of adverse events (AEs), specifically adverse drug reactions (ADRs), a major cause of morbidity and mortality [3-6]. ADRs are the leading cause of hospitalization and the fourth or sixth leading cause of death [5, 6]. As of 2022, 153 countries are full members, and 22 countries are associate members of the PIDM [4]. Member countries and regions of the PIDM work nationally and collaborate to monitor and identify medicine related harm, reduce risks related to use of medicines among patients and to establish global pharmacovigilance standards and systems [4]. To become a PIDM member, one of the requirements includes having a national pharmacovigilance centre for monitoring medicines designated and recognized by the ministry of health (or equivalent) [4].

The first African countries to join the PIDM were Morocco and South Africa in 1992, followed by Tanzania in 1993 [7]. Ethiopia, Kenya, and Rwanda joined the PIDM in 2008, 2010 and 2013 respectively. The respective national pharmacovigilance centres of Ethiopia, Kenya, Rwanda, and Tanzania are hosted at their respective national medicines regulatory authorities (NMRAs) [8].

1.2 PHARMACOVIGILANCE IN AFRICA

In Sub-Saharan Africa (SSA), there is increased access to medicinal products mainly through the global health initiatives and the commitment of national governments to address diseases of public health concern such as malaria, neglected tropical diseases (NTDs), tuberculosis and human immunodeficiency virus (HIV), amongst others [7, 9]. However, the increased access to medicinal products is not well-matched with the capacities of the NMRAs to monitor the safety of medicines [7, 10, 11]. According to the WHO, the 54 NMRAs in Africa have varying capacities but most of them are incapable of performing the core NMRA functions [12]. In 2005, WHO reported that less than 10% of the NMRAs had a moderately developed medicine regulatory capacity in SSA and only 13% had a functional pharmacovigilance system [10, 12]. In 2011, an assessment of the national pharmacovigilance systems in SSA showed that four out of 46 countries (9%) had pharmacovigilance systems with the capacity to detect, evaluate, and prevent safety issues, indicating the limited capacities of these countries to monitor medicines safety. 25 (54%) had minimal or no pharmacovigilance capacity [10] as shown in **figure 1**.

None of the NMRAs in Africa have reached the WHO Global Benchmarking Tool maturity level 4. In SSA, only two NMRAs namely Ghana and Tanzania have attained maturity level 3, which depicts stable and well-functioning systems [13].

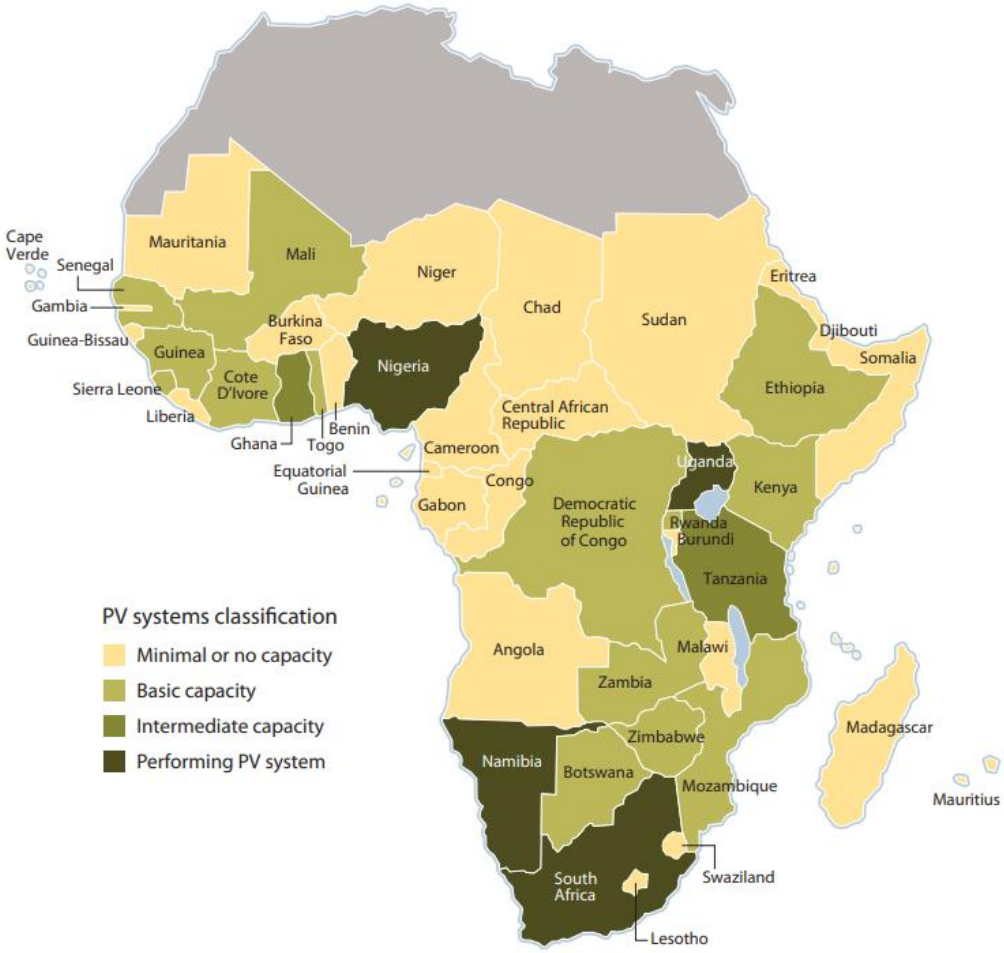

Figure 1. Performance of Pharmacovigilance systems in Africa (2012). Source: Choi et al., 2012 [10].

The inadequate national pharmacovigilance systems are partly due to fragile infrastructure, limited government commitment, limited financial and human resources. The limited capacity of national pharmacovigilance systems in Africa is highlighted by the number of Individual Case Safety Reports (ICSR) sent to the PIDM from Africa [14-16]. Less than 1% of ICSRs were from Africa [17]. SSA has an expectedly higher risk of adverse events due to high disease burden and poorly pharmaceutical governance which can result in medicines that do not meet acceptable standards of safety, quality, and efficacy [18]. Therefore, it is imperative that national pharmacovigilance systems hosted by the NMRAs have the following: governmental and public support, policy and legal frameworks defined by law and regulation, adequate human and financial resources, adequate stakeholder coordination as well as proper management and enforcement systems [8, 19]. In the last decade, there have been efforts to strengthen the NMRAs capacity to regulate medical products and increase patient access to quality, safe, and efficacious medical products in SSA [19]. Therefore, there is a need to

monitor and assess the national pharmacovigilance systems hosted by NMRAs to identify gaps for interventions thereby strengthening the safety monitoring of medicines.

1.3 KEY PHARMACOVIGILANCE RESPONSIBILITIES AND STAKEHOLDERS

The national pharmacovigilance centres are responsible for:

i. Promoting the reporting of suspected adverse events;
ii. Collecting case reports of suspected adverse events;
iii. Clinically evaluating case reports;
iv. Collating, analysing and evaluating patterns of adverse reactions;
v. Recommending or taking regulatory action in response to evidence-based
vi. findings;
vii. Initiating studies to investigate significant suspected adverse reactions;
viii. Alerting prescribers, manufacturers and the public to new risks of adverse reactions; and
ix. Submitting Individual Case Safety Reports to the WHO Programme for International Drug Monitoring [20].

To do the above-mentioned activities, functional collaboration between the national pharmacovigilance centre and key stakeholders is imperative [21]. Key pharmacovigilance stakeholders include Marketing Authorization Holders (MAHs), healthcare professionals, consumers (patients) and Public Health Programs (PHPs) as shown in **figure 2**. Each of these key stakeholders play a fundamental role in pharmacovigilance. One of the core aims of pharmacovigilance is to improve patient safety by monitoring the safety of medicines used by PHPs.

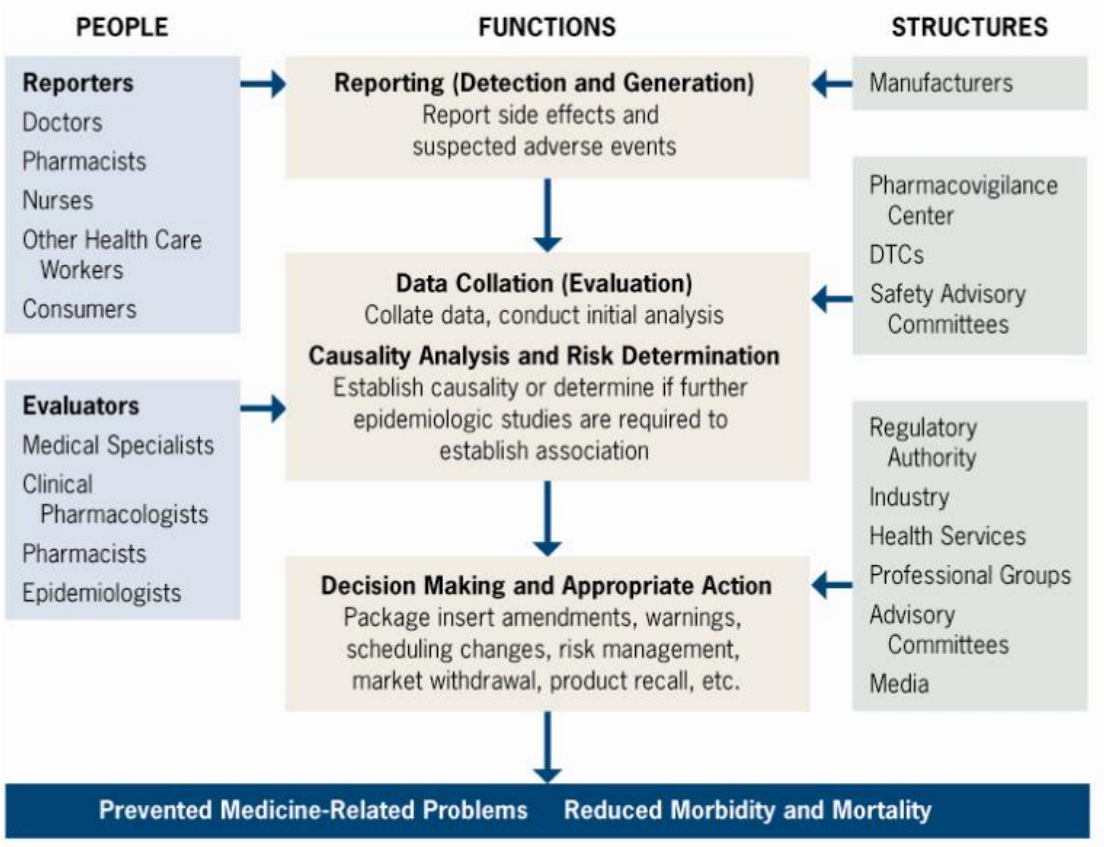

Figure 2. The Pharmacovigilance Framework. Source: Strengthening Pharmaceutical Systems (SPS). 2009. Supporting Pharmacovigilance in Developing Countries: The Systems Perspective [22].

1.4 NEED FOR PHARMACOVIGILANCE WITHIN PUBLIC HEALTH PROGRAMS

Public Health Programs (PHPs) aim to reduce disease morbidity, mortality and subsequently eradicate selected diseases. PHP interventions are based on the direct administration of vaccines or medicines for the prophylaxis, treatment, and control of a disease. The interventions include mobilization of resources both nationally and internationally to support the different aspects of the program, including the mass distribution of free medicines [20]. The large population covered, and the use of new medicines/regimens can be beneficial or harmful. The possibility of harm is high, especially if AEs are not monitored, detected timely and reported for review and management [20].

Integration of pharmacovigilance into the PHPs is essential because clinical trials of medicinal products usually have a relatively small sample size so rare but serious AEs will not be captured and follow-up is often limited. As a result, late-onset AEs related to the use of the medicinal products will be missed. Also, large patient populations, such as pregnant women, people with multiple morbidities, and children are usually excluded in clinical trials [23]. Furthermore, the safety profiles of the medicines used by the PHPs are rarely known in SSA because the safety data are usually generated in other countries whose populations differ socioeconomically, epidemiologically, and genetically [24]. Therefore, pharmacovigilance will contribute to the

ongoing assessment of the risks, benefits and effectiveness of medicines especially in the local context.

A study conducted by the Strengthening Pharmaceutical Systems (SPS) program assessed 32 PHPs including malaria, HIV and immunization programs. The study found that only 12 programs included pharmacovigilance in their policy documents and none of the PHPs had adequate risk management activities [25, 26]. PHPs for Neglected Tropical Diseases (NTDs) were not included in the abovementioned study, according to my knowledge, the pharmacovigilance systems of the NTD programs in Africa have never been assessed.

1.5 BURDEN OF NEGLECTED TROPICAL DISEASES IN AFRICA

Neglected Tropical Diseases (NTDs) represent a group of 20 protozoa, helminths, bacterial and viral infections that prevail in tropical and subtropical regions in 149 countries worldwide [27]. NTDs are a public health challenge. Globally, more than 1.5 billion people suffer from at least one NTD, 600 million of whom live in Africa [27-29]. NTDs are associated with disfigurement, disability, and/or premature death. Every year, over half a million people die due to NTDs or NTD related complications [29]. In 2012, the global burden of NTDs was reported to be 56.5 million disability-adjusted life years (DALYs), which was higher than that of tuberculosis (34.7 million) and malaria (46.5 million) [30]. The most common NTDs in Sub-Saharan Africa are trachoma, helminthic infections especially soil transmitted helminths (STH), schistosomiasis, and filarial infections such as lymphatic filariasis (LF) and onchocerciasis [31]. Fortunately, these NTDs can be treated, controlled, and subsequently eliminated by preventive chemotherapy (PC), the large-scale distribution of medicines to eligible populations within an endemic area, without prior individual diagnosis [32]. Sub-Saharan Africa is one of the most affected regions, 41 out of 45 countries (91%) are endemic and require PC for two or more NTDs and 13 countries (29%) are co-endemic and require PC for LF, onchocerciasis, Schistosomiasis, STH and Trachoma [33, 34].

1.6 OVERCOMING NTDS TO ATTAIN THE SUSTAINABLE DEVELOPMENT GOALS

NTDs adversely affect the key components of the Human Development Index (HDI), for instance, years of life lived with good health, standard of living, as well as level and quality of education [35]. Additionally, NTDs have also been linked to the delay in achieving Sustainable Development Goal (SDG) 1 (no poverty), SDG2 (hunger) SDG4 (quality education), SDG8 (productive working lives) and SDG3 (good health and wellbeing for all at all ages), specifically SDG target 3.3 which refers to " end the epidemics of neglected tropical diseases" by 2030 [35-37]. Therefore, NTDs must be overcome to attain the SDGs and ensure universal health coverage [37]. The WHO has four global targets for 2030 to prevent, control, eliminate and eradicate NTDs; i) 90% reduction in individuals requiring interventions against NTDs, ii) 75% reduction in NTD-related DALYs, iii)100 countries to eliminate as least one NTD and iv) eradication of 2 NTDs [37]. One of the ways to achieve this target includes improving PC coverage and geographical reach of NTD program which means more people are expected to

receive PC for NTDs. It is estimated that at least 1.74 billion individuals who require interventions against NTDs will be reached between now and 2030 [37].

1.7 PREVENTIVE CHEMOTHERAPY TO HALT TRANSMISSION OF SELECTED NEGLECTED TROPICAL DISEASES

The WHO established global programs to eliminate selected NTDs including onchocerciasis, LF, schistosomiasis, STHs and trachoma. The aims of the respective elimination programs were to interrupt transmission, thereby halting the spread of infection and reducing the suffering of the affected poor communities [38-40]. The main intervention of these programs is PC. The delivery of PC is usually undertaken by periodic targeted mass drug administration (MDA) campaigns to all at-risk populations without prior individual diagnosis. These activities are usually organized by the national NTD program (the PHP for NTDs) within each member state. Globally, 1.137 billion NTD treatments were delivered to 797 million people in 2020 [41, 42] as presented in **figure 3**.

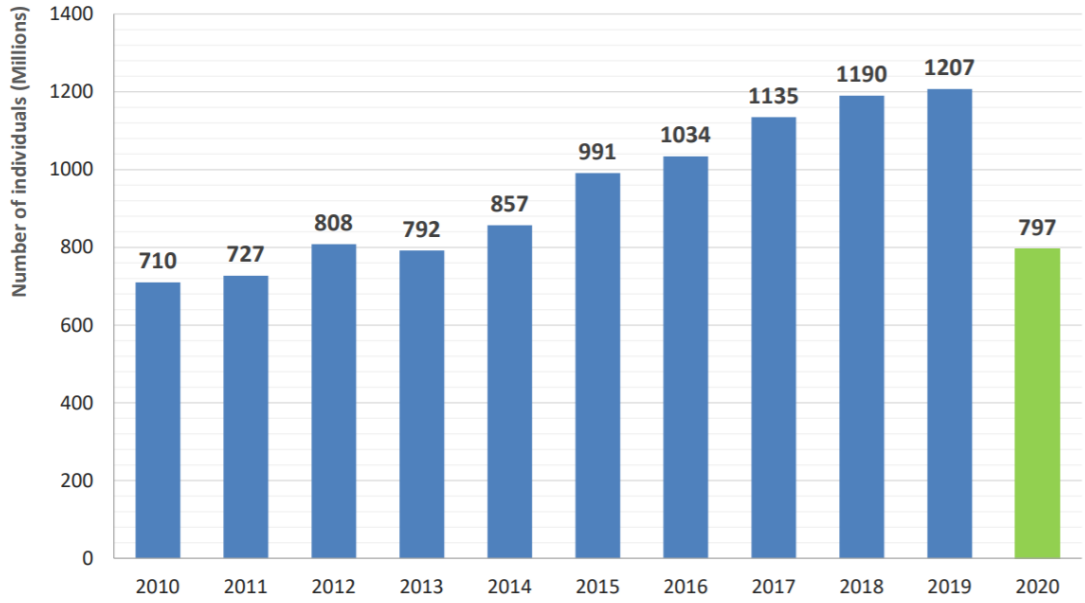

Figure 3. Number of individuals that received Preventive Chemotherapy (PC) for at least one NTD, 2010/2020. Source: WHO, 2022 [42].

In Ethiopia, Kenya, Rwanda, and Tanzania, MDA campaigns for the treatment and control of selected NTDs are organized by the NTD programs that were launched in 2009, 2002, 2008, and 2002, respectively. Since the establishment of the NTD programs, the countries have been involved in conducting MDAs for the treatment and prevention of selected NTDs.

1.8 NEED TO HAVE A PHARMACOVIGILANCE SYSTEM WITHIN THE NTD PROGRAM

The drugs used for mass administration deployed under the NTD programs such as azithromycin, albendazole, diethylcarbamazine, ivermectin, praziquantel (PZQ) amongst others have been reported to have a good safety profile when used as a single dose in PC. In situations where adverse reactions occur, most of them are reported to be mild and transient

[43]. However, although rare, serious adverse events (SAEs) such as hospitalization and death have been reported to be related to medicines used in MDA campaigns [43]. Nevertheless, AEs are not always related to the medicinal products, rather how the medicinal product is used in the given context. AEs including SAEs may occur due to medications, operational errors or coincidental [43]. Therefore, without a safety monitoring system, it is very challenging to ascertain the cause of an AE/SAE and implement measures to prevent or minimize re-occurrence. Additionally, due to the co-endemicity of multiple NTDs in most Africa countries, concomitant administration of the medicines against multiple NTDs is given in MDA to optimize the use of resources, save operational costs, and increase the impact of the interventions [44]. The co-administration of multiple drugs further highlights the need for rigorous safety monitoring systems. Furthermore, medicines used in MDA were tested in another population that are different and not comparable to the target MDA population, thus another strong rationale for safety monitoring. Moreover, medicine safety surveillance in MDA campaigns is particularly important for ethical reasons because the medicines are given regularly, sometimes annually and biannually to all at-risk populations in the absence of individual diagnoses [45]. Therefore, the individuals exposed to these medicines are generally much larger than the infected individuals. Thus, from a benefit–harm perspective, uninfected individuals are also exposed to risks of medicine-related harm [43, 46]. To detect, evaluate and prevent AEs associated with the medicines used in MDA, a comprehensive pharmacovigilance system within the NTD programs is essential.

Pharmacovigilance has not been given the same prominence as treatment coverage, partly because of limited financial resources amongst other factors. Therefore, the safety of treatment regimens used in MDA for selected NTDs in infected and uninfected populations is not well established. Globally, approximately 1 billion people receive MDA for NTDs every year, despite this, little attention has been given to research and funding on pharmacovigilance of the NTD programs [28, 41, 47]. In 2020, despite the COVID-19 disrupting the implementation of MDA [48], 797 million people were exposed to medicines for treatment and control of NTDs globally.

The safety profile of the drugs may vary depending on population type partly due to genetic variation, environmental factors and nutritional status, presence of infection, severity of infection and drug interactions due to co-administration of multiple drugs [49-51]. The predisposing factors and their influence on AEs can only be determined by having a comprehensive pharmacovigilance system in place. Due to limited scientific research in this area, policy makers, NTD program managers and health workers are unaware of the safety profile of drugs and treatment regimens used in MDAs in Africa. To the best of my knowledge and review of literature, no studies have evaluated the pharmacovigilance systems and practices within the NTD programs in Africa.

A well-established pharmacovigilance and post MDA surveillance system to monitor drug safety is also critical in boosting MDA compliance, public trust, and confidence in the national NTD program, which will all contribute to increase coverage and subsequently accelerate

efforts to end the NTD epidemic. The control of NTDs have been shown to be associated with achievement of the SDGs [35, 36, 52] and the current global agenda is to end the NTD epidemic by 2030 (Goal number 3.3) of which schistosomiasis is among [53].

1.9 SCHISTOSOMIASIS AS A PUBLIC HEALTH PROBLEM

Schistosomiasis more commonly referred to as Bilharzia is a NTD caused by a blood fluke parasite or trematode of genus *Schistosoma* [54]. The main three *Schistosoma* species that can infect humans are *Schistosoma haematobium* found in Africa and the Middle East, *Schistosoma mansion* found in Africa and South America, and *Schistosoma japonicum* found in China and the Philippines [54, 55]. Schistosomiasis is considered the most important helminthic disease of humanity in terms of morbidity and mortality rates, although the precise extent is disputed. The global burden has been reported to be between 1.7–4.5 million DALYs [56-58]. It is endemic in more than 50 countries, over 200-243 million people are infected worldwide, and approximately 800 million are at risk of infection [55, 59, 60]. SSA has the highest global schistosomiasis burden, approximately 90% of schistosomiasis cases are from this region where approximately 20 million suffer from schistosomiasis related complications and up to 280,000 deaths annually [27, 61].

Although, Schistosomiasis is preventable and treatable, the infection primarily affects the intestinal or urinary tract system causing upper gastrointestinal bleeding, renal failure, hydronephrosis amongst others depending on the infecting species [31]. Schistosomiasis is associated with increased susceptibility to malaria, an increased risk of HIV transmission and progression as well as cancer due to chronic inflammation resulting from migrating parasites eggs in tissues [62, 63].

1.10 CONTROL AND ELIMINATION STRATEGIES FOR SCHISTOSOMIASIS

According to the WHO, the five public health interventions for the morbidity control and elimination of schistosomiasis as a public health problem in endemic countries include PC, basic sanitation and hygiene, vector control, health education and access to safe and clean drinking water [40]. Although there is evidence that the most successful strategy for long term schistosomiasis control and subsequent elimination is snail control because snails are the intermediate host and play an essential role in the schistosomes life cycle [58, 64, 65] see **figure 4**. However, at present, periodic MDA using PZQ, the only available drug efficacious against schistosomiasis, is the main intervention strategy for the control and elimination of schistosomiasis in SSA including Rwanda [64, 65]. PZQ acts by affecting the permeability of the cell membrane resulting in the contraction of schistosome by disrupting the calcium channels. The drug further causes vacuolization and disintegration of the parasites' outer tegument. The effect is more marked on adult worms compared to immature/juvenile worms [66].

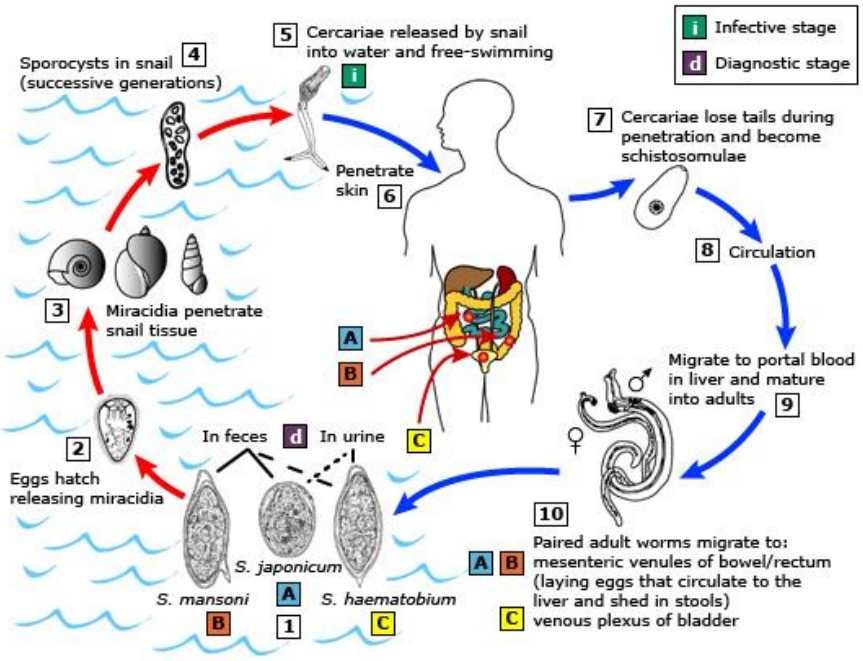

Figure 4. Life cycle of schistosomiasis. Source: Centers for Disease Control and Prevention [67].

The WHO 2020 target is to control schistosomiasis morbidity by reducing the prevalence of heavy-intensity infections to ≤5% among school-aged children (SAC). The WHO's next target for 2025 is to control and eliminate schistosomiasis as a public health problem (defined as ≤1% prevalence of heavy intensity infections) among SAC [40, 68].

In SSA, SAC are the target group for schistosomiasis PC because they are an important high-risk group for schistosomiasis due to poor hygiene and frequent contact with water bodies. According to the WHO, in 2019, over 90 million people including approximately 75 million SAC and over 15 million adults received MDA for schistosomiasis in areas where PC was required [34, 42]. In 2020, due to COVID-19 related disruptions in MDA implementation, 77.2 million (60.1 million SAC and 17.1 million adults) received MDA for schistosomiasis globally. Out of the 77.2 million, 70.1 million were from the African region alone (55.4 million SAC and 14.7 million adults) [34, 42]. Currently there are efforts to increase access to Schistosomiasis PC as part of the initiatives to control and eliminate the diseases. Therefore, in the coming years, the number of people receiving MDA for Schistosomiasis will increase [68].

The frequency of MDA for schistosomiasis varies depending on the prevalence of the disease. According to the WHO, high risk areas with a prevalence of ≥50% received MDA annually, areas with moderate burden with a prevalence of ≥10% – <50% received MDA once every 2 years and areas with low burden with a prevalence of <10% received MDA once every three years [45].

1.11 SCHISTOSOMIASIS IN RWANDA

According to epidemiological surveys, the transmission of schistosomiasis in Rwanda has been reported since the late 1940s, with the lakes in Northern Rwanda identified as the main sources of infection [69]. It was in the 1970s and 1980s that transmission of intestinal schistosomiasis was reported across the country, with the most affected age group being children aged 5-10 years [69]. The national control program for schistosomiasis in Rwanda was launched in 2007. After the establishment of the program, a baseline mapping survey was conducted, the prevalence of schistosomiasis ranged from 0-70% in the schools that were included in the survey [70]. The difference in prevalence across multiple settings can be attributed to variations in the geographical distribution of potential risk factors, such as large water bodies amongst other factors [69]. Based on the mapping results, in 2008, the first PC for the control and elimination of schistosomiasis was conducted in endemic areas with a schistosomiasis prevalence of 10% or higher [71]. In 2011, a study done in Nkombo Island along lake Kivu in the western province of Rwanda found that the prevalence of *Schistosoma mansoni* was 62.1%, ranging from 28.6% - 77.9% across the schools. The prevalence of *Schistosoma mansoni* among the SAC of Nkombo Island was found to be the highest in Rwanda [72].

1.12 MASS PRAZIQUANTEL ADMINISTRATION FOR THE PREVENTION, CONTROL, AND ELIMINATION OF SCHISTOSOMIASIS IN RWANDA

Due to the overlap of schistosomiasis and STH in some areas in Rwanda and burden of the two NTDs in SAC, MDA for control and elimination of schistosomiasis and STH are done together [69]. PZQ and albendazole are given together in the schistosomiasis and STH PC. In 2019, more than 1 million SAC and approximately 100,000 adults received PZQ PC for schistosomiasis in Rwanda [73]. Despite several rounds of mass PZQ and albendazole administration, the safety of this treatment regimen is yet to be investigated in Rwanda.

1.13 VARIABILITY IN DRUG RESPONSE

Drug response vary widely in individuals due to the heterogeneity of the treated disease and clinical variables of the individuals such as age, sex, diet, concomitant use of other drugs, and renal or hepatic functions [74] as shown in **figure 5**.

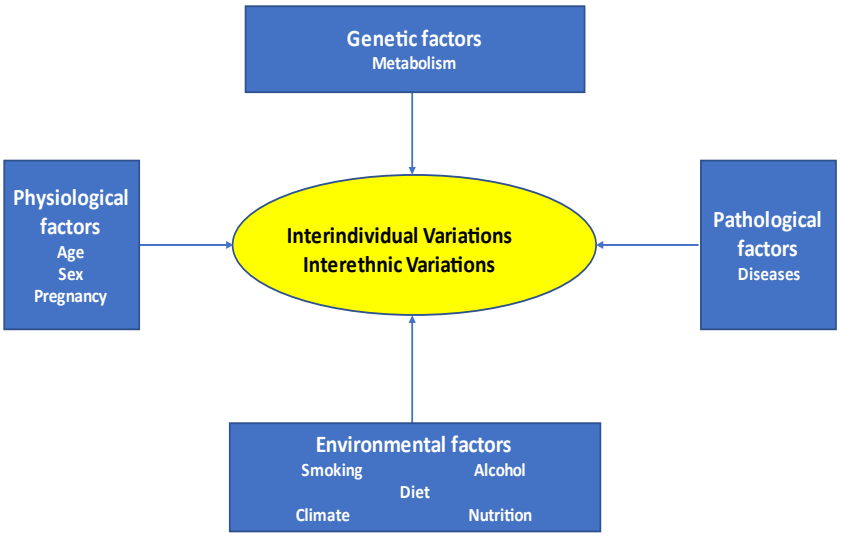

Figure 5. Variability in Drug Response. Adapted from: Presentation at ISoP Patient Safety Day "Pharmacogenomics in Pharmacovigilance" [75].

1.13.1 Safety of Praziquantel co-administered with Albendazole

Generally, the use of single dose PZQ is safe but like any other drug, PZQ has been reportedly associated with adverse events such as fainting, abdominal pain, nausea, vomiting, diarrhea, and many others among SAC [76, 77]. A meta-analysis including 134 studies of which 70% (94 studies) were conducted in Africa reported that AEs associated with PZQ were reported to be mild to moderate, however, up to 10% of the studies reported severe or SAEs. However, the follow up duration of the studies included in the meta-analysis were short (few hours) [77]. Some AEs were associated with the pre-treatment infection intensities and other medical conditions such as poor nutritional status and anemia [49, 76]. Individuals with heavy infection intensity have been found to suffer more severe AEs compared to those with light to moderate infection, partly due to immunologic reactions as a result of parasites' treatment induced death [49, 76]. Since the AEs are associated with pre-treatment infection severity, this further corroborate the need to monitor safety as recommended by the WHO [43]. Additionally, the concomitant administration of PZQ and albendazole (for STHs) as well as the limited information on the safety of the co-administration is another rationale for monitoring the safety of MDA for the control and elimination of schistosomiasis and STH. Comprehensive safety data on PZQ co-administered with Albendazole is scarce.

1.13.2 Role of Pharmacogenetics in Pharmacovigilance

Cytochrome P450 (CYP450) enzymes are involved in the bioavailability and metabolism of many drugs, these enzymes convert lipophilic drugs to hydrophilic metabolites prior to the drugs' excretion and play a key role in the metabolism of endogenous molecules and xenobiotics including drugs [78, 79]. Of more than 100 CYP450 isozymes, only a dozen of them is responsible for the metabolism of the majority of drugs, CYP1, 2, and 3 families, are

responsible for the metabolism of 70-80% of all drugs in clinical use [80]. CYP3A4, CYP3A5, CYP2C9 and CYP2C19 are among the highest expressed forms in the liver [80].

Some of the variation in drug response is related to genetic variations which may affect the drugs pharmacokinetics (PK) and/or pharmacodynamics (treatment outcomes specifically safety and/or efficacy) [74, 81-85]. Genetic variation in drug metabolizing enzymes and transporter proteins may affect treatment outcome including safety and efficacy by altering drug metabolism and disposition. Increased or decreased metabolism or transport of a drug may influence its plasma concentration, consequently its active, inactive, or toxic metabolites hence altering drug response and possibly resulting in ADRs [81-83]. For instance, increased adverse events of drugs metabolized by *CYP2C19*, such as the omeprazole, an antiulcer agent in individuals who are homozygous for the defective variant alleles *CYP2C19* (poor metabolizers) is reported [86]. Another example is eliglustat, a drug used for the long-term treatment of Gaucher disease [87]. Prior to initiating treatment, patients should be genotyped for *CYP2D6* to determine the phenotype (poor metabolizers, intermediate metabolizers, or extensive metabolizers) for appropriate dosing [87]. Metabolism and treatment outcome of efavirenz, an antiretroviral drug, display wide between-population variation partly due to variation in the defective variant *CYP2B6**6 allele frequency [88, 89]. *CYP2B6**6 allele is more common in black Africans compared to white and Asian populations. Higher efavirenz plasma concentration in patients homozygous for *CYP2B6*6* allele is associated with increased risk for treatment-associated central nervous system toxicity, which was more commonly observed in blacks [88, 90-92]. This provided the basis for lowering the standard daily efavirenz dose from 600mg to 400mg to minimize the occurrence of ADRs without having significant difference in efficacy treatment outcomes [89]. Indeed, CYP2B6 genotype- based dose modification of efavirenz in black Africans is advocated to lower toxicity. The above-mentioned examples highlight how pharmacogenetic tests of drug metabolizing enzymes can be useful in minimizing the likely occurrence of ADRs and optimize the safety of drugs as well as identifying subpopulation that are at increased risk of experiencing ADRs [81, 83-85].

1.13.3 Effect of pharmacogenetics variations on praziquantel plasma concentration and safety outcomes

As clearly highlighted above, the role of pharmacogenetics is important in drug pharmacokinetics and treatment outcomes including safety. PZQ is a chiral compound with R-PZQ and S-PZQ enantiomers that is primarily metabolized by CYP450 enzymes including CY2C19, CYP2C9, CYP3A4 and CYP3A5 [93, 94]. The genetic variation in drug metabolizing enzymes can affect plasma drug concentration, and treatment outcomes such as safety of therapeutic drugs [74, 95]. Further underscoring the need to investigate the effect of PG on plasma concentration and treatment outcomes particularly safety. To the best of my knowledge, only one recent study conducted in Tanzania investigated the effect of PG variations in CYP450 enzymes on PZQ PK and schistosomiasis treatment outcomes among infected children [96] despite the reported variability in drug response (adverse events) profile in previous studies [76, 77]. Findings from that study may not be directly extrapolated or

generalized to other African populations due to vast genetic diversity among black African populations [97]. The effect of PG variations on PZQ plasma concentrations and treatment outcomes among Rwandan population has not been investigated.

Although personalized treatment (genotype-based) in MDA is a challenge at present, data on the effect of PG variations on PZQ plasma concentration and schistosomiasis treatment outcomes are important for immediate future use and evidence based treatment guidelines [98]. Furthermore, recently, PG data utilization efforts have also been intensified in Africa [99].

2 RESEARCH AIMS

The aim of this thesis was to

i. assess the pharmacovigilance systems to identify gaps for targeted interventions to strengthen the systems in four East African countries (Papers I & II); and
ii. investigate the variability of PZQ response when co-administered with albendazole to identify risk factors associated with safety and plasma concentrations (Papers III & IV).

2.1 SPECIFIC OBJECTIVES

1. To assess the national pharmacovigilance systems at the respective NMRAs in Ethiopia, Kenya, Rwanda, and Tanzania to identify key gaps for intervention to further strengthen the systems (**Paper I**).
2. To assess the pharmacovigilance systems of the national NTD programs in Ethiopia, Kenya, Rwanda, and Tanzania to identify key gaps for intervention to further strengthen the systems (**Paper II**).
3. To investigate the safety of mass PZQ co-administered with albendazole administration to quantify AE incidence and identify the type, severity as well as risk factors for AEs among SAC in Rwanda (**Paper III**).
4. To investigate the effect of pharmacogenetics variations on PZQ plasma concentrations and safety outcomes among school children who received mass PZQ and albendazole adminstration in Rwanda (**Paper IV**).

3 MATERIALS AND METHODS

3.1 ASSESSMENT OF THE PHARMACOVIGILANCE SYSTEMS (NMRAS AND NTD PROGRAMS) - STUDIES I & II

For **studies I and II**, a pharmacovigilance assessment of the national pharmacovigilance centres hosted at the NMRAs and NTD programs were conducted in Ethiopia, Kenya, Rwanda, and Tanzania.

3.1.1 Study Design, Setting and Assessment Tool

Studies I and II were cross-sectional descriptive studies assessing and comparing the present pharmacovigilance systems within the national pharmacovigilance systems of the NMRAs and NTD programs in Ethiopia, Kenya, Rwanda, and Tanzania using the EAC Harmonized Pharmacovigilance Indicators tool.

The studies included four East African countries, specifically, Ethiopia, Kenya, Rwanda, and Tanzania. All the countries except for Ethiopia are members of the East African Community (EAC). The EAC is a regional intergovernmental organization of 7 Partner States including Kenya, Rwanda, and the United Republic of Tanzania. The work of the EAC is guided by its Treaty, which established the Community [100]. The EAC has a Pharmacovigilance Expert Working Group that supports the EAC Medicines Regulatory Harmonization (MRH) Program. The EAC has a Pharmacovigilance Expert Working Group that supports the EAC-MRH Program. The Expert Working Group put together the EAC pharmacovigilance indicators tool using the WHO- pharmacovigilance indicators and Indicator-Based Pharmacovigilance Assessment Tool (IPAT) taking the context of the community into consideration [22, 101]. Though not an official member of the EAC, Ethiopia and the EAC countries collaborate and work together on selected issues including pharmacovigilance.

The EAC Harmonized Pharmacovigilance Indicators tool used in the two studies was developed to assess the status of pharmacovigilance systems, specifically the structures, processes, and outputs/outcomes to identify key pharmacovigilance gaps for intervention to strengthen drug safety monitoring systems. The tool can be used to assess the NMRAs/national pharmacovigilance centres and other pharmacovigilance stakeholders such as PHPs, MAH, and health facilities. The tool has indicators that are categorized in different pharmacovigilance components.

For the assessment of national pharmacovigilance centres at the NMRAs, the tool comprised more than 50 indicators categorized into five pharmacovigilance components as outcome measures: (1) policy, law, and regulation; (2) systems, structures, and stakeholder coordination; (3) signal generation and data management; (4) risk assessment and evaluation; and (5) risk management and communication. In addition to the tool, few additional indicators from the WHO Global Benchmarking Tool (GBT) [102], were included. Those indicators were about the engagement and encouragement of stakeholders to report ADRs and the legal requirements of MAHs and their contribution in the pharmacovigilance systems.

For the pharmacovigilance assessment of NTD programs, the EAC Harmonized Pharmacovigilance Indicators tool for PHPs was used. The pharmacovigilance indicators are designed to assess the integration of pharmacovigilance related activities in PHPs. The tool for the assessment of the PHPs contained approximately 20 indicators categorized into four medicine safety and pharmacovigilance components: (i) systems, structures, and stakeholder coordination; (ii) data management and signal generation; (iii) risk assessment and evaluation; and (iv) risk management and communication.

3.1.2 Document Review

For the assessment of the national pharmacovigilance systems at the NMRAs, prior to travelling to the participating countries key staff with the overall responsibility and knowledge of the respective national pharmacovigilance system to be interviewed were identified. Once the respondents were identified, they were told about the pharmacovigilance assessment and asked to share the legal and statutory documents and other relevant information two weeks before the interview.

The documents that we requested for and received included:

• Extracts of national legislation defining relevant responsibilities for the function of the national pharmacovigilance system

• Pharmacovigilance regulations and guidelines promulgated by the Ministry of Health or the national regulatory authority defining the roles and responsibilities of different stakeholders contributing to the pharmacovigilance system

• Standard Operating Procedures (SOPs) describing routine processes to be followed in the management and routine operation of the pharmacovigilance system

• Terms of reference for external advisers, e.g., members of adverse reaction advisory committees

• Agreements or contracts signed with other authorities or organizations of relevance to the function of the national pharmacovigilance system.

For **studies I and II**, during the country visit assessments, additional documents were reviewed. Many of the indicators in the EAC Harmonized Pharmacovigilance Indicators tool require verification/information from official documents to answer the assessment indicator question or to validate the answers of the respondents.

3.1.3 Data Collection – Key informant interviews

The assessment and data collection for **studies I and II** in Ethiopia, Kenya, Rwanda and Tanzania were conducted from July to December 2018. The assessment team consisted of several pharmacovigilance experts including myself (the PhD candidate), the same team conducted the assessment in all four countries.

It is important to interview the right individuals who have adequate knowledge about the pharmacovigilance system and activities in the respective countries to give accurate responses and contextual information to enrich the interpretation and understanding of the results that is reflective of the situation. So, for the NMRA assessment, there were between two and four respondents who were NMRA staff working in the pharmacovigilance department/unit. The respondents were mainly pharmacists, except two; one was a medical doctor (Tanzania) and the other was a public health professional (Ethiopia). For the NTD program assessment, respondents were between two and three, except for Ethiopia, where only one staff member was available for the interview. The respondents were staff of the national NTD program and were pharmacists (in Tanzania and Kenya), a medical doctor and a public health officer (in Rwanda), and a public health officer (in Ethiopia). For both assessments (NMRA and NTD program), the adopted EAC Harmonized Pharmacovigilance Indicators tool was used during the interviews. The assessment team asked follow-up questions as required to have a good understanding of the availability and functionality of the relevant structure, process, systems, or outcomes/outputs.

The responses of the respondents were recorded on a template specifically developed for the EAC harmonized indicators. The responses were then sent to the respondents to ascertain that what was recorded was reflective of the discussions during the assessment. Once we got verification from the respondents, we proceeded with the data analysis.

3.1.4 Comparison of Results from Individual Country Assessments

The data gathered from the individual country assessments (NMRA and NTD programs) using the EAC Harmonized Pharmacovigilance Indicators tool were entered into the template that was developed based on five and four pharmacovigilance components for the NMRA and NTD programs respectively. For **studies I and II**, tables, figures, and bar charts were used to compare the performance of indicators within the same component.

3.1.5 Ethical Considerations

Studies I and II assessed pharmacovigilance health systems, namely the national pharmacovigilance centre of the NMRAs and the national NTD programs in Ethiopia, Kenya, Rwanda, and Tanzania to identify absence of key pharmacovigilance performance indicators for future targeted interventions to strengthen the systems. All the data generated in the studies were health systems and programmatic data. We did not collect individual level data and the NMRA and NTD program staff that were interviewed (respondents) did not disclose any personal data. Therefore, ethical approval was not required, the studies received ethical waivers

from respective IRBs in Ethiopia (CDT/586/18), Kenya (KNH-ERC/01/MISC/46) and Tanzania (DA.282/298/01/C/41), and ethical approval from Rwanda (440/RNEC/2018) instead.

3.2 ACTIVE SAFETY SURVEILLANCE AND PG-PK-PD STUDIES – STUDIES III & IV

Schistosomiasis was the NTD that was prevalent in all the four countries (Ethiopia, Kenya, Rwanda and Tanzania) so that was the NTD that I focused on in **studies III and IV**. Due to practical, human and financial resources amongst other reasons, it was more ideal to do it in one country only so **studies III and IV** were conducted in Rwanda.

3.2.1 Study setting area, design, and population

The studies (**III and IV**) included up to four districts on the belt of lake Kivu namely, Nyamasheke, Rubavu, Rusizi, and Rutsiro in the western province of Rwanda as shown in the map in **figure 6**. The western province covers an area of 4724.8 km^2 and includes land, forests, and large water bodies, especially Lake Kivu. The province has seven administrative districts and 96 sectors and a population of approximately 2.5 million. Most inhabitants of the selected districts carry out their daily activities including fishing, farming, bathing, washing, and swimming in close contact with water bodies such as Lake Kivu.

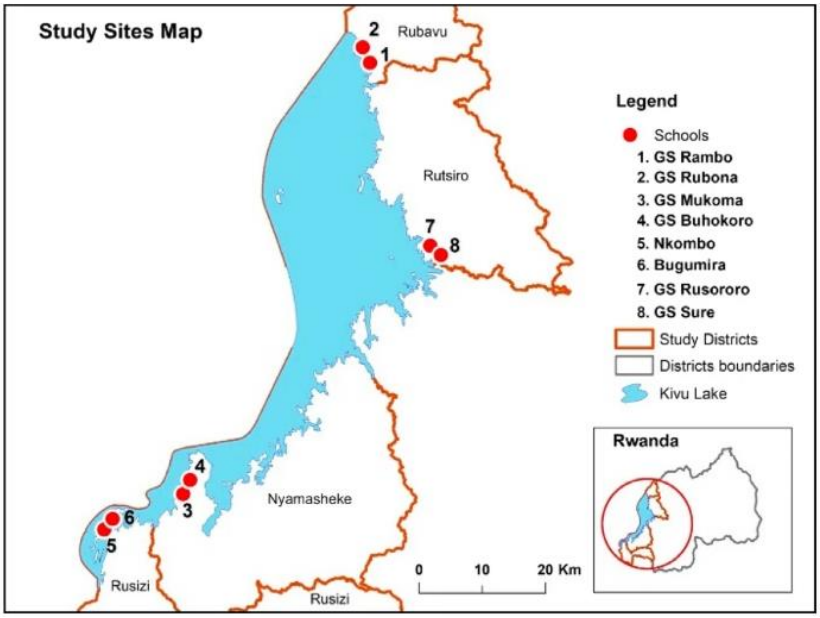

Figure 6. Map of Rwanda including the selected study districts and schools. Source: Kabatende et al., 2020 [103].

The four districts in the western province were selected using a purposive sampling method based on schistosomiasis prevalence data from previous studies. Within each district, two schools were selected based on three criteria: (1) proximity to the lake, proximity of selected schools was located about five kilometers from the lake (2) the number of school children attending, (3) previous schistosomiasis and STH prevalence data and (4) inclusion in the national NTD program for distribution of PZQ and albendazole MDA in 2019. A sample

proportion of each school to contribute to the whole study sample was based on each student population size (**study III**). Schoolchildren were systematically sampled in each class using class lists.

The study population for **studies III and IV** included school children aged 5-15 years attending one of the schools in the selected districts. In **study III**, 8037 school children attending one of the eight schools in the four districts were included in the active safety monitoring study. The target sample size for our study was 10,000, based on the WHO's estimation of event frequency. The sample size to detect at least three events at a frequency of 1 per 3333 with 95% confidence (95% probability) is 10,000 [104]. Therefore, a sample size of 8,037 will detect at least three events that occur at a frequency of 1 per 2679 with 95% confidence. For the **4th study**, 462 children from six schools in 3 districts specifically, Nyamasheke, Rubavu, and Rusizi were included.

Studies III and IV were prospective, observational cohort studies with a follow up period of 7 days. One was a cohort event monitoring study, an active pharmacovigilance safety surveillance study design to investigate the safety of mass PZQ co-administered with albendazole (**study III**). The other was a PG-PK-PD (safety) study investigating the effect of PG on PZQ PK and treatment outcome specifically safety (**study IV**).

3.2.2 MDA procedure

Study participants in **studies III and IV** only included school children who received single dose oral administration of PZQ co-administered with albendazole as PC provided through MDA under the Rwandan NTD program. The number of PZQ tablets given was height-based (**figure 7**), it was dependent on the height of the children (≥ 94 cm dose pole, designed to deliver a dose of at least 40 mg/kg) and one tablet of albendazole 400 mg according to the national and WHO MDA guidelines for Schistosomiasis and STH, respectively [45, 105]. The Rwanda NTD program hosted at the Rwanda Biomedical Centre under the supervision of the Rwanda Ministry of Health provided PZQ and albendazole as PC to prevent transmission and control of schistosomiasis and STH.

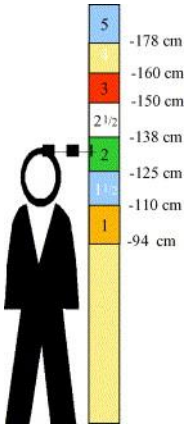

Figure 7. The WHO dose pole for Praziquantel. Source [105].

3.2.3 Assessment of nutritional status

To establish the nutritional status of the study participants, anthropometric measurements such as body weight (kilograms) and height (centimeters) (cm) were measured to generate body mass index (BMI). BMI and height were then converted to BMI-for-age Z score (BAZ) and height-for-age Z score (HAZ), respectively, using WHO Anthro-Plus software for children [106]. Children whose HAZ and BAZ scores were less than 2 standard deviations (SD) were considered stunted and wasted/thin, respectively.

3.2.4 Safety (Adverse Event) Monitoring

The primary outcome of **study III** was MDA-associated AEs (post-MDA AEs), described as any event that was not reported before PZQ and albendazole administration but occurred only after treatment exposure. The secondary outcomes included the type and severity of AEs. Before MDA, study participants were interviewed by trained data collectors to find out if they were experiencing any pre-existing clinical symptoms (pre-MDA event), such as fever, nausea, headache, loss of appetite, stomach pain, dizziness or fainting, vomiting, confusion, drowsiness, cough, difficulty in breathing, diarrhea, itching, rash, and any other symptoms. All study participants were interviewed 1-, 2-, and 7-days post MDA to record any AEs that they experienced. Between days 3 and 6, participants only reported if they experienced any AE.

Events reported by each study participant before and after MDA were checked and verified to distinguish preexisting clinical symptoms from treatment-related adverse events after MDA of PZQ and albendazole. Events reported after MDA (post-MDA) were considered MDA-related AEs if the same type of event was not reported before drug administration (pre-MDA).

All reported AEs were classified into five grades of severity using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 [107] as follows:

Grade 1—Mild: Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2—Moderate: Minimal, local, or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).

Grade 3—Severe or medically significant but not immediately life-threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.

Grade 4—Life-threatening consequences: urgent intervention indicated.

Grade 5—Death related to AE

3.2.5 Data collection

Data was collected through in-person interviews using case record form (CRF), study participants (respondents) were interviewed by trained data collectors. The type of data

collected included sociodemographic information, concomitant medication, chronic medical condition, breakfast status, type of meal, and pre-MDA symptoms were collected at baseline before receiving MDA. After MDA, study participants were actively followed to document treatment-associated AEs 1-, 2-, and 7-days post MDA through in-person interviews. Data collectors entered the data that collected in the electronic database using tablets. A data manager reviewed submitted data daily to cross-check and rectify errors. Each study site had a study coordinator to supervise activities such as study enrolment, data collection, and data entry into the database.

3.2.6 Whole blood and plasma sample collection

For the PG-PK-PD study (**study IV**), 2 mL whole blood sample was collected in EDTA tube from 462 children for genomic DNA extraction and genotyping. After drug administration, a 2-mL sample of whole blood from each study participant was collected into heparinized tubes 2 hours after drug administration and immediately centrifuged at 1,000 rpm for 10 min to obtain plasma. The plasma samples and blood samples were stored in -80°C freezer pending shipment to Karolinska Institutet (Stockholm, Sweden) for laboratory analysis.

3.2.7 Pharmacokinetic Quantification of plasma Praziquantel, praziquantel, cis-4-hydroxy-praziquantel and trans-4-hydroxy-praziquantel Concentrations

Plasma quantification of PZQ and *trans*- and *cis*-4-OH-PZQ metabolites was done using Ultra high Performance Liquid Chromatography tandem- Mass Spectrometry (UPLC-MS/MS), the methodology was adapted from Nleya et al., 2019 with slight modifications [108] as described in a recent publication [96]. 300µL of internal standards solution (rac-PZQ-d11, and *trans*-4-OH-PZQ-d5) prepared by the chemist were added to each well in the 96-well plate. Then, 100µL of plasma collected from the study participants was added to each well. After which, the plate was covered using a plate cover and vortexed for approximately 3 minutes followed by centrifugation at 5362 rotations per minute (rpm) for 20 minutes at 4^{o} Celsius. After centrifugation, 75 µl of the supernatant was diluted with 75 µL MilliQ water in a new 96-well plate. Then, 5 µL of the prepared mixture was injected into the UPLC-MS/MS system for analysis by the chemist. The chromatographic run was 4.7 minutes, *Trans*-and *cis*-4-OH-PZQ eluted first at a retention time of 1.22 and 1.32 minutes respectively, followed by PZQ at 1.94 minutes (**figure 8**). For quality control purpose, standards, and quality control (QC) samples were prepared in the same manner by adding 10µL standard and QC 10 x concentrated solutions to 90 µL blank plasma and precipitated as above.

To evaluate the linearity of the method, calibration curves were constructed within the range of 2.4 to 2500 ng/mL for PZQ and *cis*-4-OH-PZQ. For *trans*-4-OH-PZQ, the range of the calibration curve was constructed within 24 to 25000 ng/mL because the levels of *trans*-4-OH-PZQ in the plasma samples were very high.

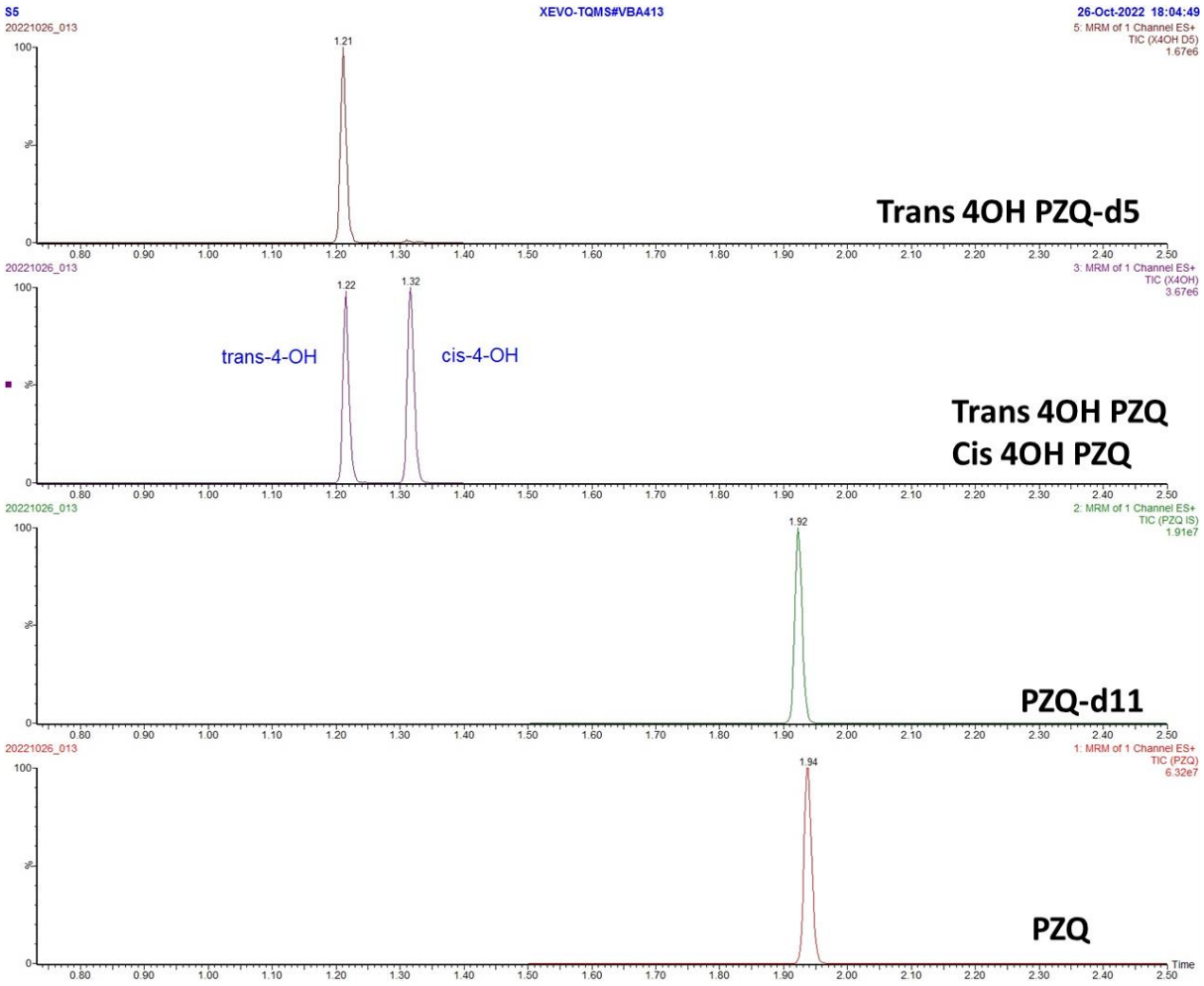

Figure 8. Liquid Chromatography Mass Spectrometry Chromatogram showing retention times and peak shape for PZQ, trans-and cis-4-OH-PZQ with internal standards.

Quantification of the analytes namely PZQ, *trans*-4-OH-PZQ and *cis*-4-OH-PZQ was performed using the analyte to internal standard integrated peak area ratio with the MassLynx application manager TargetLynx (Waters). *Trans*-4-OH-PZQ d5 was used as internal standard also for *cis*-4-hydroxy-PZQ since their retention times were similar (**figure 8**). 7 – 9 calibration points were injected twice before the samples and once after. The QC samples were injected for every 20 samples. Quality control samples at 9.8, 78.1, and 1250ng/mL were injected at regular intervals during each analysis.

3.2.8 DNA Extraction and Genotyping (*CYP3A4*, *CYP3A5*, *CYP2C19*, *CYP2C9* and *CYP2J2*)

The 2mL of whole blood samples collected from the study participants was used for genotyping. Genomic DNA was extracted from the 2mL of whole blood collected from the study participants using the QIAamp DNA Midi Kit (Qiagen GmbH, Germany) according to the manufacturer's instructions. The isolated DNA was then temporarily kept at -20° Celsius pending genotyping.

Genotyping for *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*17*, *CYP2C9*2*, *CYP2C9*3*, *CYP2J2*7*, *CYP3A4*1B*, *CYP3A5*3*, *CYP3A5*6*, and *CYP3A5*7* was performed as previously described [96, 109]. Genotyping was performed using TaqMan® drug metabolism genotyping assay reagents for allelic discrimination (Applied Biosystems Genotyping Assays) with the following ID numbers for each SNP: C__25986767_70 for *CYP2C19*2* (rs4244285), C__2,7861809_10 for *CYP2C19*3* (rs4986893), C__469857_10 for *CYP2C19*17* (rs12248560), C__25625805_10 for *CYP2C9*2* (rs1799853), C__27104892_10 for *CYP2C9*3* (rs1057910) C__9581699_80 for *CYP2J2*7* (rs890293), C__11711730_20 for *CYP3A4*1B* (−392A > G, rs2740574), C__26201809_30 for *CYP3A5*3* (c.6986A4G, rs776746), C__30203950_10 for *CYP3A5*6* (g.14690G4A,rs10264272), and C__32287188_10 for *CYP3A5*7* (g.27131_27132insT rs41303343). Genotyping was done using 7500 Fast Real-Time PCR (Applied Biosystems, United States). The final volume for each reaction was 10 μL, consisting of 1 μL genomic DNA and 9 μL DNA/RNA free water, TaqMan fast advanced master mix (Applied Biosystems, Waltham, MA, United States), and TaqMan drug metabolism genotyping assays mix (Applied Biosystems).

The PG data were analyzed to obtain the genotype and allele frequencies. The *CYP2C19*, *CYP2C9*, *CYP2J2*, *CYP3A4*, and *CYP3A5* genotypes were then linked to plasma concentrations specifically PZQ, *trans*- and *cis*-4-OH-PZQ and their metabolic ratios (*trans*-4-OH-PZQ/PZQ and *cis*-4-OH-PZQ/PZQ) and schistosomiasis treatment outcome, in particular, safety (**study IV**).

3.2.9 Data management and statistical analysis

For studies **III and IV**, data was collected using tablets and were transferred into a database created by National Reference Laboratory. Data collectors from the national reference laboratory were trained by the PhD student and supervisors on study protocol and good clinical and laboratory practices (GCLP). The data collected in the electronic database were imported into STATA 13 (StataCorp LLC, College Station, TX, USA) for cleaning and analysis for **studies III and IV**.

Descriptive statistics was used to analyze sociodemographic and anthropometric characteristics of the study participants (studies III and IV). Categorical and continuous variables were presented as proportions and median (interquartile range), respectively. Associations between a categorical dependent variable and independent categorical variables were analyzed using the Chi-square or Fishers exact tests. A p value < 0.05 was considered statistically significant.

For **study III**, in addition to the analysis mentioned above, the cumulative incidence of overall adverse events during the 7 days follow-up period was calculated. Furthermore, univariate, and multivariate log binomial regression models were used to identify predictors of any adverse events (binary dependent variable). Biologically plausible predictor variables with a p value ≤ 0.2 in the univariate regression models were included in the final multivariate regression model.

In **study IV**, in addition to the above-mentioned descriptive statistics, chi-square test was used to compare the genotype frequencies between the observed and expected according to the Hardy-Weinberg equilibrium. Independent sample t-test or one-way ANOVA were used to compare means of log transformed PZQ concentration and *cis*- and *trans*-4-OH-PZQ metabolic ratios between different CYP450 genotypes. To compare the means of log transformed PZQ concentration, and *cis*-4-OH-PZQ/PZQ and *trans*-4-OH-PZQ/PZQ metabolic ratio among those who experienced any adverse event and those who did not, independent samples t-test was also used. Univariate and multivariate linear regression analysis were used to identify the predictors of PZQ plasma concentrations and its cis and trans metabolic ratios. Chi-square or fisher's exact tests was used to test for associations between adverse events (binary dependent variable) and the different CYP450 genotypes. Univariate and multivariate log binomial regression was used to quantify the effect of association between the different CYP450 genotypes and adverse event.

3.2.10 Ethical considerations

Studies III and IV were approved by the Rwandan National Ethics Committee (Review Approval Notice No. 0064/RNEC/2019). Prior to the start of the studies, meetings for awareness and sensitization were held. The meetings were attended by relevant individuals such as heads of district hospitals, health centres staff, district education offices staff, schoolteachers, school administrators, and parents/guardians. Participants and their parents or legal guardians were informed about the study prior to enrollment. For participants ≤ 12 years of age, verbal and written informed consent was obtained from their parent or guardian, and for participants > 12 years of age, verbal and written informed consent was obtained from the parent or guardian and assent was obtained from the study participant. To ensure confidentiality, participant IDs were used to make the collected information anonymous.

Studies III and IV did not include children whose parents or guardians did not provide informed consent and or dissent. However, these children were still able to take part in the national MDA and received PC deployed under Rwanda's NTD program, though no data were collected from them.

Study IV was also approved by Stockholm Ethics Committee for the PG and PK analysis that was conducted at Karolinska Institutet, Sweden (Ref. No.2020-00845).

4 RESULTS AND DISCUSSION

For **studies I and II**, the pharmacovigilance centres of four NMRAs and pharmacovigilance systems of the four NTD programs were assessed, respectively. For **study III**, 8037 school children were enrolled. 462 school children from the study III cohort were enrolled for **study IV**.

4.1 NATIONAL PHARMACOVIGILANCE SYSTEMS OF THE NMRAS IN ETHIOPIA, KENYA, RWANDA, AND TANZANIA

The four NMRA are supported by legal instruments such as acts, regulations, and policies that defined the role of the authorities and their responsibilities to monitor the quality, safety, and efficacy of medicinal products [8].

At the time of assessment (2018), Ethiopia, Rwanda, and Tanzania had legal provisions that mandated Marketing Authorization Holders (MAH) to conduct post-marketing safety surveillance (PMS) and report ADRs. In addition to the requirement above, in Ethiopia and Tanzania, MAHs were mandated to regularly submit Periodic Safety Update Report (PSURs) or Periodic Benefit–Risk Evaluation Report (PBRERs). In Tanzania, MAHs were also required to have a Qualified Person Responsible for Pharmacovigilance (QPPV). In Kenya, there were no such legal provisions that required MAHs to conduct post-marketing safety activities and report ADRs or medicine safety issues, to submit PSURs/PBRERs and/or to have a QPPV. However, these responsibilities were written in the pharmacovigilance guidelines. The involvement of MAHs in the national pharmacovigilance systems in the four countries should be strengthened. For example, in Tanzania, it is a requirement for MAHs to submit PSURs and PBRERs every 6 months, although this requirement was not adhered to. MAHs should comply with the mandatory requirements, to further improve compliance, in Ethiopia, Kenya and Rwanda, the where applicable the pharmacovigilance requirements of MAHs should be at the level of regulation rather than being based on guidelines. The appointment of a QPPV by MAHs, performance and funding of Post Authorization Safety Studies (PASS) relating to the identified safety signals will contribute to MAHs playing an active role in collecting data from the local/national markets and not just submit data from the rest of the world.

A similar challenge that all the four countries had was low ICSR. Since joining the WHO PIDM, Kenya (2010), Tanzania (1993), Ethiopia (2008), and Rwanda (2013) have respectively submitted 11,373, 1899, 1331, and 30 ICSRs to VigiBase. In 2018, when we conducted the assessment, the rates of ICSRs in Kenya, Ethiopia and Tanzania were 35, 6.7, and 4.1 per million respectively. The Rwanda FDA submitted zero ICSR to WHO PIDM in 2017/2018. The rate of reports from African countries submitted to WHO PIDM is low compared to other parts of the world. In 2019, the proportion of reports from Africa was 0.9%, this is not adequate to identify significant drug related issues [110]. Therefore, African countries need to report more because the safety information based on the WHO global database might not always be relevant for local settings [110].

The low reporting rates may be due to limited financial and human resources as well as limited stakeholder coordination amongst other factors. In this study, we observed that the fulltime equivalent staff in Tanzania, Ethiopia, Kenya, and Rwanda working in the pharmacovigilance unit were twelve, ten, five and two, respectively. Furthermore, only two countries, namely Kenya and Tanzania had an allocated annual budget for pharmacovigilance activities. Ethiopia and Rwanda did not have a specific budget allocated for pharmacovigilance activities. Limited financial and human resources was observed in all four countries, including the two countries that had a designated budget for pharmacovigilance. Therefore, financial and human resources should be increased so that they are well-matched with the pharmacovigilance activities in the respective pharmacovigilance regulations and guidelines.

Another gap identified in the four countries was limited stakeholder coordination between the national pharmacovigilance centres and hospitals and PHPs. In 2017/2018, the proportion of health facilities that reported suspected ICSRs to the national pharmacovigilance systems in Ethiopia, Kenya, and Tanzania was≤1% of the total number of health facilities per country. Therefore, the national pharmacovigilance centres can engage hospitals as partners of the national pharmacovigilance system through their Drug and Therapeutics Committees (DTC). Where such bodies do not exist, they could be established. Guidelines for DTCs should be written to include responsibility for collection, assessment, and further reporting of ICSRs to the national pharmacovigilance centre. To motivate committee members, training programs could be designed and offered. The DTC members could be made responsible for pharmacovigilance training of healthcare professionals in their facility. To increase PHP engagement, it may be beneficial for the national pharmacovigilance centres in the four countries to establish/strengthen relationships with PHPs that are using medicines and vaccines. Engage them as important partners in the national pharmacovigilance system by developing joint guidelines for safety surveillance of medicines/vaccines used, designing pharmacovigilance trainings for healthcare workers in the PHP, and conducting joint active safety surveillance when new therapeutic regimens are being introduced in the PHP.

Another important gap identified was that none of the four national pharmacovigilance systems had a source of data on consumption and prescription of medicines. Population-level data on drug use is important to weigh the potential risk of drug related harm and assess the public health impact of ADRs. National pharmacovigilance systems should establish a mechanism to collect data on drug use (which is the denominator for calculating the reporting rate), weigh drug risk at the population level, prioritize safety signals, and follow-up the impact of regulatory actions such as restrictions and warnings.

Since the assessment, they have been interventions that have been implemented in the four countries. For instance, Rwanda FDA has just launched its pharmacovigilance guidelines, in Kenya, MAHs are mandated to appoint QPPVs, the EFDA has recently introduced an electronic AE reporting system for healthcare professionals. Therefore, some of the gaps identified may have been addressed, hence, there is a need for continuous assessment of the systems to identify the real gaps that need to be addressed.

The four countries were at different levels of performing pharmacovigilance and the difference in pharmacovigilance performance in SSA has been previously reported in a recent review [24]. Therefore, the pharmacovigilance harmonization initiatives may contribute to improve the pharmacovigilance systems in African countries, this is particularly useful and a cost-effective use of limited financial and human resources [111]. The African Medicines Regulatory Harmonization (AMRH) initiative was launched in 2009 and has served as a foundation for the establishment of the African Medicines Agency (AMA). The AMRH initiative was established to strengthen medicines regulation in Africa by promoting the effectiveness, efficiency, transparency, and collaboration of regulatory mechanisms [111-113].

4.2 PHARMACOVIGILANCE SYSTEMS OF THE NATIONAL NTD PROGRAMS IN ETHIOPIA, KENYA, RWANDA, AND TANZANIA

Based on our findings specifically the limited coordination between the national pharmacovigilance centres and PHPs, we assessed the PHP for NTDs in the second study. This study was the first pharmacovigilance assessment of the NTD programs in the four countries.

The NTD programs in all the four countries had pharmacovigilance components such as pharmacovigilance information in their operational documents specifically the five-year strategic masterplan. Furthermore, the NTD programs had tools for reporting suspected AEs and mechanisms to disseminate pharmacovigilance information [114]. Though the dissemination mechanisms can be strengthened, the presence of these pharmacovigilance indicators highlights the programs' intent to monitor the safety of the medicines they use [25].

All four NTD programs had MDA cascaded trainings, although the trainings were mainly focused on the implementation and coverage of MDA, a small component of medicine safety was included. This indicates that pre-MDA preparatory activities included the planning of safety during MDA. However, in 2017/2018, none of the NTD programs reported/submitted an ICSR following MDA. This seems unlikely because many millions of people were exposed to medicines that year, so mild and even serious AEs temporally related to treatment are likely to occur. The lack of ICSR may indicate that the medicine safety component of the pre-MDA trainings was either limited or not sufficiently addressed. Although the cascade training used by the four programs is cost-effective, it is also known that such a long chain (3–4 steps) of information sharing carries a risk of distortion of the message [115]. Hence, there is a need to ensure that the pharmacovigilance information in the training is sufficient and that the need for medicine safety monitoring and reporting of AEs is emphasized as recommended by the WHO [43]. Other factors related to the non-reporting of ICSRs may be due to lack of designated budget for pharmacovigilance and limited coordination between national pharmacovigilance centres and NTD programs.

Financial resources for medicine safety monitoring during MDA was limited. None of the four programs had a designated budget specific for pharmacovigilance activities. For the NTD programs to implement the pharmacovigilance activities in the strategic masterplans, a

pharmacovigilance budget as reported by other PHPs, such as malaria, HIV/AIDS, TB, and immunization programs [25] is essential.

As observed in the pharmacovigilance assessment of the national pharmacovigilance centres (**study I**), in this assessment we noted that there was no/limited stakeholder collaboration between the NTD programs and their respective national pharmacovigilance centres. In this study, only the NTD program in Ethiopia had collaborated with the NMRA on the development and review of the treatment guidelines and pre-MDA training. The lack of collaboration between the two institutions was reported by another study, that study found that national pharmacovigilance centres in Africa found it challenging to engage PHPs in a sustainable way due to several factors, including limited collaborations [14]. As discussed in the assessment of the national pharmacovigilance systems in Ethiopia, Kenya, Rwanda and Tanzania (study I), there is a need for the NMRAs specifically the national pharmacovigilance centres and NTD programs to collaborate on key pharmacovigilance activities such as developing pharmacovigilance guidelines. Also, for the safety monitoring of the drugs used in the programs, training healthcare workers on pharmacovigilance and conducting active safety surveillance when the need arises. Doing these key activities together will prevent duplication of efforts and optimize use of resources.

When this assessment was conducted, the identification and reporting of suspected AEs associated with MDA were indicated but not captured in all the four countries. This may be because initially increased access to medicines was more prioritized compared to pharmacovigilance [7, 10, 11], the immediate benefits of delivering potentially life-saving medicines overshadowed risk considerations including safety monitoring. In all the four countries, pharmacovigilance within the NTD programs is as neglected as the diseases and needs to be strengthened especially when there are different optimization studies combining up to three different medicines (triple therapy) [116], increasing treatment doses [117, 118], repeated doses [119-122] and combination therapy including artemisinin derivatives [123-127] to improve efficacy outcomes. None of the four programs had conducted an active surveillance study to determine the safety of the medicines given in MDA. Therefore, for **study III,** we investigated the safety of mass PZQ and albendazole administration for the control of Schistosomiasis and STH, respectively.

4.3 SAFETY OF MASS PRAZIQUANTEL AND ALBENDAZOLE COADMINISTRATION AMONG SCHOOL CHILDREN IN RWANDA

Study III included 8037 children aged between 5 and 15 years who received albendazole and PZQ during the 2019 MDA campaign from the selected 8 schools in the four districts. 52.6% (n= 4224) and 63.6% (n=5112) were males and 10-15 years old, respectively. 41.1% (n=3301), 30% (n=2415) and 28.9% (n=2321) received one, two and three PZQ tablets, respectively. Prior to drug administration, during the baseline assessment of self-reported symptoms (pre-MDA), 22.3% (n=1795) reported that they were experiencing at least one type of clinical symptom [51]. Baseline characteristics of the study participants are shown in **table 1**.

Table 1. Socio-demographic and baseline characteristics of study participants

Variable		N	%
Sex	Male	4,224	52.6
	Female	3,813	47.4
Age categories	5 - 9 years	2,925	36.4
	10 - 15 years	5,112	63.6
District	Rubavu	2682	33.4
	Rutsiro	1589	19.8
	Nyamasheke	1357	16.8
	Rusizi	2409	30
School	Rambo	1,441	17.9
	Rubona	1,241	15.4
	Rusororo	808	10.1
	Sure	781	9.7
	Buhokoro	423	5.3
	Mukoma	934	11.6
	Bugumira	1,111	13.8
	Nkombo	1,298	16.2
Stunting status (HAZ)	Non stunted	5,232	65.1
	Stunted	2,805	34.9
Wasting status (BAZ)	Not wasted	7,204	89.6
	Wasted	833	10.4
Have eaten breakfast	Yes	4305	53.6
	No	3732	46.4
Type of food taken before MDA	Fatty meal	107	2.5
	High Protein	281	6.5
	Carbohydrate meal	3917	91
Number of Praziquantel tablets taken	1	3301	41.1
	2	2415	30
	≥3	2321	28.9
Concomitant medication	Yes	275	3.4
	No	7762	96.6
Having any chronic medical condition	Yes	220	2.7
	No	7,817	97.3
Pre-MDA Events	Yes	1795	22.3
	No	6242	77.7

Out of 8037 children who participated in the study, 1658 (20.6%) reported at least one adverse event during the 7-day follow-up period. The overall cumulative incidence of experiencing at least one AE among the study participants was 20.6% (95% CI: 19.7–21.5%, n = 1658) during the 7-day follow-up. Studies have reported varying AE incidence associated with PZQ and albendazole MDA. Compared to our study, higher AE incidence was reported by other studies conducted in Kenya (25.3%), Tanzania (28.5%), Angola (55.9%), and Ethiopia (83%) [49, 128-130]. A recent study in Ethiopia investigating the safety of mass PZQ and albendazole administration reported a lower incidence of AE compared to our study [131]. However, they reported that incidence of AE was significantly higher amongst those who were either positive for Schistosomiasis (17.0%) and STH (14.1%) compared to children who were non infected (8.4%) [131]. The difference in reported AE incidence can be due to infection status and severity of the study population (treatment in infected children versus PC in the target population with unknown infection status). A important epidemiological feature of schistosomiasis is its focal distribution (that is highly variable prevalence and intensity of infection even within a small area, from one village to another), which is partly determined by the interaction of humans, intermediate host snails and human–water contact patterns [58, 132]. Other plausible reasons for variability in reported incidence in different studies could be due to study follow-up time, genetic, physiological, pathological, and environmental factors [129, 133, 134]. The variability in AE incidence in different sub-populations highlights another rationale for safety monitoring because results from other studies may not be generalizable to other populations.

The cumulative incidence of AE was significantly higher among children who reported pre-MDA events (27.5%, 95% CI 25.4–29.6%) compared to those who did not (18.7%, 95% CI 17.7–19.7%). This finding was also observed in recently published studies in Kenya and Tanzania [135, 136]. Hence, children with underlying clinical symptoms should be closely monitored during and after MDA.

1658 children reported a total number of 3196 AEs during the follow-up period. The most commonly reported AEs included Headache (21%), dizziness or fainting (15.2%), nausea (12.8%), and stomach pain (12.2%), this was also observed in other studies from Angola, Ethiopia, Kenya, and Tanzania [49, 128-130]. Rash (1.9%), other symptoms (1.6%), and confusion (1%) were the least reported AEs. The AEs observed were transient, most of the AEs occurred on days 1 (2588 AEs) and 2 (570 AEs) post MDA. Like other studies including a randomized controlled trail and meta-analysis, we found that 91.3% of the AEs were mild, 8.4% were moderate, and 0.3% were severe [49, 128, 137, 138]. The severity of AEs could potentially be due to several factors, thus, safety surveillance during PZQ and albendazole mass administration in various settings is imperative.

Risk factors associated with experiencing AE post mass PZQ and albendazole administration among children in our study included sex, age, type of food taken before MDA, number of PZQ tablets and having pre-MDA events. The cumulative incidence of AE among females was

23.2% and 17.75 among males. Additionally based on the log binomial regression, after adjusting for potential confounder, in our study, females had an increased 18% risk of experiencing at least one AE compared to males. Generally, women have a higher risk of developing AEs compared with men, however the reason for this is unclear but is possibly due to physiological and sex-related hormonal differences, which can affect drug metabolism [135, 139, 140]. Children aged 10-15 years reported more AEs (24.8%) than those 5-9 years (13.4%) and we observed a 36% increased risk of AE among the older age category after controlling for selected confounders. This may be due to the higher STH prevalence in the older age group, which could be associated with an increased risk of experiencing AEs, as previously described [103, 131, 134]. Children who had a fatty meal before MDA reported more AEs (30.8%), followed by those who had a high protein (29.5%) and carbohydrate (20.4%) meals. Study participants who had a fatty meal and high protein meal had a 52% and 39% increased risk of experience an AE compared to those who had a carbohydrate meal, respectively. This finding is supported by a recent study, Khaemba et al., reported an association between fatty or high protein meal before MDA with a higher incidence of AEs after mass diethylcarbamazine and albendazole administration for the elimination of LF in Kenya [135]. Changes in drug absorption and bioavailability influenced by fatty or high protein diet has also been reported [141], food–drug interactions influencing drug absorption could possibly alter the susceptibility to AEs following PZQ and albendazole MDA. Children who took three or more PZQ tablets reported more AEs (29.6%), followed by those who had taken two tablets (21.8%), children who took one tablet reported the lowest AEs (13.5%). In our study population, after adjusting for several confounders, those who had 3 or more PZQ tablets and those who had two tablets had a 63% and 38% increased risk of AE compared to children who took one PZQ tablet, respectively. This could be due to the plasma concentration of PZQ, therefore there is need to investigate the effect of PK on safety.

4.4 EFFECT OF PHARMACOGENETICS ON PRAZIQUANTEL PLASMA CONCENTRATIONS AND SAFETY OUTCOMES AMONG SCHOOL CHILDREN IN RWANDA

A total of 462 school children from study 3 attending one of the selected six school in the 3 districts along lake Kivu participated in this study. The characteristics of the study population is presented in **table 2**. The median age (interquartile) was 12 (10-13) years and 50.4% were females.

Table 2. Characteristics of the study population (n=462)

Variable		Median (IQR)
Age (years)		12 (10-13)
Weight (kg)		32 (27-39)
Height (cm)		137 (129-146)
BMI (kg/m^2)		16.9 (15.7-18.5)
		N (%)
Sex	Male	229 (49.6)
	Female	233 (50.4)
District	Nyamasheke	63 (13.6)
	Rubavu	216 (46.8)
	Rusizi	183 (39.6)
Wasting status (BAZ)	Wasted	14 (3.0)
	Not wasted	448 (97.0)
Stunting status (HAZ)	Stunted	173 (37.4)
	Not stunted	289 (62.6)
Adverse Event (n=436)	Yes	157 (36.0)
	No	279 (64.0)

*CYP3A4*1B* (72.0%), *CYP3A5*6* (20.0%) and *CYP3A5*3* (18.2%) were the most frequent variants. *CYP2C9*2* and *CYP2C9*3* alleles occurred at the lowest frequency (0.2%). The overall geometric means ± SD concentrations of PZQ, *trans*-4-OH-PZQ and *cis*-4-OH-PZQ in the study population were 318.4±4.1, 8770.0±2.2 and 571.5±2.8 ng/mL, respectively. The overall means± SD concentrations of the metabolic ratios (MRs) namely *tr*ans-4-OH-PZQ/PZQ and *cis*-4-OH-PZQ/PZQ were 27.5±2.7 and 1.8±2.9, respectively.

Our finding indicates that there was a significant association between *CYP2C19* genotype and PZQ concentration and *cis*- and *trans*-4-OH-PZQ/PZQ MR. Children who were carriers for **2, *3* alleles (intermediate and poor metabolizers) had the highest PZQ concentration compared to those with *CYP2C19 *1/*1* (extensive metabolizers). The mean of *trans*- and *cis*-4-OH-PZQ/PZQ MRs were highest among children carrying *CYP2C19 *1/*17* or **17/*17* (ultra-rapid metabolizers). This is in line with a recent study that investigated the influence of PG variation on PZQ plasma concentration among *Schistosoma mansoni* infected children in Tanzania [96]. The findings indicates that ultra-rapid metabolizers produce more metabolites compared to the other phenotypes, as **17* allele is associated with increased CYP2C19 enzyme expression. Based on the t-test, *CYP2C9 *2, *3* carriers had a significantly higher concentration of the parent drug, PZQ and lower *trans*- and *cis*-4-OH-PZQ/PZR MRs compared to children with *CYP2C9*1/*1*. In the linear regression, after adjusting for confounders, there was a borderline association between *CYP2C9* genotype and PZQ concentration (p=0.08). *CYP2C9* *2 and *3 carriers had significantly lower *trans*-4-OH-PZQ/PZQ mean MR compared to those

with *CYP2C9 *1/*1* genotypes (p=0.03). There was a borderline association between *CYP2C9* genotype and *cis*-4-OH-PZQ/PZQ MR (p = 0.06). *CYP3A4* was also associated with *cis* MR, *CYP3A4*1B* carriers had a higher *cis*-4-OH-PZQ/PZQ MR compared with those who were *CYP3A4 *1/*1* in our study cohort (p=0.04).

These findings may indicate that CYP2C19 is a major metabolic pathway for the formation of *trans*- and -*cis*-4-OH-PZQ metabolites. A previous study has also found that CYP2C19 and CYP2C9 are the main enzymes responsible for metabolizing PZQ to its metabolite 4-OH-PZQ [94]. Indeed, PZQ is reported to be mainly metabolized by *CYP2C19* and to a lesser extent by *CYP2C9* and even lesser by *CYP3A4* [94, 142].

Our study also found an association between *cis*-4-OH-PZQ/PZQ MR and safety. The mean MR of *cis*-4-OH-PZQ/PZQ concentration was significantly lower among those who experienced adverse events compared to those who did not (<0.0001). After controlling for confounders, children who experienced adverse events had a mean decrease *cis*-4-OH-PZQ/PZQ concentration of 0.131 (p <0.01) compared to children who did not experience adverse events. There was no statistically significant mean difference in PZQ (p = 0.15) and *trans*-4-OH-PZQ/PZQ MR (p = 0.47) concentration among those that experienced adverse events compared to those who did not.

Univariate followed by multivariate log binomial regression analysis indicated no association between *CYP3A4*, *CYP3A5*, *CYP2C9*, *CYP2C19* and *CYP2J2* genotypes and MDA-associated adverse events. Therefore, there is need for more studies to investigate if PG affects safety treatment outcome.

5 CONCLUSIONS

The findings of this PhD research will contribute to bolstering the pharmacovigilance systems to improve safety monitoring of medicinal products and the global efforts to fight NTDs specifically schistosomiasis. The main conclusions and recommendations for relevant stakeholders and policy makers include:

- The national pharmacovigilance systems in the four countries have similarities but they do have differences as well, they are at different levels in performing pharmacovigilance responsibilities and tasks. Despite having legal instruments and pharmacovigilance systems and structures, limited stakeholder involvement and engagement in the pharmacovigilance systems manifested in very low reporting of ICSRs. Thus, the pharmacovigilance systems did not have the full capacity to systematically identify new problems related to pharmaceutical products happening in healthcare delivery systems. The gaps identified should be targeted for intervention to improve the pharmacovigilance systems in Ethiopia, Kenya, Rwanda, and Tanzania.
- The NTD programs in the four countries had some pharmacovigilance components in place. However, several key elements related to the safety monitoring of their medicines including reporting of AEs, specific budget for pharmacovigilance, sustainable collaboration between the NTD programs and the national pharmacovigilance centers (NMRAs) amongst others were limited or non-existent. Our findings identified key gaps for targeted intervention to promote public medicine safety and increase the success of the NTD programs in Ethiopia, Kenya, Rwanda, and Tanzania.
- Mass single-dose PZQ co-administered with albendazole administration for the control of schistosomiasis and soil-transmitted helminthiasis is generally safe and tolerable. Although, more than 20% of the children experienced transient mild-to-moderate AEs and few cases of severe AEs. This highlights the need to monitor the safety and integrated pharmacovigilance for the timely detection and management of AEs.
- *CYP2C19* may influence or affect plasma PZQ concentrations and cis- and *trans*-4-OH-PZQ MRs. On the other hand, *CYP2C9* was associated with decreased *trans*-4-OH-PZQ MR and borderline association with PZQ and *cis*-4-OH-PZQ MR. *CYP3A4* was only associated with increased *cis*-4-OH-PZQ MR. Furthermore, mean *cis*-4-OH-PZQ MR was significantly lower among those who experienced adverse event compared to those who did not. There was no association between the tested genotypes and safety outcome. More studies are needed to evaluate the effect of PG on PK and pharmacodynamic especially among those carrying defective variants of *CYP2C9* and *CYP2C19*.

6 POINTS OF PERSPECTIVES

My thesis for doctoral degree (Ph.D.) answered several research questions. Based on the findings, below are suggestions/recommendations to be considered by national and international stakeholders in the future.

- The access to medicinal products including new drugs, vaccines and diagnostics will continue to increase in Sub-saharan Africa as per the global development agenda. This underscores the need to have comprehensive pharmacovigilance systems to monitor the safety of medicinal products thereby preventing medicine related problems and improving patient safety.
- Though the national pharmacovigilance centres at the NMRAs had similarities, they were at different levels of pharmacovigilance performance. The establishment of African Medcine Agency (AMA) will likely contribute to improving the NMRAs capacities including strenghtening pharmacovigilance which may result in closing the gap in pharmacovigilance performance across different countries in Africa. After the establishment of AMA, the NMRAs in the member states especially those who have minimal pharmacovigilance capacity should be assessed to identify gaps for intervention thereby strengthening the pharmacovigilance systems so that they are adequate to monitor the safety of their medicinal products in their markets.
- In this thesis, for the first time, the pharmacovigilance systems of the NTD programs in Africa were assessed. Based on our findings, the NTD programs had started to include some pharmacovigilance elements in their programs but several key pharmacovigilance components relevant for the safety monitoring of the medicines were absent, this is evident in the lack of AE reporting despite the millions of individuals that received MDA. There is need to continuously assess the pharmacovigilance systems of the NTD programs to identify gaps for timely interventions. This assessment of the pharmacovigilance systems should not be limited to the NTD programs, it should be extended to the other PHPs as well so there is need to assess the pharmacovigilance systems of other PHPs too.
- For the first time in Rwanda, the safety of mass PZQ and albendazole administration among SAC was investigated. Based on our findings, there are sub populations that are at an increased risk of experiencing AEs. There is need for more studies to investigate the safety of mass PZQ and albendazole administration among SAC in Rwanda to establish our study findings for appropriate actions as some sub populations may benefit from closer monitoring post MDA. Also, in some areas in Rwanda, adults receive MDA for Schistosomiasis, therefore, there is need to investigate the safety among adults as the safety results of the SAC may not be generalizable to adults.
- Again, for the first time in Rwanda, the effect of PG on PZQ plasma concentration and safety, one of the treatment outcomes was investigated. *CYP2C19* and to a lesser extend *CYP2C9,* and *CYP3A4* genotypes were associated with PZQ concentrations and its *trans*- and *cis*-4-OH-PZQ MRs. Furthermore, *cis*-4-OH-PZQ/PZQ MR was associated

with safety. There is need for more studies to confirm these findings. Also, there is a need to investigate the role of PG and PK on the other treatment outcome, specifically efficacy.

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