Safety of the Co-Administration of Azithromycin, Albendazole and Ivermectin Versus Standard Treatment Regimens During Mass Drug Administration (MDA) in Ethiopia: A Cluster Randomized Trial

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Declaration:

I declare that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated within the thesis.

Signature:

Scott McPherson

Preface

This thesis is presented as a 'Research Paper Style Thesis' in accordance with submission guidance provided by the London School of Hygiene and Tropical Medicine. Three of the chapters comprise papers that have been published, submitted for publication or that are in preparation for submission to particular peer-reviewed journals. These are highlighted in italics in the Table of Contents. In view of the differing requirements of the journals in which the work has been published there is by necessity some repetition of material and variation in the formatting of these chapters. Publication details and acknowledgement of co- author contributions are included on the individual cover sheets for each paper. The remainder of the thesis is comprised of 'linking material' and includes an introduction to the overall research project.

All material within this thesis was written by Scott McPherson.

Abstract

Traditionally, health ministries implement mass drug administration programmes for each neglected tropical disease (NTD) in separate and distinct campaigns. Many NTDs have overlapping endemicity suggesting co-administration might improve programme reach and efficiency, helping accelerate progress towards 2030 targets. Safety data are required to support a recommendation to undertake co-administration. For my PhD thesis, I sought to establish the safety profile and assess the community acceptance of a three-agent MDA combining albendazole (Alb), azithromycin, and ivermectin (Ivm) in comparison to the standard MDA regimen which separates the administration of azithromycin from the co-administered ivermectin and albendazole by a period of two weeks.

I first conducted a literature review aimed at compiling and summarizing existing data on co-administration of ivermectin, albendazole and azithromycin, including both data on pharmacokinetic interactions and data from previous experimental and observational studies conducted in NTD-endemic populations. The results of the literature review showed that there was relatively limited data on the safety profile of co-administering these three drugs but that the available evidence suggested such a strategy is safe with an absence of clinically important drug-drug interactions, no serious adverse events reported and little evidence for an increase in mild adverse events

I then lead an open-label, non-inferiority cluster-randomized trial comparing the frequency of adverse events in communities receiving the co-administered ivermectin, albendazole and azithromycin to that in communities given albendazole and ivermectin MDA followed by azithromycin MDA after a two-week interval. The study took place in 58 gares (small administrative units) across two kebeles (sub-districts) in Kofele woreda (district) in the Oromia region of Ethiopia from November 2022 to January 2023. We randomly assigned 29 gares to the combined treatment arm and 29 gares to the control arm.

The qualitative study I conducted was nested within the safety trial. Using semi-structured question guides, we conducted 16 key informant interviews (KII) with selected individuals involved in implementing MDA within the participating district. These individuals included health care providers and health department staff members, local government leaders, traditional governance leaders, religious leaders and elders. To better understand the perceptions of recipient communities, we also conducted four focus group discussions with key representational groups: male adults, female adults, female youths and male youths.

The results of the trial showed that co-administration arm was non-inferior to the control Arm. The combined MDA arm consisted of 7292 individuals who were eligible to participate, of whom 7,068 received all three medications. The separate MDA arm consisted of 6219 eligible individuals of whom 6,211 received ivermectin and albendazole and 4,611 received azithromycin two weeks later. Overall, adverse events were reported by 197 (1.2%) of individuals. The most commonly reported adverse events included headache, gastrointestinal disturbance and dizziness. There were no serious adverse events in either arm. The results from the nested qualitative study showed that while there were some misgivings amongst community beneficiaries surrounding pill burden and refusals, the majority of participants appreciated the time and effort saved via the co-administered MDA strategy and preferred it to the standard, stand-alone MDAs.

Collaborating Institutions

Further details given in Appendix 1:

Federal Ministry of Health NTD case team of Ethiopia

Armauer Hansen Research Institute (AHRI)

International Trachoma Initiative

World Health Organization

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This study has largely been driven by the dedication of the Ethiopian FMOH and the Oromia Regional Health Bureau to create the strongest national NTD program possible. Dr. Endamalaw, a co-principal investigator for this study from AHRI, has drawn from his many years of experience implementing clinical trials to help create a workable operational framework within the Ethiopian landscape. Thanks to Oumer Shafi, Nebiyu Negussu, Biruck Kebede, Teshome Gebre and so many more for helping me to navigate challenges around Ethiopia IRB approval, security, drug procurement… the list goes on and on. Most importantly, I'd like to extend our gratitude to the health workers and communities in Kofele woreda for not only participating in the study but doing so with an open and welcoming collaborative spirit.

My sincere thanks to my PhD supervisors: Professor David Mabey, Dr. Michael Marks, and Dr. Anthony Solomon. I can't thank you enough for your guidance, steadfast encouragement, and patience through the years. I am also grateful to those on my uprgrading advisor panel: Drs. Shunmay Yeung, David McCleod and Melissa Parker. Thank you to my incredibly supportive employer, RTI International, for allowing me to purse this PhD part time while working full time and for providing generous tuition support.

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Abbreviations/Acronyms

ALB Albendazole
APOC African Programme for Onchocerciasis Control
CNTD Centre for Neglected Tropical Diseases, Liverpool School of Tropical Medicine
CY Calendar Year
DFID Department for International Development (U.K.)
DSA Disease-Specific Assessment
EOEEAC Ethiopia Onchocerciasis Elimination Expert Advisory Committee EPHI Ethiopian Public Health Institute
F and E Facial Cleanliness and Environmental Improvement (part of the SAFE strategy) FMOH Federal Ministry of Health
FPSU Filariasis Programmes Support Unit, Liverpool School of Tropical Medicine (formerly known as CNTD)
GTMP Global Trachoma Mapping Project
HDA Health Development Army
HEW Health Extension Worker
ICT Immunochromatographic Test
IEC Information, Education and Communication
ITI International Trachoma Initiative
IVM Ivermectin
LF Lymphatic Filariasis
LFTW Light For The World
M&E Monitoring and Evaluation
MDA Mass Drug Administration
MEB Mebendazole
MMDP Morbidity Management and Disability Prevention Program
MOH Ministry of Health
MOU Memorandum of Understanding
NGO Nongovernmental Organization
NTD Neglected Tropical Disease
OEPA Onchocerciasis Elimination Program for the Americas
OV Onchocerciasis
PCR Polymerase Chain Reaction
PC Preventive Chemotherapy
PHCU Primary Health Care Unit
PZQ Praziquantel
REMO Rapid Epidemiological Mapping of Onchocerciasis
RHB Regional Health Bureau
RTI RTI International
SAC School-Aged Children
SAE Serious Adverse Events
SAFE Surgery-Antibiotics-Facial cleanliness-Environmental improvements SCH Schistosomiasis
SCI Schistosomiasis Control Initiative
SNNPR Southern Nations, Nationalities, and People's Region
STH Soil-Transmitted Helminths
TAS Transmission Assessment Survey
TF Trachomatous Inflammation–Follicular
TIPAC Tool for Integrated Planning and CostingTOT Training of Trainers
TT Trachomatous Trichiasis

UIG Ultimate Intervention Goal
USAID U.S. Agency for International Development WASH Water, Sanitation, and Hygiene WHO World Health Organization
ZTH Zithromax®

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STUDY PROTOCOL SUMMARY

Title	**Safety of the co-administration of azithromycin, albendazole and ivermectin versus standard treatment regimens during mass drug administration (MDA) in Ethiopia: a cluster randomized trial**
Objective	To establish the safety profile and assess the community acceptance of a three-agent MDA combining albendazole (Alb), azithromycin, and ivermectin (Ivm) in comparison to the standard MDA regimen which separates the administration of azithromycin from the co-administered ivermectin and albendazole by a period of two weeks.
Hypothesis	The study hypothesized that administration of appropriate doses of all three drugs during one distribution event would be non-inferior, in terms of the rate of SAE/AE occurrence, in comparison to the standard MDA regimen and that co-administration would be acceptable to the community.
Design	A cluster-randomized non-inferiority trial that assessed the safety and local acceptance of combined MDA with albendazole, azithromycin, and ivermectin in one district in Oromia region, Ethiopia. Within this district, a study group of 8,000 people received the triple drug co-administration. A control group of 8,000 people within the same district received the standard MDA treatment beginning with Ivm/Alb followed two weeks later with azithromycin. The study randomly sorted sub district communities *(gares)* into the trial arm and the control arm. The study compares the "baseline" of adverse events (AEs) and serious adverse events (SAEs) between the two arms to determine if the triple drug therapy was not inferior to the standard treatment.
Outcomes	The primary outcome: The safety, as can be measured by incidence of AEs/SAEs, following the co-administered MDA in comparison to a control group that received the standard MDA regimen. Secondary Outcomes: • Understanding the perceptions of the beneficiaries receiving the co-administration of azithromycin, ivermectin, and albendazole especially surrounding pill burden and the change in MDA distribution schedule.

	• Understanding the perceptions of the co-administration strategy by the local health workforce as a means of PC-NTD drug delivery.
Field Study Duration	6 months
Interventions	All residents of the selected communities were invited to participate in the co-administered drug treatment strategy. Consenting/assenting residents of the communities were screened as per the inclusion and exclusion criteria. Dosage and treatment age groups followed WHO protocols for lymphatic filariasis, onchocerciasis, STH, and trachoma. Study enrolment continued until the sample size was attained.
Number of subjects	A total of 16,000 people: 8,000 people in the trial arm and 8,000 in the study arm.
Population	All individuals living in the selected communities that agreed to participate. See below for more information on exclusion criteria.

Thesis outline

The thesis consists of a mixture of explanatory material, data chapters based on published and submitted manuscripts and relevant linking material. Chapters highlighted in italics consist of papers that have been published or submitted for publication. The other chapters are linking material prepared for this thesis.

Chapter 1 provides an overview of the components of the PhD project and the scientific rationale for the study.

Chapter 2 addresses the first objective of my PhD and presents a systematic review of pre-existing data on the safety of co-administration of MDA with ivermectin, albendazole and azithromycin

Chapter 3 addresses the second objective of my PhD and presents results of a trial I ran on the safety of co-administration of MDA with ivermectin, albendazole and azithromycin

Chapter 4 addresses the third objective of my PhD and presents results of a nested study on the acceptability to healthcare works and recipients of co-administration of MDA with ivermectin, albendazole and azithromycin

Chapter 5 provides an overall summary of the PhD in relation to my objectives and an overview of future research questions raised by the PhD.

Chapter 1: Introduction

1.1 Disease Profile of Lymphatic Filariasis (LF), Onchocerciasis (OV), Soil Transmitted Helminths (STH) and Trachoma in Ethiopia[1]

1.2. Lymphatic Filariasis (LF): General Information

Lymphatic filariasis is a vector borne disease caused by three different nematodes: *Brugia malayi, Brugia tamari and Wuchereria bancrofti*, of which *Wuchereria bancrofti* is the most common (90% of infections). Though LF is usually not fatal, the morbidity manifested by the disease makes it the second-leading parasitic cause of disability in the world.[2] More than 15 million people globally are affected by lymphedema caused by LF, which mostly commonly manifests as swelling of the legs, but it can also occur in the arms, breasts and genitals. In addition to lymphedema, more than 25 million males suffer from uro-genital swelling caused by hydrocele.[3] Acute adenolymphangitis (ADL), known to cause painful, episodic febrile onsets, is also common and is caused by bacterial infections related to the lymphedema.[4]

Lymphatic filariasis occurs when infective larva (microfilaria in the L3 stage), spread by *Anopheles, Culex, and Aedes* mosquito vectors, enter into the human lymphatic system and develop into adults. The adults will most commonly take residence in the lymphatic nodes blocking the lymphatic drainage system, thereby causing a pooling of lymph which can cause extensive damage and the manifestations of morbidity. Female adult worms produce offspring which migrate to the blood and lymph channels with nocturnal periodicity for the optimal opportunity of infecting a new mosquito vector. To treat endemic communities, the WHO recommends five rounds of mass drug administration before conducting an impact assessment. A number of drug regimens can be used to treat LF consisting of combinations of diethylcarbamazine, ivermectin and albendazole. One of the most commonly administered combinations is ivermectin and albendazole.

1.2.1 Lymphatic Filariasis in Ethiopia

Nationwide baseline mapping was conducted between 2010 to 2014. This exercise found 75 woredas (76 now due to redistricting) were endemic for LF, and of these 45 woredas were co-endemic with OV. Subsequently, the MOH conducted additional remapping of two sites per woreda in 10 woredas that neighbored woredas that were highly endemic for LF (one in Amhara; three in Southern Nations, Nationalities, and People's Region [SNNPR]; five in Oromia; and one in Beneshangul-Gumuz) but had been thought to be ineligible for MDA based on the original 2010–2014 exercise. This additional mapping showed that nine of the 10 woredas (three in SNNPR, five in Oromia, and one in Beneshangul-Gumuz) would in fact require MDA, giving a total number of LF-endemic woredas nationally of 85. Additional mappings is currently planned in the Bambasi and Kumruk woredas of Assosa Zone. As of 2023 an estimated 6.5 million people in Ethiopia are believed to be at risk for LF nationwide and to require MDA. A further 1.7 million people, in 21 woredas, are now considered to no longer be at risk for LF as these woreda have met the criteria to stop MDA.

The Third National NTD Master Plan (2021–2025) sets a target for LF elimination by 2027 which is broadly aligned with the World Health Organization (WHO) Global LF Elimination Strategy, the MOH is. However, national progress trackers currently projects 2029 as a more realistic timeline for elimination. The Ethiopian national program uses an MDA strategy combining IVM and ALB to treat entire at-risk populations. In the 45 LF-endemic woredas that are co-endemic with OV, ALB is added to the existing IVM MDA. In areas targeted for LF MDA, school-age children do not

receive an additional separate MDA for STH unless the woreda has a prevalence >50%, and treatment twice a year is required. *Loa loa* is not endemic in Ethiopia and therefore does not represent a barrier to the use of IVM.

To address LF morbidity, the MOH National NTD Master Plan aims to determine the number of people with hydrocele and lymphedema in endemic woredas by 2025 by patient estimates. To support morbidity management the aim is for all those living within ever endemic woredas to have access to hydrocele surgery within their zonal hospitals, and those in need of lymphedema care to have access to that care within 10 kilometers of their home. As of July 2021, LF patient estimates have been completed in 56 woredas (66%),. The MOH estimates that access to hydrocele surgery is currently available in 40 (47 %) endemic woredas, and lymphedema management is available in 49 (53 %) endemic woredas. The Accelerating the Sustainable Control and Elimination of NTDs (ASCEND East) program initially planned to support generating patient estimates in an additional 21 woredas and to support the expansion of morbidity management in a further 45 woredas. However, because of the early closure of the ASCEND program this has not been possible. Based on current progress it is hoped that Ethiopia is on track to validate elimination of LF by 2029 but gaps in data, and in scale up of morbidity management remain.

1.3. Onchocerciasis (OV): General Information

Onchocerciasis is the second leading infectious cause of blindness, behind only trachoma. More than 120 million people worldwide are at risk for OV, more than 96% of whom reside in sub-Saharan Africa.[9] In addition to causing blindness, OV can cause painful skin disfiguration as well as musculoskeletal pain. Onchocerciasis is caused by the parasite *Onchocerca volvulus* which is spread by the *Simulium* fly vector. The flies breed along fast flowing streams and rivers, hence the common name “river blindness”. *Onchocerca volvulus* enters a human host while a female infected *Simulium* fly takes its blood meal. The OV larvae develop into adults in the subcutaneous tissue where they will remain for 10-12 years in pronounced nodules. A female worm can produce 1300-1900 microfilaria a day for 9 years. It is these microfilaria which navigate through the dermal layers and to the eye to cause OV-related morbidity. To address OV in an infected population, the WHO recommends annual or biannual treatment with ivermectin (further detailed below).[8-11]

1.3.1 Onchocerciasis in Ethiopia

In 2013, Ethiopia declared in the country’s National NTD Master Plan that they were shifting their strategy from an initial aim of OV control to one of elimination. In 2014, national and international experts formed the Ethiopia Onchocerciasis Elimination Expert Advisory Committee (EOEEAC) which was designed to help guide the MOH in implementing this strategic shift. In October 2014, the Committee held its inaugural meeting with a focus on creating an updated national elimination guideline. This document was informed on the WHO guidelines and draft guidelines generated by the WHO NTD Strategic and Technical Advisory Group. This new set of guidelines proposed several strategies to achieve elimination, including biannual MDA and targeted vector control. Following this the Committee also supported the creation of *Standard Field Operating Procedures for Mapping, Entomological Surveillance, Impact Assessment for Onchocerciasis Elimination in Ethiopia*.

Mapping for OV began in 1997 and has continued since then in line with the MOH’s efforts to conduct hypo-endemic delineation in accordance with the shift to as elimination focused strategy. At this time, 243 woredas are known to be OV endemic.

This number has actually risen reflecting both redistricting and the conduct of additional eastward mapping. In addition, 12 refugee camps exist within endemic woredas that receive MDA for OV. Currently, 221 districts receive semi-annual MDA; 6 districts are in post-treatment surveillance; and 16 districts have not yet started MDA.(1)

1.3. Soil Transmitted Helminths (STH)- General Information

The WHO estimates that more than 2 billion people in the world are infected with the classification of intestinal worms that make soil-transmitted helminths.[12] Roundworm (*Ascaris lumbricoides*), whipworm (*Trichuris trichiura*) and hookworm (*Necator americanus* and *Ancylostoma duodenale)* comprise the three STH nematodes and are spread through human feces either through hand/mouth contact with infected soil (roundworm and whipworm) or through the soles of bare feet (hookworm). Global morbidity caused by STH infection has been estimated at 5.18 million DALYs.[13]

1.3.1 STH in Ethiopia

Though not formally stated as a goal in the WHO NTD roadmap, Ethiopia has taken initial steps for both STH and Schistosomiasis (the latter falling outside the scope of my PhD) towards elimination as a public health problem by 2025. It is anticipated that this goal will require repeated treatment of at least 75% of school aged children (defined as 5-14 years old both enrolled and non-enrolled in school). The National STH/SCH Action Plan long-term goals associated with this include:

- *Eliminate STH-related morbidity in children by 2020*
- *Reduce the proportion of individuals harbouring heavy infection with STH by 60%*
- *Ensure that treatment coverage is expanded to pre-school children in the future*

STH is widely distributed throughout the country, and more than 62 million people are estimated to be living in STH-endemic woredas. The FMOH plans to treat hypo-endemic woredas for SCH every two years rather than every three years because of the logistical constraints involved in successfully implementing a program with such a long interval between treatments. The current plan is for the FMOH to distribute mebendazole alongside all SCH MDA regardless of whether the woreda in question is above the 20% threshold for STH, in order to maximize logistical and cost efficiency of SCH treatments. Any woreda above 20% STH prevalence is currently targeted for school-based MDA (ages 5- 14) and any community above 50% STH prevalence with twice-a-year, community-wide Alb MDA in line with WHO guidelines.(1)

1.4. Trachoma- General Information

Trachoma is caused by *Chlamydia trachomatis* and is spread by direct personal contact, fomites, and by flies (specifically *Musca sorbens*). It is the number one infectious cause of blindness in the world.[14] After many years of repeated infections, scars in the upper eyelid can cause the eyelashes to invert and press against the eye, resulting in *trachomatous trichiasis*. This stage of trachoma can lead to eventual corneal opacity through scarring of the cornea.[15] The WHO has set

the ultimate intervention goal of reducing the prevalence of follicular trachoma (TF) throughout the world to lower than 5% in children aged 1-9 years. To accomplish this, varying rounds of mass drug administration with azithromycin, dependent on the prevalence of TF in children 1-9, followed by an impact assessment are recommended: 5-9.9% prevalence requires one year of MDA, 10-29.9% prevalence requires 3 years of MDA, 30%-49.9 requires 5 rounds of MDA and areas with greater than or equal to 50% prevalence require *at least* 7 rounds of MDA.

1.4.1 Trachoma in Ethiopia

The Global Trachoma Mapping Project (GTMP) completed nationwide mapping in 2014 and this identified 700 woredas as endemic with >5% trachomatous inflammation–follicular [TF] in children aged 1-9. So far 259 (37%) of these woredas have stopped MDA after achieving a TF prevalence of <5% among children aged 1–9 years.

Globally Ethiopia is home to 49.4% of the 136 million people at risk for active trachoma. Mapping has shown a very high prevalence across much of the country—40% of woredas in Ethiopia have a baseline prevalence of TF >30% (for comparison, the percent of districts with TF >30% at baseline is 3% in Nigeria, 24% in Tanzania, and 22% in Uganda). Moreover, a higher proportion of trachoma impact survey/trachoma surveillance survey (TIS/TSS) results are above the WHO target threshold in Ethiopia than in other countries.(1)

2. Modes of Action of the study drugs and their administered dosage

2.1. Azithromycin

After ingestion, azithromycin spreads quickly and widely through the body. While albendazole and ivermectin are primarily absorbed by the plasma in the human body, azithromycin is found in much higher levels (as much as 50 times) in the tissue. It is also absorbed by immune cells such as phagocytes which help to transport it to sources of infection. Azithromycin is intracellularly active which help explains its efficacy against intracellular bacteria such as *C. trachomatis*.[16]

For mass drug administration in Ethiopia, Zithromax (Azithromycin donated by Pfizer) is given as a single observed dose, determined by a dose pole as per WHO recommendation. Everyone 5 years and older receives their dose in 250 mg tablets while children between 6 months and 5 years old will receive syrup (200 mg per 5 ml). Individuals aged 6 months and under as well as pregnant women are offered topical tetracycline. [17]

2.2. Ivermectin

Ivermectin's effect on nematodes such as *Onchocerca volvulus* is still not fully understood. The class of broad-spectrum, anti-parasitic drugs (avermectins) that ivermectin is a part of are attracted to the chloride ion channels that are found in the muscle and nerve cells of nematodes and other invertebrates. It is believed that once ivermectin moves into these channels, it essentially blocks the ability of the cells to function, thereby causing paralysis of the nematode and eventual death.(2) However, in culture, ivermectin does not have a direct effect on microfilaria, suggesting that the human immune system may also play a role. In other studies, ivermectin has been shown to reduce the ability of nematode cells

to produce a particular protein which may usually help disguise it from the host immune system.[18] Interestingly, ivermectin does not threaten the nervous system of mammals because of its inability to cross the fully-developed blood-brain barrier and enter the central nervous system, which is why the drug is safe for humans.

In terms of controlling or eliminating OV infection in a population, many years of MDA are necessary because ivermectin is useful against the larval forms *Onchocerca volvulus as a* microfilaricide, but has little to no effect against the adult forms, which live for years within nodes of the skin where the drug cannot reach. The half-life of ivermectin once metabolized is approximately 12-36 hours and is excreted in the faeces for up to 12 days.[19]

For mass drug administration in Ethiopia, those who are 5 years and older will be given a single observed dose in tablet form (3 mg each), the size of which is determined by dose pole as per WHO recommendation. Children under five are currently excluded from treatment due to theoretical concerns that they need a "fully developed" blood/brain barrier to avoid drug toxicity.[20]

2.3. Albendazole

Albendazole is delivered as a single-dose, 400 mg tablet. Albendazole is metabolized primarily into albendazole sulfoxide which has a half-life within the body of eight and a half hours. Albendazole blocks the ability of the cytoskeletons in helminthic cells by attacking the microtubules and impairing the cell's ability to absorb glucose.[21] Albendazole works against both the adult and larval stages of helminths. In terms of the focal diseases of this study, albendazole is effective against LF when combined with IVM and the three soil transmitted helminths: roundworm (*Ascaris lumbricoides*), the whipworm (*Trichuris trichiura*) and hookworm (*Necator americanus* and *Ancylostoma duodenale)*. For mass drug administration in Ethiopia, Albendazole is prescribed as a single oral dose of 400mg.

3. Programmatic Advantages of Co-Administration of Azithromycin, Ivermectin, and Albendazole in Ethiopia:

The WHO roadmap identifies integration as a key pillar of the 2021-2030 roadmap. Co-administration within MDA programmes is anticipated to have the following benefits. The recent NTD road map 2021–2030 has set global targets and milestones to prevent, control, eliminate and eradicate multiple NTDs by 2030. The platform from which we will achieve these targets is built on three pillars: (i) accelerating programmatic action, (ii) intensifying cross-cutting approaches, and (iii) changing operating models and culture to facilitate country ownership. (2) To solidify the first and second pillars, national programmes are exploring ways to integrate different aspects of many current disease-specific interventions. This should help to achieve disease-specific 2030 targets, while easing the strain on country health systems and adapting to shifting availability of financial resources. One strategy is to explore co-administration of a wider range of medicines in combined MDA regimens. Various combinations of medicines have been previously used in integrated MDA in multiple contexts, providing proof-of-concept and some experience of the viability of this strategy.(3)(4) Within

Ethiopia, the different permutations of trachoma, LF, STH, and OV demonstrate that a large number of woredas could benefit from the co-administration of ALB, Azithromycin, and IVM (Table 1)

Table 1: Co-Endemic Woredas which could be addressed through various permutations of Azithromycin, ALB, and IVM

TR, LF, OV				TR, LF, STH				TR, OV, STH			
Population At-risk	# Districts Endemic	# Districts Treating All Diseases	# Districts Not Treating For At Least 1 Disease	Population At-risk	# Districts Endemic	# Districts Treating All Diseases	# Districts Not Treating For At Least 1 Disease	Population At-risk	# Districts Endemic	# Districts Treating All Diseases	# Districts Not Treating For At Least 1 Disease
266,349	2	1	1	2,416,506	17	1	16	8,880,190	69	14	55
TR, LF				**TR, STH**				**TR, OV**			
Population At-risk for Trachoma	# Districts Endemic	# Districts Treating All Diseases	# Districts Not Treating For At Least 1 Disease	Population At-risk for Trachoma	# Districts Endemic	# Districts Treating All Diseases	# Districts Not Treating For At Least 1 Disease	Population At-risk for Trachoma	# Districts Endemic	# Districts Treating All Diseases	# Districts Not Treating For At Least 1 Disease
738,423	5	0	5	48,599,449	303	34	269	60,742	6	1	5

4. PhD Objectives

My PhD has three main objectives:

1.) Review the existing data on the safety of co-administration of ivermectin, albendazole and azithromycin
2.) Conduct a trial in Ethiopia to evaluate the safety of programmatic co-administration of ivermectin, albendazole and azithromycin
3.) Evaluate the acceptability of co-administration to both healthcare workers and community stakeholders

Objective 1: Review the existing data on the safety of co-administration of ivermectin, albendazole and azithromycin

A brief overview is given in section 5 of the introduction. The main study methods and findings are presented in the linked research paper in Chapter 2.

Objective 2: Conduct a trial in Ethiopia to evaluate the safety of programmatic co-administration of ivermectin, albendazole and azithromycin

A detailed overview of the study methodology is given in section 6 of the introduction. The results of the trial are presented in the linked research paper in Chapter 3.

Objective 3: Evaluate the acceptability of co-administration to both healthcare workers and community stakeholders

This objective was addressed by two sub-studies nested within the trial conducted for Objective 2. A brief overview is given in section 7 of the introduction. The main study methods and findings of these sub-studies are presented in the linked research paper in Chapter 4.

5. Feasibility of Triple Drug Co-Administration Based on Existing Data (Objective 1)

Below is a brief summary of some key findings from a literature review completed in order to ascertain what information and experiences surrounding co-administration already existed. This step helped to hone the initial parameters of the RCT as well as provide the evidence underpinning the ethics submissions at LSHTM and in Ethiopia. The full literature review is presented as Chapter 2: **"Pharmacodynamics, feasibility and safety of co-administering azithromycin, albendazole, and ivermectin during mass drug administration: a review".**

5.1. Pharmacokinetic Data on Combined Drug Interaction of azithromycin, ivermectin and albendazole

Pharmacokinetic studies have demonstrated that there is little to no drug-to-drug interaction between ivermectin and albendazole[22]. Mass co-administration of both drugs to treat LF has also occurred with no reported serious adverse events related to drug to drug interactions among large populations for many years. The question lies in the safety of adding azithromycin to the albendazole/ivermectin combination. In a randomized, three-way crossover pharmacokinetic study on the interaction between azithromycin, ivermectin and albendazole, 18 volunteers were administered 500 mg of azithromycin, 400 mg of albendazole, and a dose proportional to body weight of ivermectin concurrently. The results of the study found the interactions between albendazole and azithromycin to be small enough to be of little clinical importance. The total drug exposure over time for ivermectin increased by 31% among the volunteers.[23] This trend of higher peak blood levels of ivermectin when co-administered with azithromycin has been demonstrated within pharmacokinetic models to be well within safety ranges. [24]The study author goes on to say in conclusion that the population pharmacokinetic model analyses "support further study of co-administration of azithromycin with the widely used agents ivermectin and albendazole, under field conditions".[23]

5.2. Past studies involving permutations of azithromycin, IVM and ALB combined

Mali: This was a study in four randomly assigned villages (N=3, 011) endemic for trachoma and LF. Two villages were randomized for "co-administering ivermectin, albendazole, and azithromycin" and two villages were given the standard treatment of one round of OV/LF MDA followed one week later by a round of azithromycin MDA. In the study, the overall reported rates of any adverse event were similar: 18.7% (281/1501) in the co-administration arm and 15.8% (239/1510) in the standard treatment arm. No serious adverse event was reported. However, the study was too small to justify a definitive recommendation.[25]

Solomon Islands: a field trial of co-administration of azithromycin and ivermectin mass drug administration for scabies and trachoma (N=26,188) revealed no safety issues with combining azithromycin and ivermectin[26]. Follow up was completed for 21,931 participants (83.7%) and identified no serious adverse events. Adverse events were noted in 2.6% of participants across the entire study population; the most commonly reported adverse events were dizziness, abdominal pain and diarrhoea. This study did not, however, include the addition of albendazole.

Papua New Guinea: An open-label, cluster-randomized trial conducted in two study sites, Namatanai and Lihir Island, Papua New Guinea. Clusters were randomised to receive either MDA of ivermectin, diethylcarbamazine and albendazole (IDA) followed by a single dose of azithromycin administered one week later, or MDA of all four drugs together. Overall, 7,281 people received the four-drug regimen and no serious adverse events occurred.(21)

Colombia: At the programmatic level, this work involved reaching remote trachoma and STH co-endemic populations. More than 305,005 people received albendazole

and azithromycin together for three separate annual cycles (2012-14). The reported adverse events were headaches, dizziness and diarrhoea in 0.16% of those surveyed (7 out of 4,438 people). No serious adverse events were documented[27]. However, the findings are not statistically powered.

6. A trial in Ethiopia to evaluate the safety of programmatic co-administration of ivermectin, albendazole and azithromycin (Objective 2)

In this section I outline the overall methodology for the cluster-RCT which is the central component of my PhD. Results of this trial are presented in chapter 03: "*Safety of integrated mass drug administration of azithromycin, albendazole and ivermectin versus standard treatment regimens: a cluster randomised trial in Ethiopia"*

The aim of the study is to establish the safety profile, assess the community acceptance, and weigh the economic advantages of a three-agent MDA combining azithromycin, albendazole (Alb), and ivermectin (Ivm) in comparison to the standard MDA regimen which separates the administration of azithromycin from the dually administered ivermectin and albendazole by a period of two weeks.

6.1. Intended Outcomes

6.1.1. Primary Outcome:

- The safety, as can be measured by incidence of AEs/SAEs over one month, following the co-administered MDA in comparison to a control group receiving the standard MDA regimen.

6.1.2. Secondary Outcome:

- Understanding the perceptions of the beneficiaries receiving the co-administration of azithromycin, ivermectin, and albendazole especially surrounding pill burden and the change in MDA distribution schedule.

- Understanding the perceptions of the co-administration strategy by the local health workforce as a means of PC-NTD drug delivery.

These secondary objective are described in section 7.

6.2 Description of the Study Area

6.2.1. General information

Kofele woreda is divided into 18 kebeles. Each kebele is composed of a varying number of communities known as gares. Gares are defined by the government as a population of at least 350 individuals, but there is considerable variation in actual population. Within Kofele, we arbitrarily selected two kebeles, Gurmicho and Alkaso, to participate in the study. Prior to study commencement these kebeles had received four rounds of azithromycin MDA and five rounds of ivermectin and albendazole MDA. Combined, Gurmicho and Alkaso contained 58 gares.

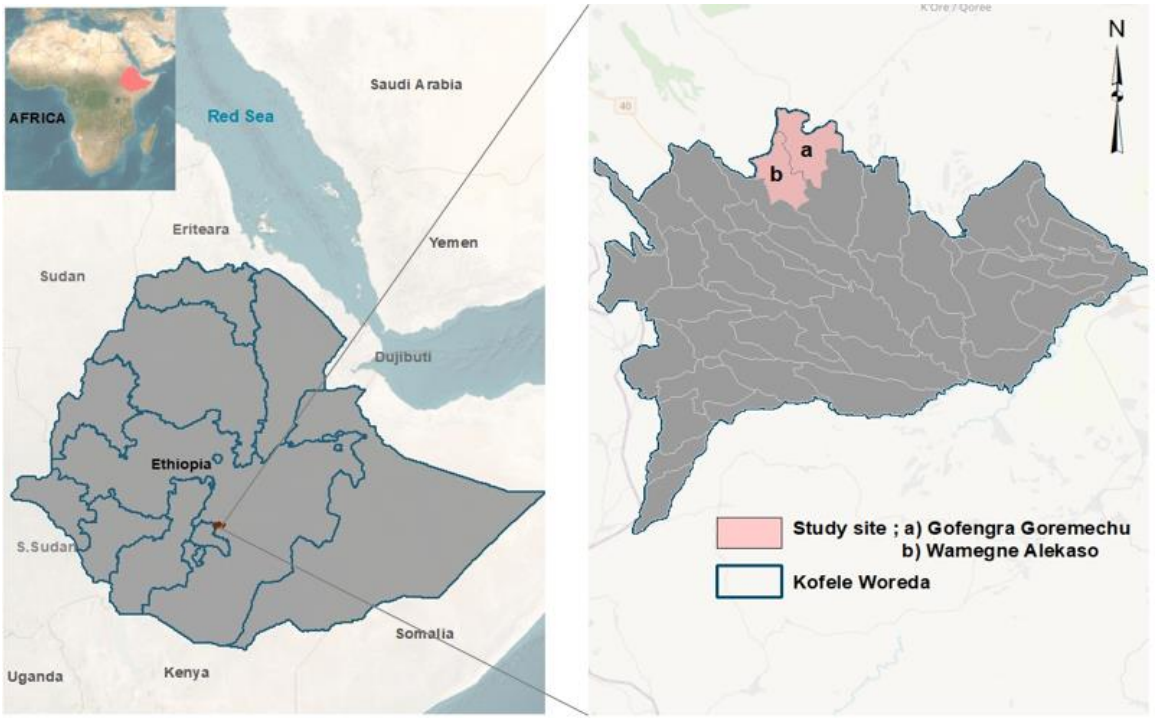
6.2.2. NTD prevalence and treatment history

The study team reviewed a number of woredas (districts) which fit the co-endemicity profile specifications of the study but eventually selected Kofele woreda both for its absence of conflict as well as the support of zonal and woreda leadership. Kofele is one

of 17 woredas in the West Arsi Zone in Oromia regional state (Figure 1). Based on the most recent data available prior to the trial, Kofele had a prevalence (estimated in 2017) of TF in children aged 1–9 years of 27.3% and a prevalence (estimated in 2020) of 1.5% for LF antigen in children aged 5–14 years. Prior to the trial, the woreda had received annual MDA for LF and trachoma delivered at separate timepoints.

In each community, individuals were eligible to receive treatment if they had been residing in the community for at least three months and were eligible to receive all three agents according to standard MDA criteria. Individuals were excluded from the trial if they were ineligible for any of the three study drugs, were unable to swallow tablets or declined to participate. Children aged under five years and pregnant or breastfeeding women were therefore considered ineligible as they could not receive ivermectin.

Figure 1: Map of the Study Site



6.3 Participant Selection Criteria

Standard FMoH criteria for individual agent MDA were used to determine eligibility of individuals to receive each drug. Individuals eligible to receive all three agents, 'co-administration', will be enrolled in the study.

6.3.1. Inclusion Criteria

- Must have been residing in the community for at least three months;
- Eligible to receive all three agents according to standard MDA criteria;[28,29] 6.3. 2.

Exclusion Criteria

- Not eligible to receive one or more drugs according to standard MDA criteria;
- Less than 5 years of age (not eligible for ivermectin)**
- Pregnant women (azithromycin only, not eligible for albendazole and ivermectin)
- Lactating women (Only administered azithromycin and albendazole, not eligible for ivermectin);
- History of allergies to the drugs being studied (azithromycin, ivermectin, albendazole)
- Those who refused to be part of the study (addressed via the normal MDA schedule if they preferred with initial treatment with IVM/ALB and azithromycin treatment two weeks later)
- Residents who cannot swallow tablets;

***Note that patients that are not eligible for IVM, received azithromycin and albendazole. Patients that received azithromycin and albendazole were followed up through the same procedure as the triple drug therapy to try to track any AEs attributed to the two-drug combination.*

6.4 Statistical Methods

Clinical Randomized Controlled trials often try to demonstrate that one form of treatment is better than an existing treatment, typically known as a superiority trial. However, within this co- administration study, the goal was not to demonstrate the superiority of triple-drug administration over standard MDA in terms of efficacy. Rather, the study demonstrated whether administering all three drugs together is no worse, within a specified margin, than giving all three drugs via the standard distribution format.(3) The possible benefit of the co-administration trial lay within improved convenience and cost without any increase in negative outcomes, not necessarily in improved treatment results. For that reason, the study used a non-inferiority trial model.

Within our standard arm, the study deduced the average adverse event rate for azithromycin administered alone using information from previous trials and assumed an average adverse event rate for azithromycin, ivermectin and albendazole administered together. For azithromycin, there was a wide-range of reported adverse event rates.(4)(5) A previous coadministration trial in Mali assumed an adverse event rate of 8%.(6) Meanwhile, Pfizer labelling reports the following: "Side effects that occurred in patients on the single one-gram dosing regimen of Zithromax with a frequency of 1% or greater included diarrhea/loose stools (7%), nausea (5%), abdominal pain (5%), vomiting (2%),

dyspepsia (1%) and vaginitis (1%)."(7) Therefore, for the purposes of this study, we set a conservative adverse event percentage at 7% for azithromycin distribution. In terms of the adverse even rate during co-administration of all three drugs, adverse events related to IVM and ALB distribution are largely due to the death of microfilariae(8) , particularly after the first round of MDA in a community. Given that this community has received several years of treatment with both drugs, we assumed an acceptable increase in adverse events during co-administration would be 1.5% (Delta), or put another way it would be acceptable for 8.5% of our intervention arm to experience an AE. We designed the study to have a power of 90% using a two-sided 95% confidence interval for the difference between rates. Given that gares were randomly selected from within the same woreda, have all had the same number of years of treatment with each drug, and share the same cultural and environmental factors, we assumed a low variability between each cluster. In case there were unforeseen differences between the clusters, we included a variance between 6-8%. Conservatively assuming that each gare had a population of 190 individuals, the study required at least 36 gares in each study arm to reach 13,600. To take non-compliance, etc. into account, the study randomize the 53 gares into each study arm to reach 8,000 participants in each arm from the list of gares in Kofele woreda into the control and study arms until each arm has 8,000 participants (to account for non-compliance, loss to follow-up, etc.). Gares were chosen via the RANDNUM function in excel. The randomization itself was conducted via public randomization ceremonies.

Table 2: Assumption Summary

Adverse event prevalence	7% on average
Acceptable adverse event percentage during co-administration:	8.5%
Delta	1.5%
Variance	Adverse event prevalence between clusters will be 6-8%
Power	90%
CI	95%
Minimal Number of Gares Required for each arm	36
Population per cluster	190 individuals per cluster (gare) on average
Total Population of Study	13,600 (Rounded to 16,000 for refusals/loss to follow-up)

6.5. Awareness Creation, Community Mobilization Mechanism, and Training

The roll-out began with a joint training of trainers (TOT) in Addis Ababa led by the FMOH, AHRI and LSHTM. Each study team included medical and public health professionals experienced in clinical trials and NTD MDAs. The TOT was an opportunity to review the training modules, assess the monitoring plan, and establish agreed upon courses of action for predictable eventualities.

Before the study began, the FMOH and appropriate RHBs worked with the zonal and woreda-level offices where the study took place to ensure full understanding and compliance with the study parameters. It is important to note that the communities in Kofele woreda were excluded from the usual MDA training cascade which began at the regional level and then descended down the zonal, woreda-level, and kebele-level tiers where Health Extension Worker (HEW) and Health Development Army (HDA) were the final training recipients. In place of this cascade, the FMOH, AHRI and LSHTM team provided protocol specific training to the woreda health officers and the health extension workers. The training modules included an overview of the national NTD training manual followed by an in-depth explanation of the study protocol and how it differed from the common MDA procedure. Training modules were modified from the usual NTD training to include:

- Given the possible pill burden of co-administration (up to nine pills for an adult), HEWs were be taught to allow beneficiaries a maximum swallowing regimen (two pills, swallow, two pills, swallow) in order to discourage rushed administration and any possibility of choking. HEWs were taught to encourage patients to take one pill at a time if they prefer.
- The study team trained the HEWs and Woreda Health Officers on the protocol for reporting to the local medical team that were stationed nearby during the study.
- The FMOH and the study team created a mobilization plan with the HEWs relied on the Health Development Army and local leaders to create awareness of the study which in turn helped ensure participation. This enabled the project to get a collective informed consent for the activity by the community.

After getting the collective informed consent of the community, the HEWs updated the MDA register with the population and household information within the community as per the usual pre-MDA registration activities. While going house to house, the HEWs read the study consent form to all members of the household and gain their verbal (or signed if literate) permission to participate in the study. For those participants that refused consent, they were allowed to receive MDA treatment via the usual MDA schedule of IVM/ALB dose followed by azithromycin dose two weeks later.

6.6 Recording of any AE/SAEs

The study defined AEs and SAEs per the national guidelines which were also found in the Serious Adverse Events handbook created by RTI ENVISION and the Task Force for Global Health(9):

"**Adverse event from MDA (AE-F-MDA)** is a medical event that takes place in an MDA program, causes concern in the medical and wider community and is believed to be caused by the drug(s) used. It can be caused by either administration of the drug or by a coincidental event that by chance happened after drug administration. Most AEs-f-MDA (adverse events from MDA) are self-limiting and treatable using simple remedies and are not usually required to be reported to national or international regulatory authorities.

Serious Adverse Event (SAE) is a regulatory term describing any untoward medical occurrence with any of the following characteristics:

- Results in death;
- Requires in-patient hospitalization;
- Results in persistent or significant disability;
- Is life-threatening; or
- Results in a congenital anomaly/birth defect."

The team recorded all adverse events that were reported during follow up. This was conducted systematically and in compliance with national AE/SAE reporting guidelines to avoid any bias related to the wording of the question(s). While the difference between "adverse events" and "serious adverse events" have been described above, there is also a level of severity which the study monitored: The term "severe" is often used to describe the intensity (severity) of a medical event, as in the grading "mild", "moderate", and "severe". (10) Reported adverse events were classified according to their intensity (none, mild, moderate, and severe).

- Mild: easily tolerated, does not interfere with daily activity,
- Moderate: uncomfortable enough to interfere with daily activity,
- Severe: precludes daily activity (Given that a "severe" adverse event includes inability to complete daily activities, it was classified as a possible SAE for the purposes of this study.)

The evolution of older complaints was classified as exacerbated, ongoing, and improved or resolved/none.

6.6.1 Analysis Plan of Reported AEs/SAEs

We coded adverse events per the WHO Adverse Reaction Terminology (WHO-ART) and Medical Dictionary for Regulatory Activities (MedDRA). They were also defined according to level of severity (mild, moderate, severe) as defined above. The study created an independent Data Safety Monitoring Board (DSMB) composed of members of the FMOH as well as national and international medical experts. (See **Appendix 12: Charter of Data and Safety Monitoring Board**) As a safety measure, the study lead had planned to convene an immediate teleconference with the medical doctor participating in the study and the DSMB given the following criteria*:*

• IF the rate of adverse events ranked as mild/moderate by participants is significantly more in the trial group as compared to the control group during the first two "Follow-up Days" (Day 2, Day 4) as well during subsequent review of the data at Day 15, and at the conclusion of the study on Day 31 (to determine if the remainder of the woreda can safely be treated via triple drug therapy).

• IF an SAE occurs, the study lead and the medical doctor will conduct an immediate analysis and convene a call with the DSMB members. The DSMB members will advise the medical doctor in making an initial decision about attribution and whether a formal DSMB meeting is required. (Note: Given that a "severe" adverse event includes inability to complete daily activities, it will be classified as a possible SAE for the purposes of this study.)

• At conclusion of the study on Day 31 (to determine if the remainder of the woreda can safely be treated via triple drug therapy).

The causal relationship of serious adverse events observed with the triple therapy was assessed as: *Unrelated, Unlikely, Likely*. The study utilized information collected by the clinical nurses using the "Conduct an AE Investigation" steps detailed in the Serious Adverse Event Handbook. It is important to note that the study did not follow-up "minor" or "moderate" adverse events up with the full investigative checklist prescribed by the handbook but reserved this for "severe" adverse events and SAEs. The PI, supervisors, and independent monitors met to review these determinations. If the supervisory group questioned the results of the clinical nurses investigations, it planned to perform its own investigation of the report as an addendum to the original report. The study team planned to analyse incidences based on preferred terms and body system levels. "Severe" adverse events and SAEs occurring during exposures would have been analysed based on 3 levels of selection per pre-existence and causality:

- Treatment emergent signs and symptoms (TESS), i.e., all AE during exposure to treatment or that were not pre-existing
- TESS without causality 'unlikely'
- TESS with causality 'likely'

6.7 Co-administration Team Composition

Both the trial and the control arm were allocated 4 distribution teams. Each distribution team was comprised of 8 people. This resulted in 32 people on each arm with both arms together equalling 64 people.

6.7.1 Team breakdown:

2 clinical nurses

2 HEWs (or 1 HEW and 1 health officer)

3 HDA

1 supervisor

TOTAL: 8 members of on each team x 8 teams= 64 total team members

6.7.2 Team Description

2 clinical nurses: Before the drugs were given, the nurses (one for each line) confirmed that the beneficiaries have given consent and that there was a corresponding signature/mark for that consent. The nurses filled out the register questionnaire detailed in the appendix that established if any previous medical conditions exist. Once the MDA portion was complete, the nurses remained at the distribution site for the night in case any of the beneficiaries need to self-report adverse effects. The next morning, the nurses, with the aid of the HDA, conducted house-to-house follow up visits.

2 Health Extension Workers: HEWs (one for each line) were responsible for co-administering the drugs to consenting/assenting beneficiaries. The HEW assigned the dosage according to different dose poles for IVM and azithromycin as well as the single dose of Albendazole. The HEW was responsible for organizing the MDA schedule within the cohort as explained in Figure 1. The HEW was also responsible for providing access for any reported AE/SAEs through passive follow-up should any community members have any complaints throughout the one-month period.

3 HDA: Three members of the Health Development Army (one for each line and one to give line assignments to beneficiaries) had the responsibility of assisting the HEW with community mobilization and crowd control once the co-administered MDA began. These HDA members also acted as guides to help the clinical nurses go house to house during the follow up day. The HDA stayed within each gare as this was their station. They were within the community they were assigned for the rest of the study to provide passive surveillance.

1 supervisor: The study assigned one supervisor from the RHB, zonal office, or woreda health office to each team to ensure that the protocol was followed. The supervisors reported to the study managers who travelled between all the teams and provided general oversight and technical guidance.

6.7.3 External monitoring

The study also invited independent study monitors to ensure that the trials was conducted in an un-biased manner. The study team hoped this would encourage adoption of the triple drug therapy by the WHO assuming non-inferiority was established.

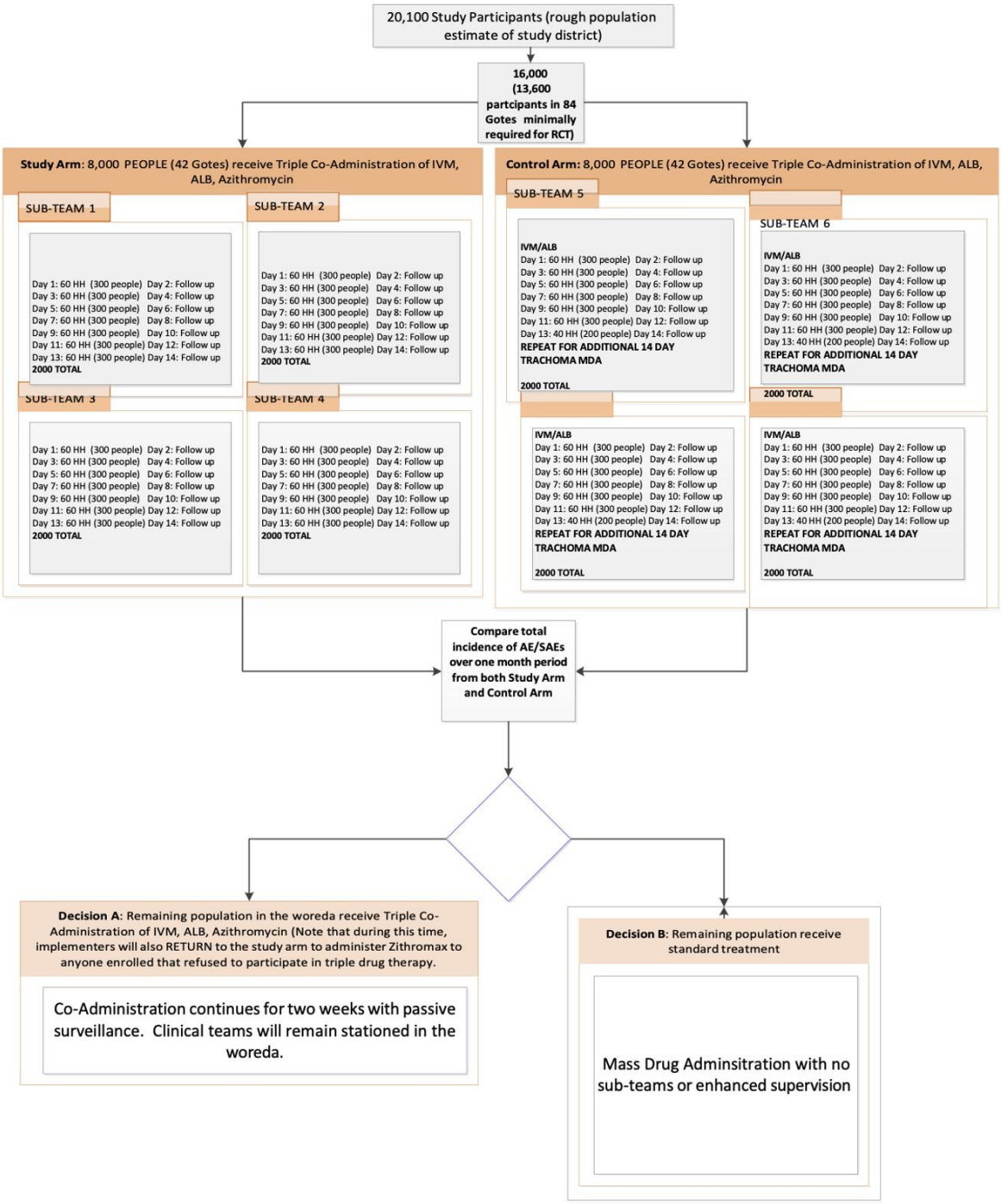
6.8 Co-administration Team Training

The co-administration study placed additional safety measures in addition to the National AE/AE reporting protocol. As mentioned in the training section, all health extension workers and Health development armies within the targeted kebeles were provided with a specially adapted training before the MDA addressing how to conduct the directly observed coadministration and how to administer the study questionnaire. Two clinical nurses for each of the four teams working in a cohort supervised the co-administration and conducted the next-day follow up for all the beneficiaries that received triple drug administration. The study also placed a study physician at the study site for the duration of the 14-day coadministration exercise. The nurses conducted active house-to-house surveillance starting the morning after the study and regularly communicated with the assigned study physician stationed within the kebeles. A nearby referral centre (district/regional hospital) was informed and on stand-by should any reactions occur. The study team had three dedicated four-wheel drive cars to allow supervisors and study physician to travel between the targeted gares and evaluate the work of the teams and for use in case evacuation to the health facility became necessary.

6.9 Co-Administration Schedule

As determined, the study required 13,600 people divided into two cohorts of 6,800 people each. However, the study targeted enough gares for a total population of 16,000. The study team conducted the training and the actual co-administration for a 17-day period (three days for training and 14 days for actual co-administration and surveillance). In total, the study team planned for 45 days to complete.

Figure 2: Planned Randomization and MDA schedule



6.10 Data Collection and Statistical Analysis

Data about individual participants were collected by the study team using structured questionnaires and coded, de-identified labels which were held in strict confidence. All results were presented in a way that did not allow individuals to be identified. No information concerning the study or the data was released to any unauthorized third party. These questionnaires are presented in the appendix of this protocol. The study team relied on electronic data capture and converted these forms for collection on REDCAP.

Table 3: Data Collection Summary for AE reporting

Forms	**Timeline**	**Person responsible for filling out the form**
Informed Consent	Pre-MDA Census days and Distribution Day	HEW/Clinical Nurses
Socio-demographic/health Information	Distribution Day	Clinical Nurses
Study drug registry	Distribution Day	Clinical Nurses
Contra-indication/AEs reporting to the Co-Administration team (HEW and clinical nurse)	Day 2, Day 4, Day 6, Day 8, Day 10, Day 12, Day 14, Day 17+18 follow up or at any time during passive surveillance	Clinical Nurses/HEW
Contra-indication/AEs reporting to the local health post (HEW)	Day 19-30	HEW

Data were entered in STATA. All variables were summarized using descriptive statistics as appropriate. The co-administration safety was characterized as safe or unsafe.

Parameters to be determined were:
- Population of study kebeles: composition by age group and sex.
- Prevalence and incidence of adverse events by age group, sex, and kebele
- Severity of adverse events in each kebele
- Average age of participant experiencing adverse events

The null hypothesis was that the occurrence of adverse events was not significantly higher in the co-administration trial communities in comparison to the standard MDA control communities. The study reported the proportion of individuals in each arm experiencing an AE adjusting for clustering. It also reported the proportion of AEs stratified by age group. Logistic regression was used to assess the association between treatment arm and adverse events after adjusting for covariates (age, gender) and clustering.

6.11 Ethical Clearance

For this study, LSHTM and the FMOH joined together with the Armauer Hansen Research Institute (*AHRI- see Appendix 1 for full description of AHRI*). The study sought and was granted ethical clearance from LSHTM as per the requirements of both the donor (BMGF/ITI) and the PhD program. AHRI then gained ethical clearance via the AHRI ethical review board. Given this study was a randomized controlled trial involving different drug regimens, AHRI and Ministry of Health then jointly sought the highest level of ethical clearance possible within Ethiopia from the National Ethical Clearance Review Committee (NERC). Once ethical clearance was granted from NERC (including three site change amendments due to security challenges which are detailed in the Delays/Challenges section above), the study gained the permission of zonal, woreda and community leaders.

Ethical Protocol Reference numbers:
Clinicaltrials.gov (identifier: NCT03570814).
London School of Hygiene & Tropical Medicine: reference 11985.
AHRI: reference PO33/108
National Research Ethics Review Committee (NRERC) of Ethiopia: reference 3-10/195/2018

Based on low levels of literacy in the study population, permission to use verbal consent was specifically provided by the ethics committees. Study teams read the study consent form to all prospective participants and requested verbal permission to participate in the study. Individuals who declined to participate received treatment according to the usual MDA schedule. The study team established an independent Data Safety Monitoring Board to review any reported severe adverse events (see Appendix 9).

7. Evaluating the acceptability of programmatic co-administration of ivermectin, albendazole and azithromycin (Objective 3)

In this section I outline the overall methodology for nested sub-studies which were conducted alongside the cluster-RCT. More details on the methods and the results of these sub-studies are presented in Chapter 4: *"Perceptions and acceptability of co-administration of albendazole, ivermectin and azithromycin during as mass drug administration, among the health work force and recipient communities, in Ethiopia"*

Sub-Study 1: Better understand the perceptions of the beneficiaries/recipient population of co administration of azithromycin, ivermectin, and albendazole especially surrounding pill burden and the change in MDA distribution schedule.

Background: Currently, mass drug administration takes place through three distinct phases depending on the number of NTDs for which a woreda is endemic. Assuming a community is endemic for trachoma, LF, and OV, the first MDA round that takes place addresses OV an LF through a height dependent dosage of up to four pills of ivermectin and, regardless of height or age, one pill of albendazole. The second round of MDA takes place two weeks later for the administration of azithromycin involving a height-dependent dosage of up to four pills for azithromycin (with TEO administered to children under a height of 48 cm). According to the Ethiopian national strategy to eliminate onchocerciasis, almost all the OV endemic woredas in Ethiopia have been moved to a twice a-year treatment strategy. Notably, though STH and SCH are usually treated through school-based MDA, communities that are co-endemic for STH with prevalence over 50% and IVM will receive a second round of albendazole (or mebendazole) together with the OV second round of ivermectin.

The Challenge: While cost, supply chain, and the work load of the local health work force are important considerations (and further explored through the other secondary outcomes of the study in this section), the most important aspect to consider is that of the beneficiary. Depending on the dosage, determined by a beneficiary's height for ivermectin and azithromycin, an adult of certain height will find him or herself taking up to nine pills (four for ivermectin, four for azithromycin, and one for albendazole). While the swallowing regimen (a maximum of two pills at a time or one at a time according to the beneficiaries' comfort level) is meant to control for the possibility of choking during MDA, taking up to nine pills at one time can create both physical and mental duress. The level of duress, if any, must be ascertained and considered in conjunction with the physiological assessment of side effects and the operational benefits before any adoption of the co-administration strategy can take place by a national program.

Study Goal: Triple drug administration may present an opportunity to significantly lessen the time investment required for beneficiaries to participate in all the necessary mass drug administrations, time that could otherwise be used for farming, time at the market, etc. Lessening the time a beneficiary needed to invest to receive drug administration may subsequently improve MDA coverage. This sub-study sought to discover, through a series of in-depth interviews and focus groups within the trial arm and control arm the benefits and disadvantages of the co-administration strategy.

Study area: The study took place within gares selected for the trial and control arm

Study Sample: The target participants were selected among the beneficiaries living within the gares where the trial took place.

Patient Interview Structure: Patients were interviewed within the community by an Afan Oromo speaking interviewer. Each FGD consisted of key representational groups: male adults, female adults,

female youths and male youths. Individuals were selected from both the trial arm (integrated MDA) and the control arm (standard MDA) to provide a means of comparison and discussion. The focus group discussions took place within the interviewees' home or in a private area surrounding the distribution point, and in an environment which is secluded from members of the surrounding community to discourage peer and community influence on the interviewees. The interviews took place either immediately after the beneficiary received his/her co-administered dose or during the post-MDA active follow-up that took place the following day. Topics included: 1.) A description of the recipient's "average day" in terms of work, child-rearing, etc. 2.) A description of what the recipient believed are the biggest health issues within the community, 3.) The recipient's thoughts on the role of the HEW, 4.) Perceptions surrounding the "usual" MDA distribution and how it affects the "average day" of the recipient, 5.) Perceptions of "usual" MDA versus the co-administration, 5.) Perceptions of pill burden, both for the recipient and the recipient's family. Interviewers were trained in the reduction of biases when conducting these interviews.

Study Analysis: All interviews were recorded and transcribed. I sorted through all the transcribed interview data and flagged statements from participants that are significant/insightful/often repeated. Using NVIVO, I created both pre-defined codes based on identified themes (via both published literature and practical experience in Ethiopia) as well as from insights that occurred during the review of the transcripts themselves. I also created categories for "descriptive" codes relating to the participants themselves (age, gender, etc.) and "thematic" codes relating to what was said by the participants. I assigned the previously identified "significant statements" of the participants to the codes, resulting in one statement having several different codes attached. I explored patterns in responses and linkages between the thematic and descriptive codes.

Sub-Study 2: Better understand the perceptions of the co-administration strategy by the local health workforce as a means of PC-NTD drug delivery

Background: The FMOH and RHBs currently carry out many health initiatives at three levels: Primary Health Care Units (PHCUs), the Health Extension package, and the Health Development Army (HDA). PHCUs are woreda-level medical clinics. On average, there are five PHCUs per woreda. The Health Extension Program, which was created to address medical intervention needs at the community level, consists of an integrated set of 16 health packages, including NTD intervention through MDA. The FMOH has trained and deployed approximately 38,000 health extension workers (HEWs) across the country to implement these health packages. They are government-salaried, community-based health workers. The HDA is a community-level cadre composed of six women health volunteers per community. Each member of an HDA is assigned five households. The HEWs lead groups of HDA members to form health development teams. Overall, there is an average of 30 development teams in each kebele. Given that HEWs are salaried positions, they are hired by the woreda health office through a competitive interview process while HDA volunteers are recognized as "community influencers" and are selected by community leaders. Both HEWs and the HDA are predominantly female.

In terms of NTD interventions, use of the HEWs and members of the HDA is very effective. HEWs conduct all the MDA registrations and supervision while the HDA assists with mobilization and directly observed treatment. Although HDAs can administer albendazole and ivermectin, they cannot administer azithromycin because it is an antibiotic. This task is left to the HEWs. Mebendazole and praziquantel are distributed by teachers through school-based distribution except in woredas with high-risk groups or a prevalence over 50%, in which case the HEWs lead community-wide distributions.

The FMOH adopted a campaign-style MDA in 2013 using the HEWs, HDAs, and teachers for all NTDs.

The move away from “rolling” MDAs, which was supported by the Community Directed Treatment with Ivermectin (CDTI) strategy, has been very successful in reducing the average time for MDAs from 1 month to 5 days to cover the same area.

The Challenge: With more than 80 million people at risk for at least one NTD, the investment of time and human resources to conduct all the necessary campaigns is massive. Every region currently follows its own MDA schedules determined by drug availability and the schedules of other community health initiatives. With MDA often required twice a year for OV, once a year for LF, possibly twice a year for STH/SCH depending on prevalence, and once a year for trachoma, NTD interventions are quickly becoming one of the greatest demands on the community health infrastructure. HEWs, the backbones of the MDA mechanism, may be called out of their health post to attend woreda-level NTD trainings and post-MDA reviews four or five times a year within a single woreda, meaning that the community is left without one of their healthcare providers.

Study Goal: Triple drug administration may present an opportunity to significantly lessen the work burden demanded of HEWs by NTD work in that it combines the two separate MDAs of OV/LF and Trachoma, usually provided two weeks apart, into one. This includes the reduced training time and supervisory requirement of the combined MDA schedule. However, it is also possible that the administration of so many drugs at the need to more stringently observe the various exclusionary criteria of all three drugs will present a greater burden to HEWs. For this reason, the study team composed of the FMOH, LSHTM and AHRI, conducted KII interviews with government health workforce members that had experience both with the standard MDA schedule and the co-administration study criteria to ascertain how HEWs viewed the co-administration methodology from a quality and quantity of work standpoint.

Study area: The study took place within the same gares targeted for the trial

Study Sample: KII participants were members of the government health force employed within the district where the trial took place.

Healthcare worker Interview Structure: Using semi-structured question guides, we conducted 16 key informant interviews (KII) with selected individuals involved in implementing MDA within the participating district. These individuals included health care providers and health department staff members, local government leaders, traditional governance leaders, religious leaders and elders. All interviews were led by fluent Afaan oromo speakers. Interviewers transcribed and later translated all of the responses and discussions into English. The study team synthesized and analyzed the results via the same methods described in the Patient FGD structure above.

Study Analysis: Interviewers transcribed and later translated all of the responses and discussions into English. I synthesized and analyzed the results via the same methods described in the Patient FGD structure above: Using NVIVO, I created both pre-defined codes based on identified themes (via both published literature and practical experience in Ethiopia) as well as from insights that occur during the review of the transcripts themselves. I also created categories for “descriptive” codes relating to the participants themselves (age, gender, etc.) and “thematic” codes relating to what was said by the participants. I assigned the previously identified “significant statements” of the participants to the codes, resulting in one statement having several different codes attached. I explored patterns in responses and linkages between the thematic and descriptive codes.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1513535	**TITLE**	M R
First Name(s)	SCOTT		
Surname/Family Name	MCPHERSON		
Thesis Title	SAFETY OF THE CO-ADMINISTRATION OF AZITHROMYCIN, ALBENDAZOLE, AND IVERMECTIN VERSUS STANDARD TREATMENT REGIMENTS DURING MASS DRUG ADMINISTRATION (MDA) IN ETHIOPIA: A CLUSTER RANDOMIZED TRIAL		
Primary Supervisor	DR. DAVID MABEY		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

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Where was the work published?			
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Where is the work intended to be published?	PLOS NEGLECTED TROPICAL DISEASE (PNTD-D-23-0031)
Please list the paper's authors in the intended authorship order:	Scott McPherson, Anthony W. Solomon, Fikre Seife, Hiwot Solomon,Teshome Gebre, David C.W. Mabey, Michael Marks
Stage of publication	Undergoing revision post peer review

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Conducted the literature review/Analyzed the results/Wrote the paper/Responded to revisions

SECTION E

Student Signature	
Date	25th April 2023

Supervisor Signature	
Date	25th April 2023

Chapter 2: Pharmacodynamics, feasibility and safety of co-administering azithromycin, albendazole, and ivermectin during mass drug administration: a review

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Abstract

Introduction
Traditionally, health ministries implement mass drug administration programmes for each neglected tropical disease (NTD) as separate and distinct campaigns. Many NTDs have overlapping endemicity suggesting co-administration might improve programme reach and efficiency, helping accelerate progress towards 2030 targets. Safety data are required to support a recommendation to undertake co-administration.

Methodology
We aimed to compile and summarize existing data on co-administration of ivermectin, albendazole and azithromycin, including both data on pharmacokinetic interactions and data from previous experimental and observational studies conducted in NTD-endemic populations. We searched PubMed, Google Scholar, research and conference abstracts, gray literature, and national policy documents. We limited the publication language to English and used a search period from January 1st, 1995 through October 1st, 2022. Search terms were: azithromycin and ivermectin and albendazole, mass drug administration co-administration trials, integrated mass drug administration, mass drug administration safety, pharmacokinetic dynamics, and azithromycin and ivermectin and albendazole. We excluded papers if they did not include data on co-administration of azithromycin and both albendazole and ivermectin, or azithromycin with either albendazole or ivermectin alone.

Results
We identified a total of 58 potentially relevant studies. Of these we identified 7 studies relevant to the research question and which met our inclusion criteria. Three papers analyzed pharmacokinetic and pharmacodynamic interactions. No study found evidence of clinically significant drug-drug interactions likely to impact safety or efficacy. Two papers and a conference presentation reported data on the safety of combinations of at least two of the drugs. A field study in Mali suggested the rates of adverse events were similar with combined or separate administration, but was underpowered. A further field study in Papua New Guinea used all three drugs as part of a four-drug regimen also including diethylcarbamazine; in this setting, co-administration appeared safe but there were issues with the consistency in how adverse events were recorded.

Conclusion
There are relatively limited data on the safety profile of co-administering ivermectin, albendazole and azithromycin as an integrated regimen for NTDs. Despite the limited amount of data, available evidence suggests that such a strategy is safe with an absence of clinically important drug-drug interactions, no serious adverse events reported and little evidence for an increase in mild adverse events. Integrated MDA may be a viable strategy for national NTD programmes.

Plain English Summary

Treatment of the whole community (mass drug administration, MDA) has been a major intervention strategy against many neglected tropical diseases (NTDs) over the last decade. Normally health ministries deliver individual MDA rounds targeting specific NTDs. This multiplies the training, transport and time burden for local health service personnel in districts in which several NTDs are present, imposing considerable financial and human resource costs to health ministries and their partners, and causing requiring repeated disruption to the daily life of communities receiving MDA. Delivering MDA

for several NTDs at one time could improve the efficiency of NTD programmes. We reviewed existing data on the safety and feasibility of combining MDA of albendazole, ivermectin and azithromycin into a single co-delivered MDA. Several studies had evaluated if taking these drugs at the same time changed drug levels in recipients' blood; these studies concluded that there was not an important difference in blood drug levels comparing instances when the medicines were taken separately to instances when they were taken at the same time. Two non-randomised studies assessed side effects experienced by people taking combinations of the three drugs and suggested doing so was safe. One small study in Mali had assessed combining all three drugs and also suggested this was safe but was too small to give a definitive answer. Two studies in Papua New Guinea assessed all three drugs being taken together in combination with a fourth drug, diethylcarbamazine. These studies also suggest co-administration was safe overall. Most of the identified studies had some methodological shortcomings, such as small sample sizes or issues with the way adverse events were recorded. Overall, the data suggest co-administration of azithromycin, ivermectin and albendazole is viable, but larger safety studies are needed.

BACKGROUND

Neglected tropical diseases (NTDs) are a major cause of preventable illness and death in low- and middle- income countries.(1) Through a combination of improved access to water, sanitation and hygiene; intensified disease management; mass drug administration (MDA); vector control; and veterinary public health, many countries have either eliminated or are on track to eliminate one or more NTDs. The recent road map document "Ending the neglect to attain the Sustainable Development Goals: A road map for neglected tropical diseases 2021–2030" sets out global targets and milestones to prevent, control, eliminate and eradicate 20 diseases and disease groups by 2030. The road map is built on three interlinked pillars of accelerating programmatic action, intensifying the use of cross-cutting approaches, and switching to operating models that facilitate country ownership.(2)

MDA involves offering treatment to all members of a community or population within a defined area, without individual-level diagnostic testing and regardless of whether or not any specific individual has the targeted disease or infection. Three NTDs that are aiming to achieve global elimination targets using MDA as a critical part of the intervention strategy are lymphatic filariasis, onchocerciasis and trachoma. MDA of ivermectin and albendazole is also effective against other NTDs, including soil-transmitted helminthiases, scabies and strongyloidiasis. MDA of azithromycin is also effective against yaws(3) (4) (5) (6). Subsets of these diseases can therefore be managed with a different medicine or combination of medicines in annual or bi-annual MDA campaigns; the main drivers of community-based MDA programmes that employ albendazole, azithromycin and ivermectin are currently lymphatic filariasis, onchocerciasis and trachoma. For trachoma, a number of rounds of antibiotic MDA are recommended, with the antibiotic being oral azithromycin for most individuals and 1% tetracycline eye ointment for those unable or unwilling to take azithromycin; the number of rounds indicated is dependent on the prevalence of trachomatous inflammation—follicular (TF) in children aged 1–9 years.(7) For onchocerciasis, the second leading infectious cause of blindness behind trachoma, WHO recommends annual or biannual treatment with ivermectin for at least 14 rounds.(8) Lymphatic filariasis is treated with a variety of MDA combinations, including ivermectin and albendazole, or diethylcarbamazine (DEC) and albendazole, for at least five years.(9) In some specific situations, a three-drug combination of albendazole, DEC and ivermectin is recommended but not in settings in which onchocerciasis is co-endemic.(10)

Following the NTD road map's first pillar of 'accelerating progress', national NTD programmes are exploring ways to improve upon standard disease-specific MDA strategies. MDA requires an enormous effort from every tier of a national health system to train the distribution workforce, sensitize targeted communities, deliver medicines through the national supply chain, administer medication, and collate treatment reports. In order to achieve elimination targets by 2030, ease strain on country health systems and adapt to shifting availability of resources, there is interest in combining individual drug regimens into co-administered MDA packages. Co-administered MDA could reduce the financial cost and time required on the part of health workers, as well as reduce the accompanying loss of their attention to other health initiatives. Communities could also benefit by reduced disruption to their daily activities if interventions are delivered simultaneously. Both communities and health systems may benefit if this translates into increased coverage of interventions. As lymphatic filariasis is treated through much of its endemic area with the combined regimen of ivermectin and albendzole, onchocerciasis programmes can already be integrated. However, adding in azithromycin MDA (for trachoma or yaws) could further benefit NTD programmes in many countries.

We conducted a review of existing data on the safety and feasibility of co-administration of ivermectin, albendazole and azithromycin to evaluate the potential role of combination MDA of these three medicines in accelerating progress towards 2030 targets.

METHODOLOGY

We aimed to compile and summarize existing data on co-administration of ivermectin, albendazole and azithromycin, including both data on pharmacokinetic interactions and data from previous experimental and observational studies conducted in NTD-endemic populations. We used the 'PICOT' method (BOX 1) for formally framing the question that we intended the review to address. The final question derived was "When azithromycin, albendazole and ivermectin are combined during mass drug administration, is there a documented significant increase in adverse events as compared to giving azithromycin separately?"

Box 1: PICOT approach

- **P**opulation: patients living in endemic districts receiving MDA
- **I**ntervention: co-administered albendazole, azithromycin, and ivermectin
- **C**omparison: these drugs administered together or separately
- **O**utcomes: the incidence of serious adverse events and all adverse events
- **T**rial: experimental or observational studies

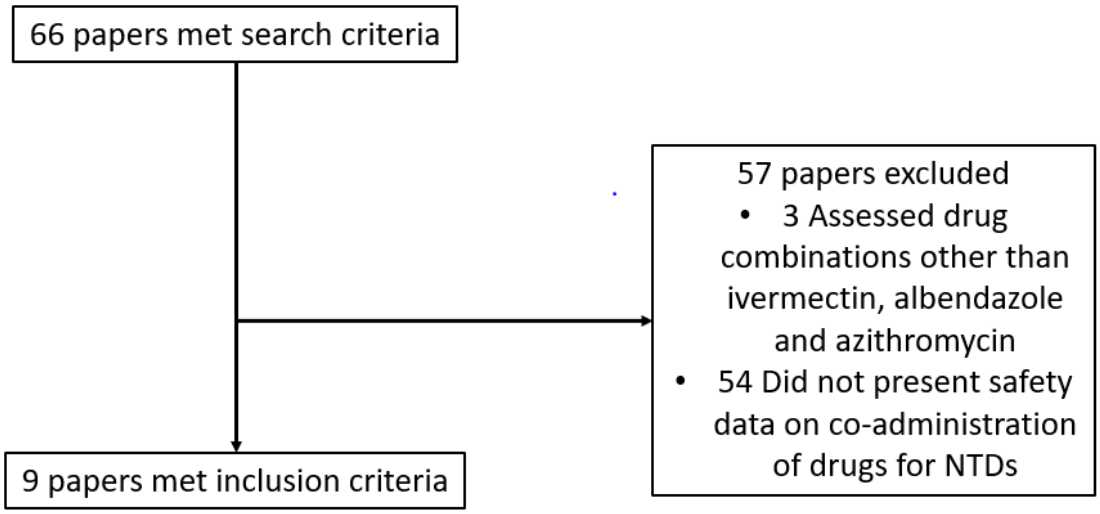
We searched PubMed, Google Scholar, research and conference abstracts, gray literature, and national policy documents. We limited the publication language to English and used a search period from January 1st, 1995 through October 1st, 2022. Search terms were: azithromycin and ivermectin and albendazole, mass drug administration co-administration trials, integrated mass drug administration, mass drug administration safety, pharmacokinetic dynamics and azithromycin and ivermectin and albendazole. We excluded papers if they did not include azithromycin and both albendazole and ivermectin, or azithromycin with either albendazole or ivermectin alone.

We identified relevant papers by screening the abstracts. For relevant papers, a standardized data extraction form was used to record data on eligibility, methods, participants, intervention groups, outcome measures and results. For the purpose of analysis, studies were grouped into pharmacokinetic studies and field evaluations and by the specific drug combinations evaluated.

RESULTS

We identified a total of 66 potentially relevant papers (Figure 1). Of these, we identified 7 studies that were relevant to the research question and met our inclusion criteria. Three papers examined potential pharmacokinetic and pharmacodynamic interactions of azithromycin, ivermectin and albendazole. Two papers and a conference presentation reported data on co-administration of at least two of the three drugs. One paper was a field study that involved the co-administration of all three drugs. A further field study reported on the co-administration of albendazole, azithromycin, and ivermectin as part of a four-drug regimen that also included diethylcarbamazine.

Figure 1: Inclusion and Exclusion Criteria



PHARMACOKINETIC STUDIES

Previous pharmacokinetic studies demonstrated that there is little to no relevant drug-drug interaction between ivermectin and albendazole and these data have underpinned the co-administration of these drugs for lymphatic filariasis.(11)(12)(13) Mass co-administration of both drugs to treat lymphatic filariasis has occurred with no reported serious adverse events related to drug interactions among large populations for many years.(14) We identified three additional pharmacokinetic studies related to the interaction of the three-drug combination including azithromycin.

The first study was a randomized, three-way crossover pharmacokinetic study of potential interactions between azithromycin, ivermectin and albendazole.(11) In this study, 18 volunteers were administered a fixed dose of 500 mg of azithromycin alone, a fixed dose of 400 mg of albendazole alone, and a dose proportional to body weight (200 ug/kg rounded to the nearest 3 mg) of ivermectin alone. All three drugs were administered together. A total of 19 blood samples were collected from each subject before the administration took place and then at intervals over a 168-hour period. The study measured total exposure to each drug over time (AUC_{0-t}) and peak concentrations of the drug after dosing (C_{max}). When all three drugs were combined, the azithromycin AUC_{0-t} and C_{max} were increased approximately 13% and 20%, the albendazole AUC_{0-t} was decreased approximately 3%, the albendazole C_{max} was increased approximately 3%, and the ivermectin AUC_{0-t} and C_{max} were increased approximately 31% and 27%, respectively.(11) These changes in drug levels were felt to be small and unlikely to be of clinical importance. The elevation in ivermectin levels was within established safety ranges for the drug.(12)

The second study was a pharmacokinetic modeling exercise to explore the mechanisms of interaction when azithromycin is combined with ivermectin and albendazole, with a particular focus on the AUC for ivermectin.(13) The authors constructed two simulated pharmacokinetic models to evaluate the impact of co-administration and other variables on ivermectin levels. One thousand interaction studies were simulated to explore extreme high ivermectin values that might occur. Using both models, the predicted highest ivermectin concentrations were 115–201 ng/mL: well inside the established safety range.

A third pharmacokinetic study was conducted in Papua New Guinea. This study was a three-arm pharmacokinetic interaction study in which 36 volunteers were recruited and randomized to either a) ivermectin, diethylcarbamazine and albendazole (IDA); b) IDA combined with azithromycin; or c) azithromycin alone. Drugs were administered to participants after a night of fasting. Drug levels were measured via repeated sampling between baseline and 72 hours. Drug levels were evaluated using mass spectrometry and reported as Cmax and AUC.(15) Total drug exposure was unaffected by co-administration when compared to the stand-alone AUC of each drug. The AUC during co-administration for ivermectin was reduced to 87.9%, for DEC to 92.9%, while albendazole's AUC was unaffected. In this small study no difference was seen in the number of adverse events between study arms.

OBSERVATIONAL STUDIES:

One observational study was identified examining the combination of albendazole and azithromycin and one observational study examining the combination of azithromycin and ivermectin. In Colombia, the Ministry of Health adopted a policy of co-administering albendazole for the treatment of soil-transmitted helminths alongside azithromycin given for the elimination of trachoma. These activities were carried out programmatically with safety monitoring done in a sub-group of recipients. More than 300,000 people received albendazole and azithromycin, taken together, over three separate annual cycles of MDA from 2012–14. Adverse events were ascertained in a subgroup of 4,438 individuals. Adverse events were reported in 0.16%, of which the most common were headache, dizziness and diarrhoea. No serious adverse events were documented.(16)

In the Solomon Islands, a team conducted a prospective, single-arm, intervention study to assess the safety and efficacy of combined MDA of ivermectin and azithromycin. Azithromycin was used to treat trachoma while ivermectin was used to treat scabies. Overall, 21,181 individuals received the combination treatment. Safety data were collected via a questionnaire administered both at baseline and one week following MDA. In most villages the questionnaire was administered by the routine health service whilst in ten villages the questionnaire was administered by a dedicated research team. There were no reported serious adverse events. Overall, 2.6% of the entire study population reported an adverse event. In the ten villages visited by a research team 4.1% of participants reported an adverse event. All adverse events reported were mild and short-lived. Gastrointestinal symptoms, dizziness and itch were the most commonly reported adverse events, in keeping with the known safety profile of the drugs. Passive surveillance in the 12 months before and after MDA showed that the number of hospital admissions (1530 vs 1602) and deaths (73 vs 83) were similar before and after MDA.(17)(18)(19)

RANDOMIZED CONTROL TRIALS

The AZIVAL study was conducted in Mali in four villages (total population 3, 011) endemic for trachoma and lymphatic filariasis. Two villages were randomized to co-administration of ivermectin, albendazole, and azithromycin and two villages received an initial round of MDA of ivermectin and albendazole

followed one week later by a round of azithromycin MDA. Safety data were collected by the study team from all participants on days 1, 8 and 15 after treatment, via clinical examination and adverse event questionnaire. The overall reported rates of any adverse event were similar in the co-administration arm (281/1501, 18.7%) and the standard treatment arm (239/1510, 15.8%). No serious adverse events were reported. The most frequent adverse events were abdominal pain, headache and diarrhoea, in line with the drugs' established safety profiles.(20)

The final identified study was an open-label, cluster-randomized trial conducted in two study sites, Namatanai and Lihir Island, Papua New Guinea. Clusters were randomised to receive either MDA of ivermectin, diethylcarbamazine and albendazole (IDA) followed by a single dose of azithromycin administered one week later, or MDA of all four drugs together. Data on adverse events were collected in the 24–48 hours following MDA. Study teams initially used a general question concerning adverse events within both study arms in Namatanai. However, because the researchers noticed a low proportion of reported adverse events, on Lihir Island, a more in-depth questionnaire concerning specific adverse events was used. Overall, 7,281 people received the four-drug regimen and no serious adverse events occurred. In clusters that received separate MDA, the rate of adverse events was 6.3% following IDA and 9.9% following azithromycin. In clusters that received combined MDA, the rate of adverse events was 6.9%. The incidence of reported adverse events was higher when the more detailed questionnaire was used. The most commonly reported adverse events were fever, headache and abdominal pain.(21)

DISCUSSION

Our review highlights the relative paucity of data on the safety profile of co-administering ivermectin, albendazole and azithromycin as an integrated regimen for NTDs. However, the available evidence suggests that co-administration is safe, with an absence of clinically important drug interactions, no serious adverse events reported to date amongst tens of thousands of recipients of combined treatment, and little evidence for an increase in more mild adverse events. Overall, our review suggests that integrated MDA is a viable strategy for national programmes.

Whilst the published pharmacokinetic studies are small, they have consistently demonstrated either an absence of any drug interaction, or that the alterations in drug levels when these agents are co-administered are unlikely to impact drug efficacy or to be of concern from a safety perspective. Multiple field studies of different drug combinations have been conducted in diverse geographic regions and in settings in which a range of NTDs are endemic. The most commonly reported adverse events are in keeping with the known safety profiles of the three drugs. The absence of serious adverse events and the absence of a significant increase in the frequency of mild adverse events are very encouraging from a safety perspective.

We identified a number of limitations in the existing literature. The AZIVAL study, conducted in Mali, had a suitable study design but too small a sample size to definitively answer the question on safety and justify a programmatic recommendation for co-administration. The study conducted in the Solomon Islands, relied on before-and-after comparisons rather than being randomized. It also was undertaken in a setting which was not endemic for onchocerciasis or lymphatic filariasis. As adverse events can be related to parasite burden, this may affect the generalisability of the findings. Although Colombia has conducted large scale integrated MDA, systematic safety data are only available from a small proportion of recipients in those campaigns. The largest co-administration trial to date, in Papua New Guinea, ended with a smaller number of people treated than originally targeted and the investigators altered the data collection method for adverse events during the study. Collectively these data highlight the

need for larger, more robust field studies in settings where onchocerciasis, lymphatic filariasis and trachoma are co-endemic, to provide greater certainty for national programmes interested in adopting integrated MDA.

Our review also has a number of limitations. We focused on published literature and may have excluded more real-world programmatic experience involving the co-administration of ivermectin, albendazole, and azithromycin. Alongside Columbia, at least anecdotally, other countries have conducted MDA using combinations of these drugs, but we were unable to identify any published safety data from those experiences. Our review focused on one particular three-drug combination, but alternative triple-drug approaches (such as the combination of ivermectin, albendazole and praziquantel) have been used in other settings.(22) Whilst such studies may not directly inform the safety profile of the combination under review here, they may provide important insights including how integrated MDA can result in higher coverage and cost savings. Finally, as noted above, there are limitations with the design and interpretation of studies included in our review.

We found multiple studies suggesting that co-administration may be a safe approach, conferring a risk of adverse events that is similar to MDA of the different drugs delivered separately. The data support the conduct of larger, well-powered trials using a standardised safety monitoring approach, to generate the evidence needed to support global adoption of co-administration.

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed <u>for each</u> research paper included within a thesis.

<u>SECTION A – Student Details</u>

Student ID Number	1513535	**Title**	M R
First Name(s)	SCOTT		
Surname/Family Name	MCPHERSON		
Thesis Title	SAFETY OF THE CO-ADMINISTRATION OF AZITHROMYCIN, ALBENDAZOLE, AND IVERMECTIN VERSUS STANDARD TREATMENT REGIMENTS DURING MASS DRUG ADMINISTRATION (MDA) IN ETHIOPIA: A CLUSTER RANDOMIZED TRIAL		
Primary Supervisor	DR. DAVID MABEY		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

<u>SECTION B – Paper already published</u>

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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	eClinicalMedicine
Please list the paper's authors in the intended authorship order:	Scott McPherson, Getinet Tafese, Temesgen Tafese, Sinknesh Wolde Behaksre, Hiwot Solomon, Birhanu Oljira, Hirpa Miecha, Kaleab A. Debebe, Biruck Kebede, Teshome Gebre, Fikreab Kebede, Fikre Seife, Fentahun Tadesse, Belete Mammo, Abraham Aseffa, Anthony W Solomon, David CW Mabey, Michael Marks and Endalamaw Gadisa
Stage of publication	**Accepted for publication**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Designed the reseach protocol/gained IRB approval from both LSHTM and the Ethiopian Ministry of Health/Created the training materials/Coordinated the training of health staff in targeted district/Coordinated implementation of the study protocol in both the trial and control arms/Liased with the DSMB daily during implementation of the trial arm/analyze the data upon completion of the study/Wrote final trial paper/Responded to reviewer comments

SECTION E

Student Signature	
Date	25th April 2023

Supervisor Signature	
Date	25th April 2023

Chapter 3: Safety of integrated mass drug administration of azithromycin, albendazole and ivermectin versus standard treatment regimens: a cluster randomised trial in Ethiopia

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ABSTRACT

Background: Neglected Tropical Disease (NTD) programs require separate and distinct drug regimens for treatment. This has required countries to undertake multiple distinct mass drug administration (MDA) programmes, each targeting one or more diseases. The possibility of safely combining different drug regimens together in one MDA may offer several advantages to national programs. We conducted a study to assess the safety of combining ivermectin, albendazole and azithromycin in one integrated MDA.

Methods: We conducted an open-label, non-inferiority cluster-randomised trial comparing the frequency of adverse events in communities receiving co-administered ivermectin, albendazole and azithromycin to that in communities given albendazole and ivermectin MDA followed by azithromycin MDA after a two-week interval. The study took place in 58 gares (small administrative units) across two kebeles (sub-districts) in Kofele woreda (district) in the Oromia region of Ethiopia. We randomly assigned 29 gares to the combined treatment arm and 29 gares to the control arm. The study team revisited all individuals within 48 hours and actively collected data on the occurrence of adverse events using a dedicated questionnaire and a pre-specified list of adverse events. The study team followed the same process in the control arm for the azithromycin distribution and again after the ivermectin plus albendazole distribution. Following this initial active surveillance, passive surveillance was undertaken for one week after the first visit. The primary outcome was the frequency of adverse events occuring following MDA. The study team determined that the safety of the combined MDA would be non-inferior to that of separate MDAs if the upper limit of the two-sided CI for the difference in rates was equal to or lower than 5%. The trial was registered on clinicaltrials.gov (identifier: NCT03570814)

Findings: The study took place from December 2021 to January 2022.The combined MDA arm consisted of 7292 individuals who were eligible to participate, of whom 7,068 received all three medications. The separate MDA arm consisted of 6219 eligible individuals of whom 6,211 received ivermectin and albendazole and 4,611 received azithromycin two weeks later. Overall, adverse events were reported by 197 (1.2%) of individuals. The most commonly reported adverse events included headache, gastrointestinal disturbance and dizziness. There were no serious adverse events in either arm. The cluster-level mean frequency of reported adverse events varied markedly between clusters (Figure 3), ranging from 0.1 to 10.4%. The cluster-level mean frequency of adverse events was 1.4% in the combined MDA arm and 1.2% following ivermectin and albendazole MDA (absolute difference 0.2%, 95% confidence interval [CI] -0.6% to +1.1%). This met the pre-defined 1.5% non-inferiority margin. For the combined MDA comparison to the stand-alone azithromycin MDA the absolute difference was -0.4% (1.4 vs 1.8%, 95%CI -0.8 to +1.5) which also met the pre-specified non-inferiority margin.

Interpretation: This study is the largest of its kind to date and demonstrates that the safety of combined MDA of azithromycin, ivermectin and albendazole is non-inferior to the safety of ivermectin-plus-albendazole MDA then azithromycin MDA conducted separately although we may not have been powered to detect very small differences between arms. Co-administration of these three medicines is safe and feasible in this setting and allows national programs to develop new strategies for integrated MDA programs.

Funding: Ivermectin (Mectizan) was donated by the Mectizan Donation Program, albendazole was donated by GlaxoSmithKline, and azithromycin (Zithromax®) was donated by Pfizer via the International Trachoma Initiative (ITI). The trial was funded by ITI using operational research funds from the Bill and Melinda Gates Foundation.

Keywords: co-administration; integration; lymphatic filariasis; trachoma; onchocerciasis; soil transmitted helminths, safety; trachoma.

Research in Context

Evidence before the study

We searched PubMed for studies on the safety of co-administration of ivermectin, albendazole and azithromycin published between 1st January 1990 and 5th February 2023. Two small pharmacokinetic studies had established that there was limited evidence for drug-drug interactions between these agents. A third study additionally included diethylcarbamazine and equally found limited evidence of drug-drug interactions. One field study had been conducted which found no evidence of an increase in adverse events when the drugs were administered together rather than separately. However, this study involved only four clusters and was underpowered to provide adequate data on the safety of co-administration. A large cluster randomised trial in Papua New Guinea had examined the safety of co-administration. However, this trial had included the use of diethylcarbmazine and had altered the mechanism used for recording adverse events during the study period, making interpretation more complex.

Added value of this study

This is the largest published trial assessing the safety of co-administration of ivermectin, albendazole and azithromycin. We randomised more than 12,000 individuals to either separate or combined administration. We observed no serious adverse events in either arm and no increase in the overall number of adverse events using the co-administration strategy.

Implications of all the available evidence

Based on the evidence from both pharmacokinetic and field-studies the evidence suggests that co-administration is a feasible and safe strategy in areas co-endemic for multiple relevant neglected tropical diseases. Switching to a co-administration strategy should support more rapid progress to the 2030 targets for the eradication, elimination and control of neglected tropical diseases.

INTRODUCTION

The group of 20 poverty related diseases called neglected tropical diseases (NTDs), affecting marginalized people in the tropics and elsewhere, represent not only health challenges but also a significant social and economic burden to affected communities and health systems. With an estimated 200,000 associated deaths and 19 million disability adjusted life years (DALYs) lost annually, NTDs cost the equivalent of billions of United States dollars each year in direct health costs, loss of productivity and reduced socioeconomic and educational attainment, reinforcing the vicious cycle of poverty. Globally, over 1.7 billion people need prevention and treatment for at least one of these diseases, every year.(1)

Mass drug administration (MDA) is an intervention strategy in which medicines are offered to every member of a targeted population within a defined area, regardless of whether specific individuals are affected by the infection or disease of interest. NTDs that can be controlled in part through MDA include lymphatic filariasis (LF), onchocerciasis, schistosomiasis, soil-transmitted helminthiases, and trachoma. Each of these is treated with specific medicines or medicine combinations delivered within MDA campaigns. Supported by large scale drug donations, MDA for NTDs is often delivered at low cost and is commonly considered one of the most cost-effective interventions in global health. Traditionally, however, control of diseases requiring separate drug regimens has required countries to undertake multiple distinct MDA programmes, each targeting one or more diseases.

The recent NTD road map 2021–2030 has set global targets and milestones to prevent, control, eliminate and eradicate multiple NTDs by 2030. The platform from which we will achieve these targets is built on three pillars: (i) accelerating programmatic action, (ii) intensifying cross-cutting approaches, and (iii) changing operating models and culture to facilitate country ownership.(2) To solidify the first and second pillars, national programmes are exploring ways to integrate different aspects of many current disease-specific interventions. This should help to achieve disease-specific 2030 targets, while easing the strain on country health systems and adapting to shifting availability of financial resources. One strategy is to explore co-administration of a wider range of medicines in combined MDA regimens. Various combinations of medicines have been previously used in integrated MDA in multiple contexts, providing proof-of-concept and some experience of the viability of this strategy.(3)(4)

A specific agent for which further data are required is azithromycin, given within MDA campaigns for elimination of trachoma as a public health problem, and also for the eradication of yaws. Azithromycin is donated to national trachoma programmes as Zithromax (Pfizer, New York, NY, USA) but current guidance provided with the donation is that administration is separated from MDA for other diseases. Practically, combining azithromycin MDA with ivermectin and albendazole, which target LF, onchocerciasis and soil-transmitted helminths, is likely to be advantageous, because of the considerable overlap in the populations affected by these diseases. A precondition for widespread adoption of integrated MDA is evidence for a lack of deleterious pharmacokinetic interactions and empirical data on the safety of co-administration. Pharmacokinetic studies have demonstrated that there is little to no drug-drug interaction between ivermectin and albendazole, or between those two drugs combined with azithromycin.(5)(6)(7) Small-scale studies of co-administration of all three medicines have been performed, but whilst those studies showed an absence of severe adverse events, they were underpowered to inform programmatic decision making.(8)

Ethiopia is endemic for LF, onchocerciasis, schistosomiasis, soil-transmitted helminthiases and trachoma. Currently, Ethiopia, follows WHO-recommended MDA guidance for each disease in endemic districts. For trachoma, annual rounds of azithromycin mass drug administration are undertaken, with the duration of intervention dependent on the prevalence of trachomatous inflammation—follicular (TF) in children aged 1–9 years.(9) To address onchocerciasis, WHO recommends annual or biannual ivermectin MDA for at least 14 rounds.(10) LF is managed with annual MDA of ivermectin and albendazole for at least five years, which also treats soil-transmitted helminths except in places where ivermectin, diethylcarbamazine, and albendazole is indicated.(3) (11) Many districts in Ethiopia could in theory receive integrated MDA combining all three agents. We set out to evaluate the safety of co-administration of albendazole, ivermectin and azithromycin compared to standard MDA delivery in Ethiopia.

METHODS

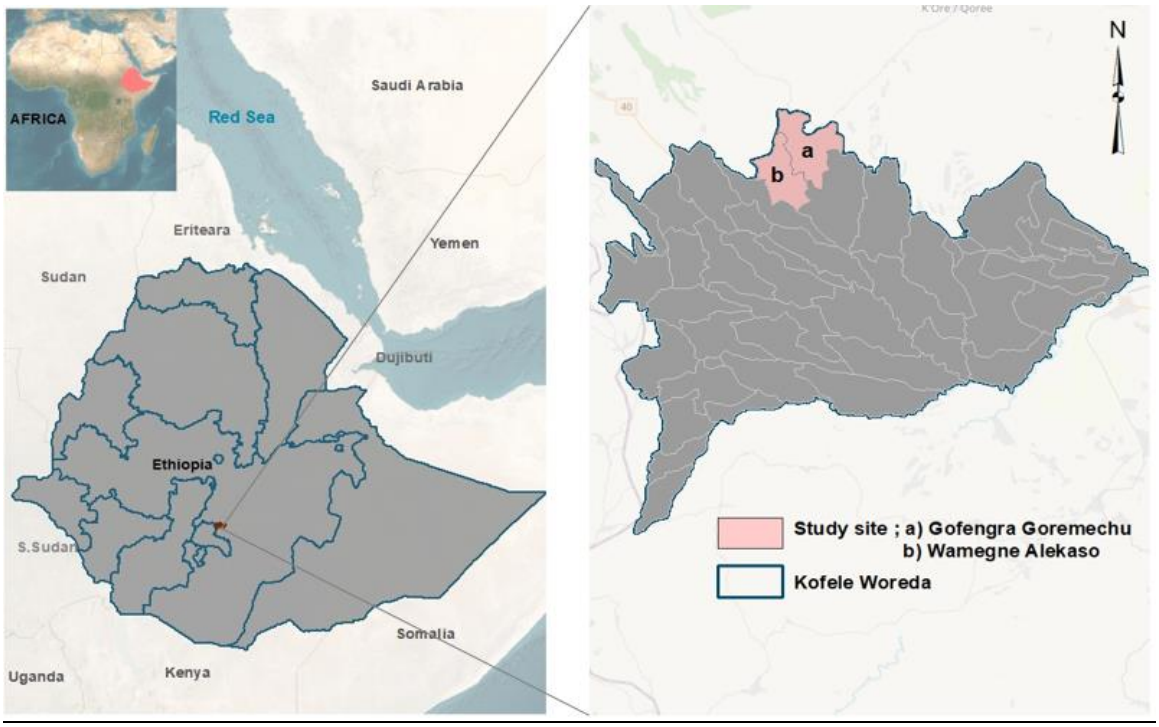
We undertook a cluster randomised, non-inferiority trial comparing the frequency of adverse events in communities receiving co-administered ivermectin, albendazole and azithromycin to that in communities given albendazole and ivermectin MDA followed by azithromycin MDA after a two-week interval. Findings are reported in line with the CONSORT guidelines.

Study Settings and Participants

The study team reviewed a number of woredas (districts) which fit the co-endemicity profile specifications of the study but eventually selected Kofele woreda both for its absence of conflict as well as the support of zonal and woreda leadership. Kofele is one of 17 woredas in the West Arsi Zone in Oromia regional state (Figure 1). Based on the most recent data available prior to the trial, Kofele had a prevalence (estimated in 2017) of TF in children aged 1–9 years of 27.3% and a prevalence (estimated in 2020) of 1.5% for LF antigen in children aged 5–14 years. Prior to the trial, the woreda had received five annual rounds of MDA for LF and two rounds of MDA for trachoma delivered at separate timepoints.

Kofele woreda is divided into 18 kebeles. Each kebele is composed of a varying number of communities known as gares. Gares are defined by the government as a population of at least 350 individuals, but there is considerable variation in actual population. Within Kofele, we arbitrarily selected two kebeles, Gurmicho and Alkaso, to participate in the study. Prior to study commencement these kebeles had received four rounds of azithromycin MDA and five rounds of ivermectin and albendazole MDA. Combined, Gurmicho and Alkaso contained 58 gares.

Figure 1: Map of the Study Site



In each community, individuals were eligible to receive treatment if they had been residing in the community for at least three months and were eligible to receive all three agents according to standard MDA criteria. Individuals were excluded from the trial if they were ineligible for any of the three study drugs, were unable to swallow tablets or declined to participate. Children aged under five years and pregnant or breastfeeding women were therefore considered ineligible as they could not receive ivermectin.

INTERVENTIONS

Before the study began, the study team provided protocol specific training to the health extension workers in Kofele woreda. Training included an overview of the national NTD training manual followed by an in-depth explanation of the study protocol and how it differed from routine MDA procedure.

Gares were randomised to receive either combined MDA or separate MDA. In the combined MDA arm, recipients received, at a single timepoint, ivermectin, albendazole (400 mg) and azithromycin. The ivermectin dose was determined using 150 µg/kg dosage based on a standard height pole (90 cm - 119 cm = 1 tablet; 120 cm to 140 cm =2 tablets; 141cm to 158 cm= 3 tablets; 158 cm and above = 4 tablets) .Azithromycin dose was determined as follows: individuals ≥120 centimeters in height AND aged 7–15 years were offered azithromycin tablets of 250 mg each; the dose was either 3 or 4 tablets, determined by height. Individuals aged ≥15 years were given a full adult dose of 4 tablets, regardless of height. Individuals <120cm in height or aged <7 years received azithromycin oral suspension instead of tablets. The separate MDA arm received ivermectin and albendazole at the first visit, followed by azithromycin two weeks later. All drugs were administered orally following standard WHO recommendations for directly observed treatment. The study team collected individual participant data using structured questionnaires.

Data were collected using computer tablets into a study specific case reporting formula in REDCAP.

Following the co-administered MDA of all three drugs in the trial arm, the study team revisited all individuals within 48 hours and actively collected data on the occurrence of adverse events using a dedicated questionnaire). The study team followed the same process in the control arm for the ivermectin plus albendazole distribution and again after the azithromycin distribution. Following this initial active surveillance, passive surveillance was undertaken for one week after the first visit following each MDA. We defined adverse and serious adverse events in line with Ethiopian national guidelines. In brief, adverse events were self-limiting or required minimal treatment. Adverse events were classified as mild, moderate or severe based on their impact on activities of daily living. Serious adverse events were those which required hospitalization, were life threatening or which resulted in death, disability or a congenital defect. All adverse events were followed up by the nurses until resolution.

STATISTICAL ANALYSIS

We estimated the anticipated rate of adverse events in the control arm based on previous studies. (12) (13) (14). For the purposes of the study, we set the anticipated adverse event percentage at 7% for azithromycin. We assumed that this would vary between 6–8% across study clusters. With a non-inferiority margin of 1.5% and clusters of 190 individuals per cluster, we calculated we would require at least 36 gares in each study arm (72 gares in total) to have 90% power to meet our non-inferiority margin. The primary analysis was a per-protocol analysis on individuals who received the study drugs. For the primary analysis we calculated the cluster-level mean frequency of adverse events between arms and compared these with a T-test. For the secondary analysis we fitted a random-effects logistic regression model to compare the odds of adverse events between arms adjusting for age, gender and clustering at the level of the gare. Analysis was performed in R version 4.1.1. The trial was registered on clinicaltrials.gov (identifier: NCT03570814).

RANDOMISATION AND BLINDING

The unit of randomisation was the gare. Randomisation was performed using the RANDNUM function in Microsoft Excel. Given that gares were randomly allocated from within the same woreda, had all had the same number of years of treatment with each medicine, and shared cultural and environmental factors, we assumed that there would be low variability of the outcome between clusters and therefore randomisation was not stratified by baseline cluster-level characteristics. The study was open label without blinding of participants or the field team.

ETHICAL APPROVAL

The study received ethical approval from the National Research Ethics Review Committee (NRERC) of Ethiopia (reference 3-10/195/2018) and the London School of Hygiene & Tropical Medicine (reference 11985). Based on low levels of literacy in the study population, permission to use verbal consent was specifically provided by the ethics committees. Study teams read the study consent form to all prospective participants and requested verbal permission to participate in the study. Individuals who declined to participate received treatment according to the usual MDA schedule. The study team established an independent Data Safety Monitoring Board to

review any reported severe adverse events. Michael Marks and Scott McPherson have accessed and verified the data.

ROLE OF THE FUNDING SOURCE

Ivermectin (Mectizan) was donated by the Mectizan Donation Program, albendazole was donated by GlaxoSmithKline, and azithromycin (Zithromax®) was donated by Pfizer via the International Trachoma Initiative (ITI). The trial was funded by ITI using operational research funds from the Bill and Melinda Gates Foundation. Funders are donors had no role in data collection, data analyses, interpretation, or writing of the report

RESULTS

Fieldwork took place from December 2021 to January 2022. A total of 58 gares were randomised 29 to integrated MDA and 29 to separate MDA (Figure 1). Overall, 13,511 people were assessed for study participation (Figure 2). The study population was 50.7% female and the median age was 14 years (IQR 10–19 years) (Table 1). The combined MDA arm consisted of 7292 individuals who were eligible to participate, of whom 7,068 received all three medications. The separate MDA arm consisted of 6219 eligible individuals of whom 6,211 received ivermectin and albendazole and 4,611 received azithromycin two weeks later. Prior to MDA, 0.4% of individuals in the separate MDA arm and 0.4% of individuals in the combined MDA arm reported any baseline symptoms.

Table 1: Age and Gender of Study Participants

		Co-Administered MDA (n = 7068)	Separate MDA – Ivermectin & Albendazole (n = 6211)	Separate MDA – Ivermectin & Albendazole (n = 4611)
Age Median (IQR)		14 (10-22)	13 (10-16)	10 (13-17)
Gender	Male (%)	3454 (48.9%)	3072 (49.5%)	2285 (49.6%)
	Female (%)	3613 (51.1%)	3124 (50.3%)	2311 (50.1%)

Overall, adverse events were reported by 197 (1.2%) of individuals. The most commonly reported adverse events included headache, gastrointestinal disturbance and dizziness. There were no serious adverse events in either arm. The cluster-level mean frequency of reported adverse events varied markedly between clusters (Figure 3), ranging from 0.1 to 10.4%. The cluster-level mean frequency of adverse events was 1.4% in the combined MDA arm and 1.2% following ivermectin and albendazole MDA (absolute difference 0.2%, 95% confidence interval [CI] -0.6% to +1.1%). This met the pre-defined 1.5% non-inferiority margin. For the combined MDA comparison to the stand-alone azithromycin MDA the absolute difference was -0.4% (1.4 vs 1.8%, 95%CI -0.8 to +1.5) which also met the pre-specified non-inferiority margin.

Figure 2: Trial and Control Arm Cluster Randomisation

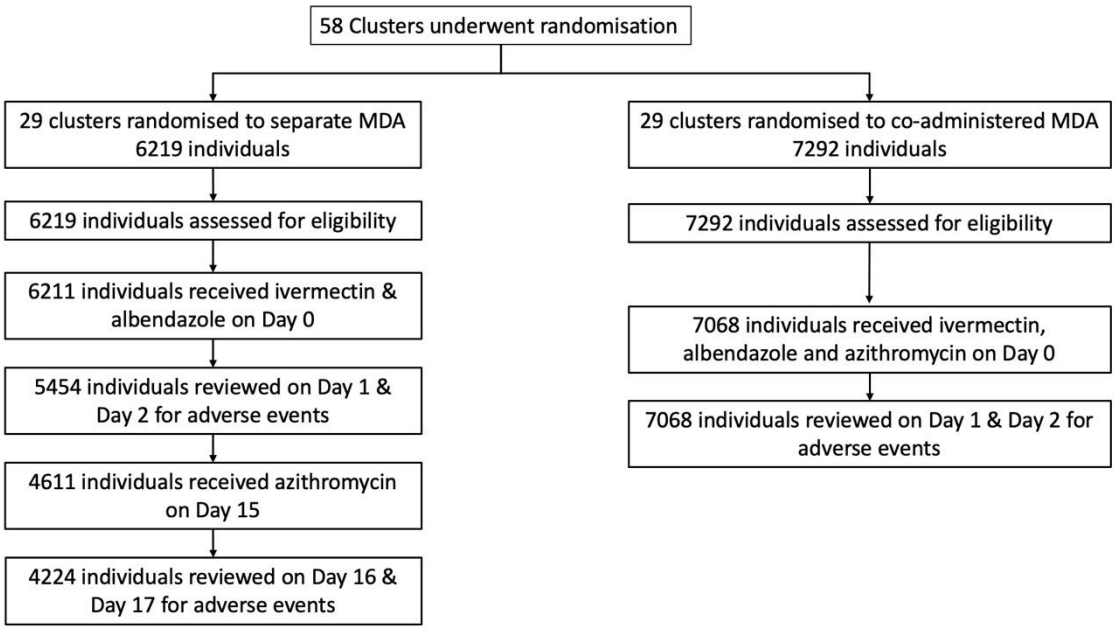
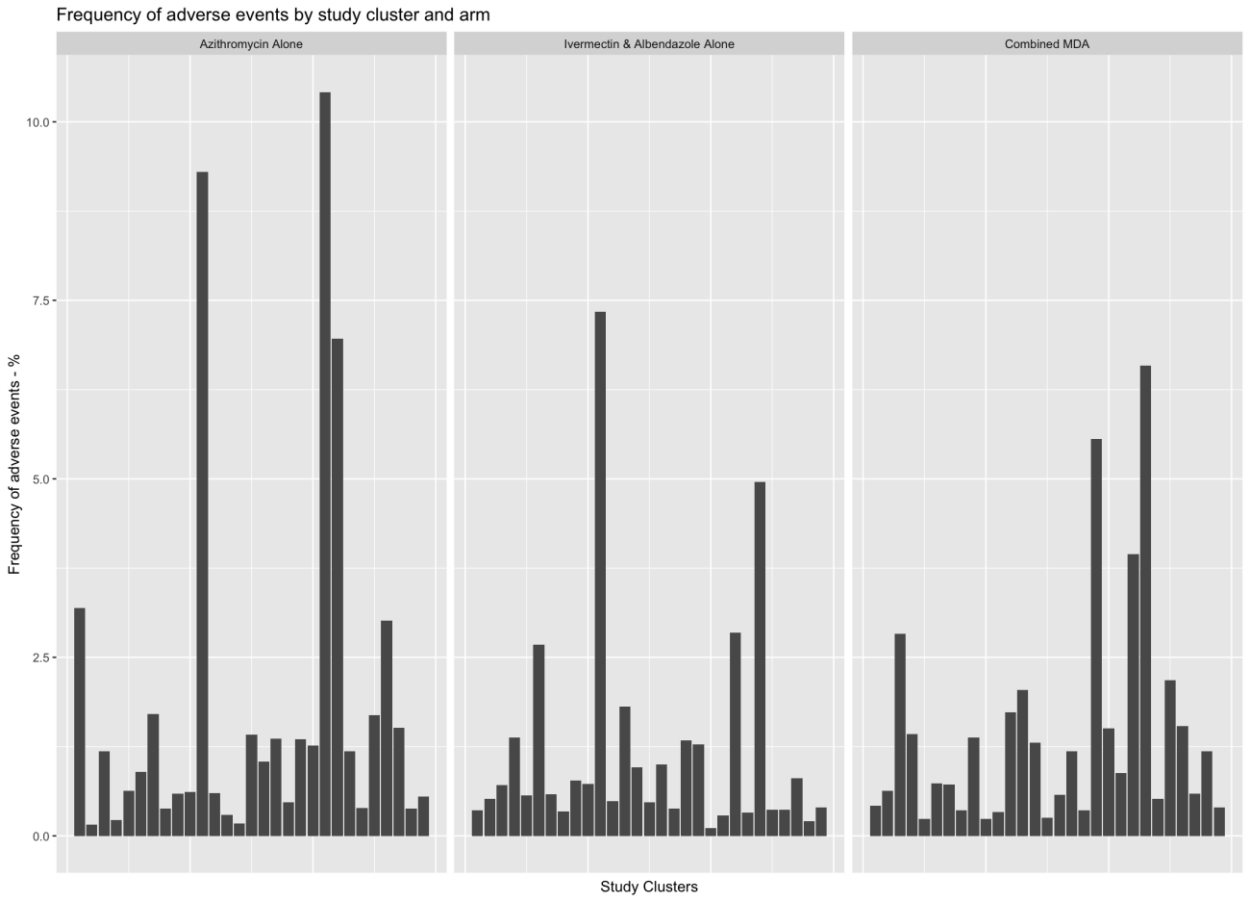


Figure 3:



We fitted a random effects model to assess the relationship between study arm and the risk of adverse events after adjusting for age and gender. The risk of adverse events was the same in individuals who received combined MDA, and individuals who received ivermectin-albendazole alone (aOR 1.28, 95% CI 0.6–2.8, p = 0.5). Similarly, the risk of adverse events was the same in individuals who received combined MDA and those who received azithromycin alone (aOR, 1.2 95% CI 0.6–2.3, p = 0.6). Neither age nor gender were associated with frequency of adverse events (Table 2).

Table 2:

	Integrated MDA vs albendazole & ivermectin			Integrated MDA vs azithromycin		
	aOR	95% CI	P	aOR	95% CI	P
Integrated MDA	1.2	0.6-2.8	0.5	1.2	0.62-2.3	0.6
Age	0.99	0.97-1.0	0.14	0.99	0.97-1.0	0.2
Gender	1.0	0.68-1.60	0.9	0.78	0.52-1.2	0.2

Discussion

In this study, the largest of its kind to date, we demonstrate that the safety of combined MDA of azithromycin, ivermectin and albendazole is non-inferior to the safety of MDA of ivermectin plus albendazole, and azithromycin distribution conducted separately. Co-administration of these three medicines is safe and feasible in this setting. We also noted a reduced coverage of the second MDA in the communities randomised to the control arm, which might suggest that co-administration can help achieve both efficiencies and improved programmatic coverage. These are critical data for WHO and for national programs of NTD-endemic countries as they consider new strategies to save resources and accelerate progress towards NTD elimination and control targets. Taken together with the existing published data discussed below, which are similarly reassuring, it is our hope that these findings will pave the way for more widespread adoption of integrated MDA.

Co-administration could have significant programmatic impact, particularly in Ethiopia, where the study was conducted. As of the time of preparing this manuscript, Ethiopia had 441 woredas requiring antibiotic MDA for trachoma, 76 woredas requiring MDA for LF, and 243 woredas known to require MDA for onchocerciasis, of which 221 received semi-annual MDA. More than 50 of these woredas are co-endemic for trachoma and at least one other NTD treated with the regimens evaluated in this study and could therefore benefit from a co-administration strategy. Combining MDA could save money through the implementation of joint supply chains, health workforce training, drug administration and supervision, as has been observed in other triple drug therapy studies.(4) MDA campaigns also require a significant time investment for the local health workforce, drawing personnel away from other duties, and multiple stand-alone MDA days may cause MDA fatigue within recipient communities. The combined MDA approach could concentrate MDA interventions for the needs and availability of the community, as has been suggested in MDA strengthening analyses published elsewhere.(15)

Our trial adds to the existing data on the safety of co-administration and importantly is the largest published study to date, overcoming a major shortcoming of previous studies. We noticed variation in the frequency of adverse events between communities, which might reflect chance or underlying cluster-level covariates; the frequency of adverse events in all clusters was within the range reported in other studies of MDA. Both randomised trial data in Mali and non-randomised data from the Solomon Islands and Colombia are concordant with our finding that co-administration is a safe and feasible strategy.(8)(16),(17)(18)(19) Our data are also in keeping with studies conducted in Papua New Guinea combining azithromycin with ivermectin, albendazole and diethylcarbamazine. A strength of the current study over this previous work is the use of consistent definitions and approaches to adverse event monitoring throughout the whole trial.(20) Collectively, these data suggest that co-administration is an acceptable and safe approach to tackling co-endemic NTDs.

Our trial has some limitations. First, we randomised a smaller number of gares than originally planned. Whilst the average cluster size was slightly larger that anticipated we did reach our pre-planned sample size. As, on average, power in a cluster randomised trial is higher when there are a larger number of smaller clusters, this will have reduced our overall power to detect differences between arms. This is likely to be more marked for the comparison of combined MDA with azithromycin-only MDA, because a smaller number of individuals took part in the azithromycin-only MDA. As such we can not exclude the possibility that there remains a small difference

between arms that we did not detect. Second, we focused on safety rather than effect on infection or disease, so we cannot assess whether co-administration increases or decreases efficacy. Previous pharmacokinetic studies have demonstrated(16) little to no drug-drug interactions between these three medicines likely to affect efficacy.(5) (21) (7). In addition, we noted a suggestion of increased coverage in the co-administration clusters which might be anticipated to result in improved efficacy. The selected study district had already received five rounds of MDA for LF and two for trachoma with reported high coverage. Therefore the intensity of infections, particularly of helminths, was likely already at low levels and this may have contributed to the low burden of adverse events. Whilst this might explain the low absolute number of adverse events, we do not believe it would affect the comparison between arms and therefore our findings are likely also of relevance to districts which have not previously undertaken multiple rounds of MDA. Third,, it was not possible to mask study participants or field teams and this might have affected reporting of adverse events. Finally,, the original intention was that the study roll out using a central point distribution strategy in each cluster to mimic standard programmatic MDA. Due to the COVID-19 pandemic, we changed our MDA delivery to a house-to-house campaign. This forced a slower, more deliberate approach by the study teams. While we have established here that taking all three drugs concurrently is feasible, this might be affected by mode of distribution. However, we feel this is unlikely to have influenced the safety comparison in the study. We undertook a nested qualitative study to explore both healthcare worker and participant perspectives of the co-administration which will be reported separately.

WHO currently recommends five possible MDA medicine combinations but not azithromycin in any combination with ivermectin or albendazole.(22) Health ministries, drug donation programmes, donors and implementing partners are showing significant interest in the implementation of integrated MDA programs to accelerate scale-up and drive greater efficiency. Our data provide the clearest evidence to date that such a strategy is safe and feasible. Adoption of integrated MDA may help accelerate progress to global NTD targets ahead of 2030.

Contributors

SM, TG, AWS,DCWM,MM,EG designed the study. SM, GT,TT,SB,HS,BO, HM,KAD,BK,FK, FS,FT,BM, AA, EG ran the trial and collected data. SM, AWS, DCWM, MM, EG analysed the data. SM wrote the first draft of the manuscript. All authors revised the manuscript. SM and MM directly accessed and verified the underlying data.

Data sharing

An anonymised copy of the data included in the analysis is available on request by email to Michael.Marks@lshtm.ac.uk.

Declaration of interests

MM was supported by the International Trachoma Initiative to present findings of this work at the Trachoma Expert Committee meeting in December 2022. TG is an employee of the International Trachoma Initiative. AS is an employee of the World Health Organization. The views and opinions expressed in this paper are those of the authors and do not necessarily reflect the views or opinions of these organisations.

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Table Legends:

Table 1: Baseline demographics

Table 2: Adverse events comparing co-administered MDA with both ivermectin & albendazole MDA and with azithromycin MDA

Figure Legends:

Figure 1: Study location. The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the authors, or the institutions with which they are affiliated, concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Figure 2: Study Profile

MDA – Mass drug administration. D0/1/2/15/16/16 refer to study days.

Figure 3: Frequency of adverse events by cluster and study arm

The proportion of individuals reporting at least one adverse event following either combined or separated MDA is shown for each cluster

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RESEARCH PAPER COVER SHEET

Please note that a cover sheet must be completed for each research paper included within a thesis.

SECTION A – Student Details

Student ID Number	1513535	**Title**	Mr
First Name(s)	SCOTT		
Surname/Family Name	MCPHERSON		
Thesis Title	SAFETY OF THE CO-ADMINISTRATION OF AZITHROMYCIN, ALBENDAZOLE, AND IVERMECTIN VERSUS STANDARD TREATMENT REGIMENTS DURING MASS DRUG ADMINISTRATION (MDA) IN ETHIOPIA: A CLUSTER RANDOMIZED TRIAL		
Primary Supervisor	DR. DAVID MABEY		

If the Research Paper has previously been published please complete Section B, if not please move to Section C.

SECTION B – Paper already published

Where was the work published?			
When was the work published?			
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SECTION C – Prepared for publication, but not yet published

Where is the work intended to be published?	PLOS NEGLECTED TROPICAL DISEASE
Please list the paper's authors in the intended authorship order:	Scott McPherson, Dereje Geleta, Getinet Tafese, Temesgen Tafese, Sinkinesh Behaksira, Hiwot Solomon, Birhanu Oljira, Hirpa Miecha, Lalisa Gemechu, Kaleab Debebe, Biruck Kebede, Teshome Gebre, Fikreab Kebede, Fikre Seife, Fentahun Tadesse, Belete Mammo, Abraham Aseffa, Anthony W Solomon, David CW Mabey, Michael Marks, and Endalamaw Gadisa
Stage of publication	**Submitted**

SECTION D – Multi-authored work

For multi-authored work, give full details of your role in the research included in the paper and in the preparation of the paper. (Attach a further sheet if necessary)	Created the protocol/designed the interview guides/designed training protoocl with engaged consultants to conduct KII and FGD interviews in Afaan oromoo. I undertook an immersion in the transcribed interview data and flagged statements from participants that were significant, insightful, or frequently repeated. Using NVIVO 12, I created codes based on key themes, identified based on both published literature and practical experience in Ethiopia, as well as from insights that occurred during the review of the transcripts themselves. Once coding was completed, I compared them to the original interview guide. I used descriptive codes relating to the participants themselves (age, gender, etc.) and thematic codes relating to what was said by the participants. I assigned identified significant statements of participants to codes. I then explored patterns in responses, linkages between the thematic and

	descriptive codes, and often repeated statements which required follow-up to avoid generalizations. I wrote the paper, circualted to the study team for comment/made subsequent revisions.

SECTION E

Student Signature	
Date	25th April 2023

Supervisor Signature	
Date	25th April 2023

Chapter 4: Perceptions and acceptability of co-administered albendazole, ivermectin and azithromycin mass drug administration, among the health workforce and recipient communities, in Ethiopia

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ABSTRACT

Several neglected tropical diseases (NTDs) employ mass drug administration (MDA) as part of their control or elimination strategies. This has historically required multiple distinct campaigns, each targeting one or more NTDs, representing a strain on both the recipient communities and the local health workforce implementing the distribution. We explored perceptions and attitudes surrounding combined MDA among these two groups of stakeholders.

Our qualitative study was nested within a cluster randomized non-inferiority safety trial of combined ivermectin, albendazole and azithromycin MDA. Using semi-structured question guides, we conducted 16 key informant interviews with selected individuals involved in implementing MDA within the participating district. To better understand the perceptions of recipient communities, we also conducted four focus group discussions with key community groups. Individuals were selected from both the trial arm (integrated MDA) and the control arm (standard MDA) to provide a means of comparison and discussion. All interviews and focus group discussions were led by fluent Afaan oromo speakers. Interviewers transcribed and later translated all discussions into English. The study team synthesized and analyzed the results via a coding framework and software. Most respondents appreciated the time and effort saved via the co-administered MDA strategy but there were some misgivings amongst community beneficiaries surrounding pill burden. Both the implementing health work force members and beneficiaries reported refusals stemming from lack of understanding around the need for the new drug regimen as well as some mistrust of government officials among the youth. The house-to-house distribution method, adopted as a COVID-19 prevention strategy, was by far preferred by all beneficiaries over central-point MDA, and may have led to greater acceptability of co-administration. Our data demonstrate that a co-administration strategy for NTDs is acceptable to both communities and health staff.

Plain English Summary

The strategy for several neglected tropical diseases is treatment of the whole community, referred to as mass drug administration. Normally these are delivered as separate rounds of treatment for each disease. This creates a burden for both the health workforce and the communities. As part of a larger study conducted in Ethiopia we used interviews and focus groups to explore perceptions and attitudes towards combined mass drug administration among both communities and health workers.

Both community members and health workers appreciated the time and effort saved via combined treatment although some community members were worried about the number of pills that had to be taken. Both health workers and community members said some people declined to take part due to a lack of understanding around the need for a combined drug regimen. Delivery of the drugs house-to-house, which had been adopted as a COVID-19 prevention strategy, was preferred over delivering the treatment at a central point in the community. Overall, our study showed that combined treatment of multiple neglected tropical diseases was acceptable to both communities and health workers.

Key words: NTD community perception; NTD health workforce perception; NTD interventions; co-administration; integration; lymphatic filariasis; trachoma; onchocerciasis; soil transmitted helminths

INTRODUCTION

Currently, mass drug administration (MDA) for neglected tropical disease (NTD) control and elimination takes place through several distinct campaigns, with the number of such campaigns depending on the number of diseases being targeted. If trachoma, lymphatic filariasis (LF), and onchocerciasis are all in frame, the first MDA round that takes place addresses onchocerciasis and LF through a height-dependent dosage of up to four pills of ivermectin and, regardless of height or age, one pill of albendazole; in some populations, diethylcarbamazine is also added. The second round of MDA takes place for trachoma two weeks later, involving a height-dependent dosage of up to four pills of azithromycin, a height-dependent dose of azithromycin oral suspension, or (for children aged <6 months or those unable or unwilling to take macrolides) tetracycline eye ointment (TEO).

Several studies have evaluated the safety of co-administration of these medicines as a strategy to tackle multiple NTDs in an integrated manner. A recently completed cluster randomized controlled trial (RCT) conducted in Ethiopia demonstrated that albendazole, azithromycin and ivermectin can safely be administered together in a single, combined MDA campaign.(1) These data add to existing evidence on the safety and feasibility of co-administration generated from both RCTs and cohort studies.(2)(3)(4)(5)(6)(7) The acceptability of the approach has not previously been formally assessed.

Ultimate uptake of integrated MDA for NTDs will depend on the acceptability of the intervention to both intervention deliverers and recipients (8). From the healthcare worker perspective, co-administration may present an opportunity to significantly reduce the time commitment demanded from the local health workforce. In theory this could free up the local health work force for other commitments. However, co-administration might be more complex and require additional training or supervision.

While the workload of the health work force is an important consideration, it's also important to consider its acceptability to those receiving the intervention. Co-administration may present an opportunity to significantly lessen the time investment required for beneficiaries to participate in MDA and reduce the indirect costs of participation. Ideally, this reduction in indirect costs would subsequently improve MDA coverage as participants would not have to choose between participating in multiple MDA rounds and their other obligations. Co-administration might alternatively result in decreased coverage if enough individuals decline to swallow the larger number of tablets offered as part of a combined MDA approach or have other safety concerns.

To assess the acceptability of the co-administration strategy from both provider and recipient perspectives, we nested a qualitative study within our recently conducted RCT in Ethiopia.

METHODS

Study Setting

The methodology of the RCT within which this study was conducted has been described elsewhere. Briefly, the study took place the two kebeles (sub-districts) Gurmicho and Alkaso, of Kofele woreda (district) in Oromia regional state. Within these kebeles, communities were randomized to receive either combined MDA, consisting of a single MDA for lymphatic filariasis and trachoma delivered on the same day, or standard MDA, consisting of MDA for lymphatic filariasis and trachoma administered separately one week apart.

Participant Selection

Participants for key informant interviews included members of the health development army and health extension workers involved in delivering MDA; religious and community leaders; and NTD focal points at woreda and zonal levels. Focus groups included both genders and ensured representation of both younger and older members of the community. Each focus group consisted of eight to ten people, each with participants evenly divided from both the trial arm and the control arm. In previous years, all participants had taken part in standard MDA.

Interviews

The study team conducted semi-structured in-depth interviews with health care workers and focus group discussions (FGD) with members of the community using a semi-structured question guide. A native Afaan oromoo speaker conducted all key informant interviews (KII) and led the focus group discussions. Interviews were conducted in a secluded settings to allow for privacy and encourage open discourse. Both the health work force key informant interview guide and the MDA recipient focus group interview guide included questions on socio-demographic information and open-ended questions including views on: pill burden; previous, non-integrated MDA campaigns; the occurrence and cause of non-compliance during MDA; and the time required for co-administered and non-co-administered MDA. The health work force key informant interview guide also included questions specific to the role the person played in the health work. *(See Appendix)*

DATA MANAGEMENT AND ANALYSIS

Interviews were recorded and transcribed verbatim into Afaan oromoo. The same interviewers that conducted the interviews translated them into English. The study team undertook an immersion in the transcribed interview data and flagged statements from participants that were significant, insightful, or frequently repeated. Using NVIVO 12, we created codes based on key themes, identified based on both published literature and practical experience in Ethiopia, as well as from insights that occurred during the review of the transcripts themselves. Once coding was completed, we compared them to the original interview guide. As Ethiopia has an established history of MDA but not of co-administration, certain codes surrounding MDA were previously identified while emerging codes were also important. We used descriptive codes relating to the participants themselves (age, gender, etc.) and thematic codes relating to what was said by the participants. We assigned identified *significant statements* of participants to codes. We then explored patterns in responses, linkages between the thematic and descriptive codes, and often repeated statements which required follow-up to avoid generalizations.

ETHICS STATEMENT

The study was nested within the larger co-administration RCT. The study received ethical approval from the National Research Ethics Review Committee (NRERC) of Ethiopia (reference 3-10/195/2018) and the London School of Hygiene & Tropical Medicine (reference 11985). Based on low levels of literacy in the study population, permission to use verbal consent was specifically provided by the ethics committees. Study

teams read the study consent form to all prospective participants and obtained verbal permission to participate in the study.

ROLE OF THE FUNDING SOURCE

The study was funded by the International Trachoma Initiative using operational research funds from the Bill and Melinda Gates Foundation. AWS is a staff member of the World Health Organization. Funders and donors had no role in the design, conduct or analysis of the study beyond review of the protocol via expert committee. For the larger co-administration trial in which this study is nested, Ivermectin was donated by the Mectizan Donation Program, the albendazole was donated by the Glaxosmithkline corporation, and the Zithromax was donated by Pfizer via the International Coalition of Trachoma Control.

RESULTS

Participant characteristics

A total of 49 participants were included in the study, including 16 health worker key informants and 33 participants who contributed to four focus group discussions. In study communities, Islam is the dominant religion. Farming is the main means of earning a livelihood followed by animal rearing. Administratively, villages are led by kebele leaders, generally politically appointed by the district administration. Besides kebele leaders, community elders and religious leaders play a significant role in different political and social activities in the community. The Gada is a traditional system of governance of the Oromo people built off of community experience over generations which encompasses of all of the socio-political issues within a community. The leader of the Gada is 'Aba Gada' or father of the Gada. Community structures like Women and Youth associations and Women health development armies in the village also contribute to various local developmental activities.

Awareness creation and community sensitization about MDA

As is standard, the trial study team carried out community awareness campaigns prior to the MDA for both intervention and control groups. Dissemination of information took place through public gatherings, community leaders, health extension personnel, development armies, and other community members. The cooperation between health workers, village leaders, and community volunteers was cited as an excellent example of how to administer drugs successfully compared to previous MDAs:

> *"…There was a big meeting conducted; they provided us the information on that meeting. The health professionals had identified the pregnant women and given special care. Those who were not available at the time the tablets were given... are eager to get them. It was not like this in the previous times. They are serving us properly. People had benefited from that. I was feeling a disturbance in my stomach (nervousness); I got relief after I took it. When they give a tablet today, they recheck it the next day. To see whether there is a side effect or not. because they were serving us just like this, the community is very happy"- (Female youths FGD)*

All participants mentioned the value of these community awareness events in ensuring village residents were aware of the MDA.

House to house MDA implementation strategy compared to central point MDA strategy

During the study, we employed a house-to-house MDA strategy. Volunteers informed each village of the day and time that the study team would conduct the distribution. This differed from the previous MDA approach in this population, in which MDA was conducted at a central point in the village and community members had to attend within a given window to be treated.

The majority of participants said that the house-to-house MDA strategy used in the trial was preferable to the central point distribution strategy and enabled the majority of the community to receive the drugs. Participants were appreciative of the house-to-house delivery method. The early morning timing of drug delivery, team makeup, counseling and advice provided, and post-MDA follow-up that formed part of the RCT were all appreciated.

> *"The drug administration was done in a good manner. It was not common for the district, health professionals, and the kebele leaders to collaborate in the way they are doing it now. They were serving each household in time. People are eagerly waiting for them [drug distributors]. They give the tablets/drugs today and revisit them the next day. It was not common before". [FGD, Adult man, 48yrs]*

Using the previous central point strategy, it was reported that many members of the community had missed the MDA for a variety of reasons, including distance, being busy, a lack of available information and limited availability of health care staff.

Within the RCT, anyone who missed treatment had the chance to take it the next day thanks to the study follow-up visit.

> "*Previously….there was no follow-up. Follow-up [re-visit] and house-to-house service is done for the first time. In the current distribution, they are telling us that there will be no problem because we are following you closely. They never move to the next group, without checking up on the one already provided to. People are very happy about this and received the drug very well*" [FGD, Female Youth]

However, some study participants mentioned that the community members were unsure of the need for the follow-up. One health extension worker (HEW) stated:

> "*They [community] are not familiar with the revisit [follow-up] after providing the drugs. They are suspicious of our revisit [follow-up]. They think that the drugs are harmful. We tell them that we are watching them if there is a side effect from the tablets. We tell them that we can give them assistance and take them to a health facility if there is any harm*" [KII, HEW].

Health workers also mentioned the effectiveness of the current MDA approach and its role in expanding coverage and reach as strengths:

> "*The current MDA is very suitable. Because we are providing it by going to their residence. They are not willing to come to the place we want them to come…. Because we go to them early in the morning, we get everyone at home. At the time we used to gather them at one place in the previous MDA, only a few old men are coming. The majority of them are mothers and their children. This time we get everyone at home*" [KII, HEW]

Perception towards pills burden during co-administration

The majority of study participants did not feel that taking a larger number of pills was more difficult compared to the previous separate MDAs. Many reported that they initially felt apprehensive but that the presence of supervisors at the time of drug administration, as well as provision of adequate information, advice, and counseling, made people feel comfortable taking the drugs.

> "*It was very nice. Many people came together and gave us the tablet. Health extension workers, health professionals, those from district and zone were together in a team while providing the tablets. We got to know each other and then they told us the details of each tablet. That is how they provided it to us. The presence of many people (study team) while providing the tablet*

increases the acceptance. I wouldn't even receive if I wasn't convinced and understood the benefit to each drugs" [FGD, Adult woman, 30 yrs]

Some community members, particularly young women, expressed concerns that the taking so much of the drug at one time might lead to infertility. These concerns were allayed by a majority of community members receiving counseling and assistance from the staff responsible for administering drugs. An elder highlighted the absence of any issue related to the burden of pills in his village's communities.

"*The number of pills did not affect anyone. People may be afraid of it but because the health professional know the way, there are no worries…… Because it is safe, the community is taking it. It has been more than 20 days since [drug distribution] began, I saw no single challenge so far*" [KII, Elder man, 60 yrs]

"*Nine tablets are not harder. I was afraid when taking it, but because I took it gradually in two rounds, it is not that hard. They were patient giving it to us. That is why we didn't feel anything*" [FGD, Youth female]

The district NTD focal point stated that, in comparison to previous MDAs, more community members took part with the notable exception of some youth:

"*Some youth refused. Some of them politicized it. Some of them argue how and why to take drugs without getting sick and get diagnosed."*. [KII, Health Worker, 37 yrs]

This hesitancy may have been linked with the recent introduction of the COVID-19 vaccine program which health workers noted had been met with hesitancy and suspicion among the youth in the communities. The introduction of a novel, multiple drug distribution strategy among the community stirred rumors that it was a replacement to COVID-19 vaccine for those who refused the injection. As the study continued and more community members received the drug, including religious and kebele leaders, the majority of youth eventually accepted the co-administered NTD medicine regimen.

Interviewees emphasized the importance of co-administration for saving time and preventing people being 'missed' during MDA:

"*I choose the nine tablets taken at once. Because re-visit (second MDA) can create a miss, as well a burden for a person delivering the drugs*" [KII, Aba Gada, 45 yrs]

"Coming twice (for different MDAs) is just wasting time. If the nine tablets did not have any harm, it is better to give them at once. It solves the problems of drop out and missing". [KII, HDA, 45yrs]

Overall perceptions of the integrated MDA compared to previous MDAs

As well as using a central point method, previous MDAs had relied heavily on community drug distributors rather than health care workers to conduct MDA. Some study participants reported that this strategy had resulted in concerns from the community that drugs were provided by volunteers.

"*…the volunteer did not get payment, but they need to get some money. It was difficult to identify who took drugs and not in previous MDA. In addition, there is a complaint on the side of the community. They complain about the MDA provided by farmers selected from the community. There are community members who say, how you dare you allow a farmer to deliver us a medicine in the previous MDA"*. [KII, Health Worker, 37 yrs]

Previously, MDA was carried out at various times of the year, such as during harvest, sowing, or cultivation depending on the timing that drugs were available. Even though our co-administered MDA occurred during harvest, the time [early morning distribution] and method [house-to-house distribution] were chosen to maximize participation. Communities in the area have a custom of staying at home until

10:00 AM before leaving for fieldwork, which made it easier to contact household members after breakfast.

Study participants advised administering MDA before or after harvest, when people are less busy, and during the dry season because transportation is also difficult during the rainy months. Participants in the study said that, with the exception of a small number of individuals who first displayed opposition, all community members, regardless of their gender, age, or religion, took part in the current MDA. Overall, all study participants acknowledged the MDA's primary strategies, such as community awareness and sensitization, house-to-house distribution, early morning distribution, a second visit the next day, the team composition, and collaboration with local leaders as major factors in the high level of acceptance.

DISCUSSION

Co-administration of drugs for multiple NTDs during MDA has the potential to accelerate progress and save time of both providers and recipients. While several combinations of NTD drugs have been proven safe (2)(3)(4)(5)(6), there remain critical lessons to learn about how to implement this strategy and how it will be perceived by those who are actually involved in its implementation. MDA can be described transactionally by categorizing a demand side (households and community members) and a supply side (the health workforce)(9). Our study demonstrates that co-administration, at least in this part of Ethiopia, is highly acceptable to both groups, with multiple perceived advantages over separate MDA delivery. In addition, our study provides insight into other aspects of optimizing MDA.

Central or fixed-point MDAs are used for many NTD elimination and control programmes. Previous studies have found that bringing the entire community together saves on both cost and time compared to house-to-house treatment, in particular in communities where houses are far apart and difficult to reach.(10)(11) A downside of this approach is that it shifts much of the participation burden on to communities and may create barriers to access. The original intention of the coadministration safety RCT in Ethiopia was to use central point MDA in order to mirror the standard MDA implementation methodology as closely as possible. However, during the COVID-19 pandemic, the Ministry of Health required MDA distributors to move house-to-house to prevent large gatherings, based on WHO recommendations (12). This model was still in place when our study took place.

Our respondents indicated that, even outside of the specific question of co-administration, a house-to-house approach is preferable. This model reduced barriers to participation, such as aligning work schedules with central point MDA schedules. In terms of co-administration, it also allowed for a more direct health education exchange with individual families to address any concerns related to this new MDA approach.

Some of our respondents described initial concerns about taking up to nine pills at one time. National NTD programs have gone to great lengths in recent years to reduce the chance of choking. Recent studies and policy documents have discussed a variety of possible causes of previous choking episodes, including pressure for compliance from the health work force, social pressure amongst beneficiaries, a lack of patient awareness and a lack of perceived right of refusal.(13)(14) We created specific diagrams for the health work force to use during co-administration, encouraging a ‘two pills, swallow, pause, two pills…’ rhythm (Appendix XX). Such reference materials could be included in future larger scale co-administration campaigns. Given that as many as three MDAs are being folded into one co-administered campaign, national programs, NGDO partners, and donors should consider increasing the implementation time to allow for house-to-house visits with built in time for awareness creation and patient empowerment, hopefully utilizing costs saved from the combined MDA platform. The use by adults of azithromycin oral suspension (in lieu of azithromycin tablets) could reduce the adult pill burden from nine tablets (four tablets of azithromycin, four tablets of ivermectin, and one tablet of albendazole) to five tablets (four tablets of ivermectin and one tablet of albendazole), though would require significant changes to manufacturing and supply chain processes. In line with existing guidance,

however, oral solution should be considered for nervous participants of any age, to help increase community compliance and comfort.(15)

As MDA was conducted as part of a trial, distribution teams consisted of the health development army, health extension workers and staff from the woreda and zonal level health departments, with support from community leaders. Previous studies have noted that new community-based medical interventions benefit from the participation of such respected individuals from the outset (16)(17). We noted that the involvement of members of the formal health system was highly valued and viewed as enhancing trust in the MDA compared to delivery solely reliant on the community health workforce.

MDA campaigns require a significant time investment for the local health workforce, draw personnel away from other duties, and multiple stand-alone MDA days may therefore cause MDA fatigue within recipient communities. Studies conducted in other countries as well as within Ethiopia have demonstrated that MDA duties prevent volunteers from pursuing other employment and income generating activities.(18) Co-administration could be a way to significantly reduce the burden on the health workforce and was viewed positively by healthcare workers in the current study. It is important to note the importance of outlining roles and responsibilities of each health worker cadre as tasks may shift within an integrated model.(19)

Co-administration could have significant programmatic impact, particularly in countries such as Ethiopia where large populations require MDA for multiple NTDs. Combining MDA could save money through the implementation of joint supply chains, health workforce training, drug administration and supervision, (20) and reduce the burden on communities. Our data suggest that with the correct implementation strategy such an approach is acceptable to both communities and staff and support widespread rollout of this approach.

Appendix 1: Position Descriptions

Health Development Army: "The Health Extension Program (HEP) launched in 2003, expanded basic health infrastructure and local human resources. In 2011, the government introduced the Health Development Army (HDA). HDA is a women-centered community movement inspired by military structures and discipline. Its special objective is to improve maternal health outcomes."

Health Extension Worker: In Ethiopia, two Health Extension Workers (HEWs) are assigned per kebele, which is the lowest administrative unit of the government structure with an average of 1,000 households and approximately 5,000 people. HEWs provide services at their health post and in the community. To extend the reach and effectiveness of the HEWs, the Women's Development Army (WDA) was organized in 2011. The WDA engages communities by organizing five or six neighboring households into teams, with each team selecting a WDA Volunteer from a model household (defined by adoption of healthy behaviors). At present, Ethiopia has approximately 40,000 HEWs and an estimated three million WDA Volunteers.

Village Elders: Village elders, known locally as "Jarsa Biyya", and respected by the community. They take part in social and cultural activities like conflict resolution. They represent community members on social issues and facilitate social activities like weddings and funeral ceremonies.

Aba Gada (community leader): The Gada is a traditional system of governance of the Oromo people built off of community experience over generations which encompasses of all of the socio-political issues within a community . The leader of the Gada is 'Aba Gada' or father of the Gada.

Muslim Religious Leader: These are persons who lead and teach Muslim religious scholars in a mosque. According to the tenants of the religion, there are different levels of leadership and teaching, such as sheiks, imams, and others.

Kebele Leader: Politically nominated individual based within the kebele that leads on aspects of sub-woreda governance.

Woreda NTD Focal Person: Woreda NTD focal persons are based within the woreda health office and usually are the focal persons for multiple different health initiatives within their district.

Zonal NTD Focal Person: Zonal NTD focal person are based in the Zonal Health Department. They report to the Oromia Regional Health Bureau and often have multiple health initiatives to manage with their zone.

Appendix 2: Compositions of focus groups and KII participants

Key Informants:

Zonal NTD Focal Person	1
District NTD focal person	1
Health Extension worker	2
Health Development Army	3
Kebele leader	2
Elder	2
Aba Gada	2
Community volunteer	1

Focus Group: Male Adultss

Code	MDA category	Kebele	Age	Educational status	Role	Marital status
R2	Control	Gurmicho	50	Grade 8	Kebele Leader	Married
R3	Control	Gurmicho	58	Grade 9	Farmer	Married
R4	Intervention	Alkaso	66	Grade 8	Farmer	Married
R9	Control	Gurmicho	35	Grade 3	Farmer	Married
R7	Control	Gurmicho	35	Grade 8	Farmer	Married
R8	Control	Gurmicho	53	Grade 4	Farmer	Married
R1	Intervention	Alkaso	50	Grade 7	Farmer	Married
R5	Intervention	Alkaso	28	Grade 10	Farmer	Married
R6	Intervention	Alkaso	48	Diploma	Farmer	Married

Focus Group: Female Adults

Code	MDA category	Kebele	Age	Educational status	Role	Marital status
R1	Control	Alkaso	35	Grade 12	Farmer	Married
R2	Control	Alkaso	25	Grade 8	Farmer	Married
R3	Control	Gurmicho	25	Grade 10+1	Farmer	Married
R4	Control	Gurmicho	40	Grade 2	Farmer	Married
R5	Intervention	Gurmicho	30	Grade 10+3	Farmer	Married
R6	Intervention	Gurmicho	25	Grade 8	Farmer	Married
R7	Intervention	Gurmicho	26	Grade 6	Farmer	Married
R8	Intervention	Alkaso	30	Grade 10	Farmer	Married

Male youths

Code	MDA category	Kebele	Age	Education	Role	Marital status
R1	Control	Alkaso	25	Grade 7	Farmer	Married
R2	Intervention	Gurmicho	23	Diploma	Farmer	Single

R3	Control	Gurmicho	22	Grade 6	Farmer	Married
R4	Control	Gurmicho	21	Grade 10	Farmer	Single
R5	Control	Alkaso	37	Grade 9	Farmer	Married
R6	Intervention	Gurmicho	25	Illiterate	Farmer	Married
R7	Intervention	Alkaso	22	Grade 10	Farmer	Married
R8	Control	Gurmicho	18	Grade 7	Farmer	Married

Focus Group: Female youths

Code	MDA category	Kebele	Age	Educational status	Role	Marital status
R1	Control	Alkaso	35	Grade 12	Farmer	Married
R2	Control	Alkaso	25	Grade 8	Farmer	Married
R3	Control	Gurmicho	25	Grade 10+1	Farmer	Married
R4	Control	Gurmicho	40	Grade 2	Farmer	Married
R5	Intervention	Gurmicho	30	Grade 10+3	Farmer	Married
R6	Intervention	Gurmicho	25	Grade 8	Farmer	Married
R7	Intervention	Gurmicho	30	Grade 6	Farmer	Married
R8	Intervention	Alkaso	25	Grade 10	Farmer	Married

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Chapter 5: Conclusions and Next Steps

This PhD set out to establish the safety profile and assess the community acceptance of a three-agent MDA combining albendazole (Alb), azithromycin, and ivermectin (Ivm) in comparison to the standard MDA regimen which separates the administration of azithromycin from the co-administered ivermectin and albendazole by a period of two weeks.

Distributing multiple drugs at the same time to address multiple NTDs is not a novel concept. National programs have successfully distributed ivermectin, albendazole and praziquantel together to address onchocerciasis, lymphatic filariasis and schistosomiasis. Diethylcarbamazine, when distributed together with ivermectin and albendazole as part of an IDA strategy, has been demonstrated to expedite the elimination of LF in endemic countries outside of Africa. National programs, eager to take advantage of the benefits of these coadministration approaches, may benefit from the similar established safety profile for Albendazole, ivermectin, and azithromycin. Given this possible benefit, I have attempted to: (i) address an evaluation of the existing published information surrounding such an approach, (ii) conduct a randomized controlled trial to establish non-inferiority of the co-administered approach compared to standard MDA approaches, iii.) ascertain the perception of co-administration amongst the health workforce and the communities receiving the MDA.

Objective 1: Review the existing data on the safety of co-administration of ivermectin, albendazole and azithromycin

> A brief overview is given in the introduction. The main study methods and findings are presented in the linked research paper in Chapter 2.

Objective 2: Conduct a trial in Ethiopia to evaluate the safety of programmatic co-administration of ivermectin, albendazole and azithromycin.

> A detailed overview of the study methodology is given the introduction. The results of the trial are presented in the linked research paper in Chapter 3.

Objective 3: Evaluate the acceptability of co-administration to both healthcare workers and community stakeholders

> This objective was addressed by two sub-studies nested within the trial conducted for Objective 2. A brief overview is given in the introduction. The main study methods and findings of these sub-studies are presented in the linked research paper in Chapter 4.

Summarized Findings:

Objective 1: Review the existing data on the safety of co-administration of ivermectin, albendazole and azithromycin

I addressed the first objective via a literature review. I identified a total of 58 potentially relevant studies. Of these I identified 7 studies that were relevant to the research question and met our inclusion criteria. Three papers analyzed the pharmacokinetic and pharmacodynamic interaction of azithromycin,

ivermectin and albendazole. Two papers and a conference presentation reported data on combinations of at least two of the drugs. One paper was a field study that involved the co-administration of all three drugs. A further field study reported on all three drugs but as part of a four-drug regimen involving the addition of diethylcarbamazine alongside ivermectin, albendazole and azithromycin.

My review highlighted that there are relatively limited data on the safety profile of co-administering ivermectin, albendazole and azithromycin as an integrated regimen for NTDs. Despite the limited amount of data, the available evidence suggested that such a strategy appears to be safe with an absence of clinically important drug interactions, no serious adverse events and little evidence for an increase in more mild adverse events. Overall, my review suggests integrated MDA may be a viable strategy for national programmes.

Objective 2: Conduct a trial in Ethiopia to evaluate the safety of programmatic co-administration of ivermectin, albendazole and azithromycin

I led a large cluster-RCT in Ethiopia which enrolled more than 7,000 individuals in both study arms. Overall, adverse events were uncommon and were reported by under 2% of the population and no serious adverse events were seen. The adverse event rate was similar when comparing co-administration to both azithromycin and ivermectin/albendazole alone and both comparisons met the pre-defined 1.5% non-inferiority margin.

This study is the largest of its kind to date and demonstrates that the safety of combined MDA of azithromycin, ivermectin and albendazole is non-inferior to the safety of combined MDA of ivermectin and albendazole and azithromycin distribution conducted separately. Co-administration of these three medicines is safe and feasible in this setting and allows national programs new strategies for integrated MDA programmes.

Objective 3: Evaluate the acceptability of co-administration to both healthcare workers and community stakeholders

I used a nested qualitative study to assess healthcare worker and community perceptions of the co-administration strategy. Trust building through community engagement was key to overcoming initial refusals. The findings demonstrate that a significant investment should be applied towards social mobilization and community awareness before the new combined MDA approach is adopted. This process should include community influencers (elders, local leaders, community leader). The house-to-house approach for drug distribution was noted to be an important component for improving satisfaction and acceptability of the integrated approach As the study took place in a broadly culturally and societally homogeneous population, more work will be required to ensure the findings hold true as the strategy of combining three drugs is scaled up throughout Ethiopia and in other countries.

Limitations

There were some limitations with my thesis. The trial was only conducted in one region of the world and the district where the study was conducted had already participated in three rounds of MDA for both LF and trachoma. The lack of adverse events, particularly concerning helminthiasis-related reactions, may not be representative for MDA naïve districts. Although data on adverse events was collected actively and prospectively, it relied on clinical data collection. Monitoring on a biochemical level might have detected additional adverse events.

The qualitative portion of the study involved a relatively small sample size within the targeted kebeles. It also took place during both the Tigray civil war as well as the COVID pandemic. As noted in the

discussion section of the trial paper both of these issues may have contributed to unforeseen perspectives surrounding trust in the government and public health initiatives.

Challenges

We obtained initial LSHTM ethical approval in May 2018 and subsequently initial Ethiopian National Ethical Clearance Committee (NERC) approval in November 2018.

Unfortunately, the approval by the NERC coincided with rise of security issues in the originally targeted woreda of Homesha in Beneshangul-Gumuz region. A separatist movement within the region led the Regional Health Bureau director to determine that it would be inappropriate to conduct a CRT within the woreda surrounding fears that reports of adverse events may further inflame anti-government sentiment. Although both the FMOH and AHRI tried to reassure the RHB, the RHB director requested an official change to the targeted district in February 2019.

The study team met with the FMOH to find another woreda in a secure area with a disease profile appropriate to the study. After an introductory meeting to discuss the study with the Oromia Regional Health Bureau, we selected Dano woreda in West Shoa zone in Oromia. This change in site selection required an amendment to the co-administration protocol that NERC had already approved. An amended protocol was submitted to the NERC in April 2019. For reasons outside of the control of the study the approval for the amendment was not provided until February 2020.

Subsequently, Ethiopia went into country wide lockdown due to the COVID pandemic shortly after this and the study could not be continued until July of 2021. Once the MOH allowed for the study to continue (in full accordance with national social distancing protocols), the ORHB requested that the study was moved from Dano woreda due to separatist militia activity within the selected woreda. I therefore again reviewed the disease profiles from a line-listing of appropriate woredas together with the MOH and AHRI and selected Kofele woreda in the West Shoa zone of Oromia. The NERC approved the amendment in October of 2021. The RCT therefore finally began in November of 2021 almost three years after the original ethics approval. Despite these delays I was able to successfully implement the trial in the finally selected woreda and I am grateful to all of my collaborators for their ongoing support through this period.

State of the field now and the next steps

My PhD adds to the existing data on the safety of co-administration and importantly is the largest study to date, overcoming a major shortcoming of previous studies. Both randomised trial data in Mali and non-randomised data from the Solomon Islands and Colombia are concordant with my PhD findings that co-administration is a safe and feasible strategy (1)(2)(3)(4)(5). These data are also in keeping with studies conducted in Papua New Guinea combining azithromycin with ivermectin, albendazole and diethylcarbamazine. A strength of the current study over previous work is the use of consistent definitions and approaches to adverse event monitoring throughout the whole trial.(6) Collectively, these data suggest that co-administration is an acceptable and safe approach to tackling co-endemic NTDs.

WHO currently recommends five possible MDA medicine combinations but not azithromycin in any combination with ivermectin or albendazole.(22) Health ministries, drug donation programmes, donors and implementing partners have shown significant interest in the implementation of integrated MDA programs to accelerate scale-up and drive greater efficiency. The data from my PhD provide the clearest

evidence to date that such a strategy is safe and feasible. Adoption of integrated MDA may help accelerate progress to global NTD goals ahead of 2030.

There are additional research questions which remain as we consider the adoption of coadministration on a larger scale. The health economics of co-administration are still not well-understood. While one would assume that there is a net cost saving when combining separate MDAs into one distribution event, there may be unforeseen costs including additional time to complete the MDA, additional days of training needed at each tier of a cascaded training, and costs in integrating or adapting supply chains and data collection processes that require consideration.

The trial excluded several groups including pregnant women and children under 7. These groups would normally receive at least some of the drugs administered, when conducting standard MDA, so it will be important to explore if they can also safely receive these drugs as part of a co-administration strategy. This is particularly important for integration opportunities such as school age children deworming campaigns.

With the coadministration of azithromycin, ivermectin and albendazole established as safe, it would be beneficial to further study the safety profile of other co-administered drugs. In particular, the coadministration of azithromycin and praziquantel would allow areas co-endemic with trachoma and schistosomiasis to use a co-administered strategy. In areas with particularly high schistosomiasis prevalence, the WHO recommends that adults are also treated meaning a mechanism for community-wide MDA with praziquantel could have a potential cost benefit.

Bringing this coadministration approach into policy will require several different steps of engagement across a number of donors, partners and national programs. Work is ongoing to engage with WHO on a full review of data from my PhD, taken alongside data from other settings with a view to informing WHO NTD guidelines. Co-administration adoption will also require buy-in from pharmaceutical companies and donors. Results of this PhD and other studies were presented to the Trachoma Expert Committee in November 2022 as a first step in this process. Results will be further presented at the Ethiopia Trachoma Advisory Group in August 2023. It is hoped that if TAG approves of the findings co-administration strategy may adopted as appropriate across Ethiopia. Uptake of this strategy nationally will be the ultimate realisation of the aims of my PhD.

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